PROSPECTS FOR REGULATION OF OFF-LABEL DRUG PROMOTION IN AN ERA OF EXPANDING COMMERCIAL SPEECH PROTECTION*

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On December 3, 2012, the United States Court of Appeals for the Second Circuit handed the government yet another setback in its quest to stem the deleterious public health effects of aggressive pharmaceutical marketing. United States v. Caronia *involved a First Amendment challenge to a pharmaceutical sales representative's criminal misdemeanor prosecution for promoting the narcolepsy drug Xyrem for multiple off-label uses by making oral statements about uses of the drug not approved by the Food and Drug Administration ("FDA") during sales calls to a physician's office. On the basis of evidence about his statements presented at trial, the representative, Alfred Caronia, was convicted of conspiracy to introduce a misbranded drug into interstate commerce. In a 2-1 decision, the Second Circuit held that the government had prosecuted Caronia, in violation of his First Amendment rights, because he engaged in constitutionally protected commercial speech.*

In this Article, we review the implications of the Caronia *decision for the FDA's ability to regulate off-label promotion and set it in the context of other major court decisions related to the scope of First Amendment protection for commercial speech concerning pharmaceuticals. After summarizing the statutory and regulatory framework governing off-label promotional communications, we*

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review relevant precedent and the Caronia *decision. Considering both the* Caronia *case and other precedents, we then consider what avenues remain for FDA regulation of off-label promotion by pharmaceutical manufacturers.*

We discuss five potential strategies. The first three revolve around key technical issues arising from Caronia*: ensuring that prosecutions are based on written rather than oral statements, emphasizing that speech is being used as evidence of intent, and focusing on the false or misleading nature of the promotional materials. The fourth involves a frontal challenge to the Second Circuit panel's decision in* Caronia*—we suggest ways in which the government could make a stronger case that its regulatory framework for off-label promotion satisfies the criteria of the* Central Hudson *test. Finally, we consider alternative regulatory regimes for off-label promotion, such as limited approvals of off-label indications paired with limits on prescribing and accelerated supplemental FDA approval for promotion of unapproved uses. These options may be useful if the government has to intervene to prevent the substantial public health risks of unfettered off-label promotion that may emerge in a post-*Caronia *world.*

INTRODUCTION

In December 2012, a three-judge panel of the United States Court of Appeals for the Second Circuit set down a decision shaking the very foundation of the U.S. Food and Drug Administration's ("FDA's") regulation of pharmaceutical approval and promotion. The case, *United States v. Caronia*,[1] involved a Department of Justice criminal misdemeanor prosecution of a pharmaceutical sales representative named Alfred Caronia who was caught on tape promoting a drug for conditions not approved by the FDA.[2] The FDA generally prohibits manufacturers and their representatives from engaging in so-called "off-label" promotion, considering intent to introduce a misbranded product in violation of provisions of the Federal Food, Drug and Cosmetic Act ("FDCA" or "the Act") that require all prescription drugs sold in the United States to be supported by substantial evidence from adequate and well-controlled trials.[3] At trial, Caronia argued that his First Amendment right to free speech protected him from being prosecuted for his statements, and the Second Circuit panel agreed.[4] The majority opinion, which covers New York, Connecticut, and Vermont, held that the FDA's prohibition on promotion of off-label drug uses was inherently suspect under the Constitution's First Amendment protection of commercial speech.[5]

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

2. *Id.* at 156. As we will later discuss, the promotional statements involved indications for which the drug was not proven to work and may have been unsafe. *See infra* Part III.

3. 21 U.S.C. § 355(d) (2012).

4. *Caronia*, 703 F.3d at 158, 168–69.

5. *See id.*; *see also* Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2674 (2011) (Breyer, J., dissenting) (remarking on "the constitutional importance of maintaining a free marketplace of ideas").

But the FDA's restriction on off-label promotion is not a capricious attempt to restrict manufacturers from communicating to physicians about their products. Rather, the FDA's approach was honed over decades of debate in response to major problems caused by the lack of such regulation. The requirement that a manufacturer must document and accurately report drug and device efficacy and side effects was a response to public health tragedies in which patients died after taking products with poisonous constituents (sulfanilamide elixir, 1938),[6] gave birth to babies with devastating congenital anomalies (thalidomide, 1962),[7] or used contraceptive devices that caused bacterial sepsis (Dalkon Shield, 1974)[8]—all occurring in the context of wide manufacturer promotion of their safety.[9] Even more common was the promotion of drugs to treat conditions for which they totally lacked efficacy.[10] Consensus grew that it was in the public's interest for manufacturers to prove that a medication actually worked before it could be sold and promoted.

Despite these rules, the past decade has revealed that off-label promotion is quite common in the drug and medical device industries. Nearly every major manufacturer has now been investigated by government prosecutors for violating the FDCA and the FDA's enabling rules on off-label promotion.[11] All of these cases also involved important risks to public health related to the off-label uses. A partial list of products for which inappropriate off-label marketing has led to widespread patient morbidity and mortality[12] includes

6. Jerry Avorn, *Two Centuries of Assessing Drug Risks*, 367 NEW ENG. J. MED. 193, 195–96 (2012).

7. *Id.*

8. *See* Mike Mitka, *IUDs Effective but Underused Options for Emergency and Long-Term Contraception*, 307 JAMA 2473, 2473 (2012); Susan F. Wood, *Women's Health and the FDA*, 353 NEW ENG. J. MED. 1650, 1650 (2005).

9. Avorn, *supra* note 6, at 194; Jerry Avorn, *Learning About the Safety of Drugs—A Half-Century of Evolution*, 365 NEW ENG. J. MED. 2151, 2151 (2011).

10. Henry A. Waxman, *A History of Adverse Drug Experiences: Congress Had Ample Evidence to Support Restrictions on the Promotion of Prescription Drugs*, 58 FOOD & DRUG L.J. 299, 299–300 (2003). *See generally* DANIEL CARPENTER, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA (2010) (discussing events in the pharmaceutical industry that preceded the regulatory inclusion of an efficacy requirement).

11. *See* Sammy Almashat & Sidney Wolfe, *Pharmaceutical Industry Criminal and Civil Penalties: An Update*, PUB. CITIZEN 4 (Sept. 27, 2012), *available at* http://www.citizen.org/documents/2073.pdf (describing a total of 239 settlements for $30.2 billion reached between federal and state governments from 1991 to 2012).

12. *See generally* John N. Joseph et al., *Enforcement Related to Off-Label Marketing and Use of Drugs and Devices: Where Have We Been and Where Are We Going?*, 2 J. HEALTH & LIFE SCI. L. 73 (2009) (describing major civil settlements and criminal pleas).

rofecoxib (Vioxx),[13] rosiglitazone (Avandia),[14] paroxetine (Paxil),[15] fenfluramine/phentermine (Fen-Phen),[16] and telithromycin (Ketek).[17] Entire classes of drugs have been affected as well, including the promotion of antipsychotic drugs in elderly patients with dementia[18] or the promotion of antiepileptic medications[19] for certain types of mood disorders, both of which have been shown to increase mortality. Settlements of government investigations of illegal off-label marketing have led to over $12 billion in civil and criminal fines.[20]

The *Caronia* case applied First Amendment scrutiny of government restrictions on commercial speech to upend FDA rules on off-label marketing and threatens to be a major step in the judicial deconstruction of our country's decades-old system of drug regulation.[21] *Caronia* draws from a line of Supreme Court cases that review restrictions on commercial speech in the pharmaceutical market and largely reject them in the name of the same core principles: a skepticism of government "paternalism" intruding into consumers' ability to receive useful information, a view of physician consumers of this information as learned consumers who can efficiently weed out useful scientific facts from promotional speech about pharmaceuticals, an unwillingness to interfere with a marketplace of ideas that leads to optimal economic decision making about therapeutic choices, and a presumption that the information

13. *See* Harlan M. Krumholz et al., *What Have We Learnt from Vioxx?*, 334 BMJ 120 (2007).

14. *See* Ray Moynihan, *Rosiglitazone, Marketing, and Medical Science*, 340 BMJ c1848 (2010).

15. *See* Meredith Wadman, *Spitzer Sues Drug Giant for Deceiving Doctors*, 429 NATURE 589 (2004).

16. *See* Gina Kolata, *How Fen-Phen, A Diet 'Miracle,' Rose and Fell*, N.Y. TIMES (Sept. 23, 2007), http://www.nytimes.com/1997/09/23/science/how-fen-phen-a-diet-miracle-rose-and-fell.html?src=pm&pagewanted=1.

17. *See* David B. Ross, *The FDA and the Case of Ketek*, 356 NEW ENG. J. MED. 1601 (2007).

18. G. Caleb Alexander et al., *Increasing Off-Label Use of Antipsychotic Medications in the United States, 1995–2008*, 20 PHARMACOEPIDEMIOLOGY DRUG SAFETY 177, 177–78 (2011).

19. Aaron S. Kesselheim et al., *False Claims Act Prosecution Did Not Deter Off-Label Drug Use in the Case of Neurontin*, 30 HEALTH AFF. 2318, 2318 (2011).

20. Brady Dennis, *Johnson & Johnson Agrees to Pay $2.2 Billion in Drug Marketing Settlement*, WASH. POST (Nov. 4, 2013), http://www.washingtonpost.com/national/health-science/johnson-and-johnson-agrees-to-pay-22-billion-in-drug-marketing-settlement/2013/11/04/a7092342-456a-11e3-b6f8-3782ff6cb769_story.html ("The Justice Department said it has recovered nearly $17 billion since 2009 by bringing cases under the False Claims Act, with about $12 billion of that involving fraud against federal health-care programs.").

21. Aaron S. Kesselheim, Michelle M. Mello & Jerry Avorn, *FDA Regulation of Off-Label Drug Promotion Under Attack*, 309 JAMA 445, 446 (2013).

imparted in pharmaceutical promotion is truthful and not misleading. However, none of these assumptions about off-label promotion stands up to closer scrutiny.

In Part I of this Article, we review current FDA off-label promotion rules and then in Part II turn to the Supreme Court's application of the commercial free speech doctrine to three key pharmaceutical promotion cases. Our goal is to crystallize the main principles guiding judicial review of regulation of pharmaceutical promotion. In Part III, we review the direct challenges to the current policies preventing off-label promotion, including *Caronia*, to dispute the rationale underlying the majority's decision.

Finally, in Part IV, we conclude by analyzing the range of options available for the FDA to maintain oversight of off-label prescription drug promotion despite the rising tide of commercial speech jurisprudence. Two strategies that cue off technical issues in the *Caronia* decision are (1) basing prosecutions on written rather than oral statements and (2) emphasizing that speech is being used merely as evidence of intent. A third strategy is to characterize promotional materials as false or misleading. A fourth strategy is to make a stronger case that the FDA regulations on off-label promotion satisfy the criteria of the *Central Hudson* test. A fifth strategy is to modify FDA regulations concerning off-label promotion to make expanded use of "safe harbors."

I. CURRENT FDA OFF-LABEL PROMOTION RULES

The FDCA does not explicitly proscribe off-label drug promotion. Rather, it prohibits introducing any new drug or biological product that has not been approved by the FDA or is misbranded.[22] For a drug to be legally marketed in the United States, the manufacturer must submit a New Drug Application ("NDA"). The FDA may approve an NDA only if it contains reports of investigations that show the drug is safe for the use or uses stated in the drug's proposed labeling.[23] In addition, since 1962, the manufacturer has also been required to demonstrate that the drug

22. *See* 21 U.S.C. § 331(d) (2012); *id.* § 355(a) ("No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application . . . is effective . . . ."); *id.* § 331(a) (forbidding the introduction of adulterated or misbranded food or drugs into commerce); *id.* § 352(a) (defining false or misleading labels as misbranded drugs or devices); *id.* § 352(f) (discussing directions for use and warnings on labels).

23. *See id.* § 355(b)(1) (listing application requirements).

shows efficacy for the uses described in the labeling.[24] Specifically, the FDA can authorize the sale of the drug if there is "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling . . . ."[25] "Substantial evidence" was first defined in the 1962 amendments to the FDCA as

> evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling . . . .[26]

When the FDA approves a drug for introduction into interstate commerce, the Act ties approval to how the drug is described in its labeling materials.[27] Each approval thus represents a careful balancing of the risks and benefits of the drug for that particular indication. A sponsor submits the "labeling proposed to be used" for the drug concurrently with submitting the product for FDA approval,[28] and must submit "mailing pieces and any other labeling or advertising devised for promotion of the drug" when they are first used.[29] Permission to sell a new drug can be withheld if the labeling is "false or misleading in any particular."[30] Violation of the labeling requirements is considered to be a criminal offense.[31]

The FDCA defines "labeling" to include "all labels and other written, printed, or graphic matters (1) upon any article or any of its containers or wrappers, or (2) accompanying such article."[32] The

24. *See* Drug Amendments of 1962, Pub. L. No. 87-781, § 102, 76 Stat. 780, 781 (codified as amended at 21 U.S.C. § 355(d)).

25. 21 U.S.C. § 355(d).

26. Drug Amendments of 1962 § 102.

27. SUSAN THAUL, CONG. RESEARCH SERV., R41983, HOW FDA APPROVES DRUGS AND REGULATES THEIR SAFETY AND EFFECTIVENESS 2–3 (2012).

28. 21 U.S.C. § 355(b)(1)(F).

29. 21 C.F.R. § 314.81(b)(3) (2013).

30. 21 U.S.C. § 352(a).

31. *See id.* § 333(a) (describing criminal sentences and fines); 42 U.S.C. § 262(f) (2006) (same).

32. 21 U.S.C. § 321(m). This definition distinguishes the broad term "labeling" from the narrower term "label," which is defined as "a display of written, printed, or graphic matter upon the immediate container of any article." *Id.* § 321(k). Although the term "off-

Supreme Court has construed the term "accompanying" in this definition broadly,[33] creating grounds for the FDA to prosecute misbranding on the basis of statements made in a variety of other fora. One of the most important components of the labeling materials is the prescribing information, a multi-page pamphlet that describes approved uses of the product, evidence upon which these uses are based, and relevant safety information about the product, such as its known adverse effects.[34] However, in subsequent regulations, the FDA has interpreted this definition to include essentially all audio or visual material containing drug information distributed by or on behalf of the manufacturer.[35]

Once a drug is approved, physicians have autonomy to prescribe it for any indication and patient population and at any dose, including those not described in the official labeling materials—so-called "off-label" uses.[36] Off-label uses are often medically appropriate, especially for patients with no other therapeutic alternatives where the drug's effectiveness is biologically plausible. There may be some evidence accumulating for the off-label use from clinical trials or

label" rather than "off-labeling" is used in the common parlance, such prosecutions can be based on statements throughout the drug's labeling.

33. *See, e.g.*, Kordel v. United States, 335 U.S. 345, 347–49 (1948) (holding that pamphlets that a manufacturer provided to drug retailers for the purpose of advertising and explaining the drugs to consumers constituted part of the drugs' labeling).

34. The product information document is mostly written by the manufacturer and is intended to educate the prescribing practitioner, although in recent years its format has been changed to make certain parts of it more accessible to non-professionals.

35. *See* 21 C.F.R. § 202.1(l)(2) (2013). *But see* Allison D. Burroughs et al., *Off-Label Promotion: Government Theories of Prosecution and Facts that Drive Them*, 65 FOOD & DRUG L.J. 555, 559 (2010) ("The statutory definition of labeling encompasses only written materials and this construction is supported by the case law."). However, this exclusion of oral statements is relevant only to an enforcement action against a pharmaceutical manufacturer for unlawful introduction of an unapproved "new drug" under § 352(a) of the misbranding statute. *See* 21 U.S.C. § 352(a). By contrast, prosecutions of pharmaceutical manufacturers for unlawful introduction of a misbranded drug due to labeling that bears "inadequate directions for use" under § 352(f) of the statute can be supported by oral statements based on the FDA's subsequent interpretation of the statute. *See id.* § 352(f). Burroughs et al. note "if any conduct by a manufacturer or its sales agents, including oral statements, suggests an intent that its drug product be used off label, then the drug would arguably be misbranded under section 352(f) because the drug's labeling would not have 'adequate directions' for such off-label use." Burroughs et al., *supra*, at 563.

36. U.S. FOOD & DRUG ADMIN., DEP'T OF HEALTH & HUMAN SERVS., HFI-22, USE OF APPROVED DRUGS FOR UNLABELED INDICATIONS 4–5 (1982); Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration, 37 Fed. Reg. 16,503, 16,503 (Aug. 15, 1972) (codified at 21 C.F.R. pt. 130); *see also* Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 214, 111 Stat. 2296, 2348 (codified at 21 U.S.C. § 396 (2012)) (enunciating a similar rule for medical devices).

other studies organized after the drug is approved. In some cases, industry sponsors may take this evidence to the FDA via a supplemental NDA and receive a secondary indication for the product; for a variety of reasons, though, companies may not always take this step.[37]

However, it is also true that the majority of off-label prescribing occurs in the absence of supporting evidence and not for patients with rare diseases and no other legitimate therapeutic choices.[38] One study of prescribing patterns for 160 drugs, including the 100 that are prescribed most in office-based practice, found a 21% off-label prescription rate and concluded that "[a]mong off-label mentions, most (73%) lacked evidence."[39]

A manufacturer who promotes off-label uses risks criminal liability under the FDCA if its drug is found to be "misbranded."[40] Drugs can be misbranded for false or misleading labeling information or labeling that does not bear "adequate directions for use."[41] Since the only legitimate source of information about directions for use is the FDA-approved labeling information, directions provided by the manufacturer for using the drug in an off-label context are not permitted.

The combination of the requirements for approval and the misbranding provision provide two avenues for restrictions on off-label promotion: a drug promoted for unapproved uses may be considered to be an "unapproved drug" for that use, or it may be deemed "misbranded." Under either statutory provision, in the FDA's view, it can be illegal for a drug's labeling to discuss uses of the drug that the FDA has not validated as being supported by substantial evidence.

37. Aaron S. Kesselheim, *Off-Label Drug Use and Promotion: Balancing Public Health Goals and Commercial Speech*, 37 AM. J.L. & MED. 227, 237 (2011) (describing administrative delays and potential for negative determinations as reasons for failing to submit a supplemental NDA for an existing off-label use).

38. *See, e.g.*, Danielle Holley, *Balancing on the Edge: The Implications and Acceptability of Off-Label Drug Use*, 19 ALB. L.J. SCI. & TECH. 633, 656–57 (2009). Holley recommends a post-approval registry for all patients receiving drugs off-label in which "[p]hysicians should be required to inform their patients of the regulatory status of the drug, with physicians noting the off-label use, and obtain consent, explaining the possible risks and the fact that most of the side-effects will be potentially unknown. Additionally, physicians then will have to publish their findings." *Id.*

39. David C. Radley, Stan N. Finkelstein & Randall S. Stafford, *Off-Label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1023 (2006).

40. 21 U.S.C. § 352 (2012).

41. *Id.* § 352(f)(1).

The FDA's prohibition on a manufacturer's ability to discuss off-label uses is not absolute. The most significant exceptions to the FDA's restriction on manufacturer off-label promotion were enumerated in the late 1990s and early 2000s. In 1996 and 1997, the FDA released guidance documents setting out some permissible forms of off-label marketing,[42] including the practice of disseminating reprints of medical journal articles and supporting Continuing Medical Education ("CME") programs that discussed off-label uses.[43] These "safe harbors" included responses to requests for scientific or medical information initiated by health care professionals.[44] The FDA enumerated circumstances under which such journal reprints could be distributed and listed formal criteria for judging the independence of a CME program from its sponsoring manufacturer for the purpose of teaching physician attendees about off-label uses of the drugs being discussed.[45] In 1997, Congress passed the FDA Modernization Act ("FDAMA"), which contained amendments to the FDCA that expressly allowed dissemination of journal reprints discussing off-label uses if the manufacturer certified to the FDA that it would file a supplemental NDA for the off-label use or submit to the FDA a

42. *See, e.g.*, Advertising and Promotion; Guidances, 61 Fed. Reg. 52,800, 52,800–01 (Oct. 8, 1996).

43. *See, e.g.*, Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64,074, 64,075–76 (Dec. 3, 1997).

44. Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices; Request for Comments, 59 Fed. Reg. 59,820, 59,823 (Nov. 18, 1994). Manufacturers may respond to unsolicited requests for information with "responsive, nonpromotional, balanced scientific information, which may include information on unapproved uses, without subjecting their products to regulation based on the information." *Id.*

45. *See* OFFICE OF THE COMM'R, OFFICE OF POLICY, U.S. FOOD & DRUG ADMIN., DEP'T OF HEALTH & HUMAN SERVS., 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 (2009) [hereinafter 2009 GUIDANCE FOR INDUSTRY], *available at* http://www.fda.gov/regulatoryinformation/guidances/ucm125126.htm.

> Scientific and medical information that concerns the safety or effectiveness of an approved drug or approved or cleared medical device for an unapproved new use that is not included in the product's approved labeling or statement of intended uses (including unapproved new uses of approved drugs and approved or cleared devices) is often published in journal articles or reference publications. These publications are often distributed by manufacturers to healthcare professionals or healthcare entities. When a manufacturer disseminates such medical and scientific information, FDA recommends that the following principles of "Good Reprint Practices" be followed.

Id. For more FDA guidance, see 62 Fed. Reg. at 64,074.

protocol and schedule for conducting the requisite clinical studies associated with filing a supplemental application.[46] The reprints had to be unabridged, published in a reputable medical journal, generally devoid of accompanying promotional content, and contain a disclaimer indicating that the uses discussed in the article were not approved by the FDA.[47]

After the conservative Washington Legal Foundation filed suit, a federal district court enjoined these guidance documents and FDAMA provisions as potentially violating manufacturers' commercial speech rights.[48] However, the dispute was resolved in the course of oral arguments before the Court of Appeals for the District of Columbia Circuit.[49] The FDA asserted that it would not use violations of the FDAMA provision or the principles outlined in the guidance documents as independent authority to prosecute a manufacturer for off-label promotion, only as supporting evidence of misbranding.[50] The court of appeals thus dismissed the case, finding the FDA's statement tantamount to its admitting that the agency had no "independent authority to regulate manufacturer speech" under the guidance documents or FDAMA provision.[51]

In January 2009, the FDA issued a guidance document that reauthorized the reprint distribution rules and widened the ability of drug manufacturers to distribute information on unapproved uses of their products.[52] The updated guidance document reiterated many of the characteristics of journal article distribution practices described in the FDAMA but loosened the restrictions on manufacturers by

46. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 401, 111 Stat. 2296, 2356–58 (repealed 2006).

47. *Id*.

48. Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 71–72 (D.D.C. 1998), *judgment vacated in part sub. nom.* Wash. Legal Found. v. Henney, 202 F.3d 331 (D.C. Cir. 2000).

> In sum, the court finds that the restrictions in the Guidance Documents are more extensive than necessary to serve the asserted government interest and that they unduly burden important speech. Therefore, the Guidance Documents fail the fourth prong of the *Central Hudson* test, rendering them incompatible with the First Amendment.

Id. at 74.

49. Wash. Legal Found. v. Henney, 202 F.3d 331, 335 (D.C. Cir. 2000).

50. *Id.* at 336.

51. *Id.* (reinforcing, despite its admission, that "the FDA retains the prerogative to use both types of arguably promotional conduct as *evidence* in a misbranding or 'intended use' enforcement action").

52. 2009 GUIDANCE FOR INDUSTRY, *supra* note 45.

allowing distribution of such materials even if a supplementary application for approval of the off-label use was not pending.[53]

II. THE EVOLUTION OF JUDICIAL PROTECTION OF COMMERCIAL SPEECH RELATED TO PHARMACEUTICALS

Commercial speech historically had no protection under First Amendment jurisprudence for nearly the first two hundred years of American history. Indeed, the first time the question of whether the First Amendment covered commercial speech came before the Supreme Court in 1942, the Court ruled that restrictions on commercial speech were a legitimate exercise of the government's power to regulate commerce.[54] In a unanimous decision in *Valentine v. Chrestensen*,[55] the Court held that while people may communicate and disseminate personal opinions on public streets without undue governmental burden, the Constitution "imposes no such restraint on government as respects purely commercial advertising."[56] Indeed, according to the Court, "[w]hether, and to what extent, one may promote or pursue a gainful occupation in the streets . . . are matters for legislative judgment."[57]

A fundamental change in the Supreme Court's interpretation of commercial speech protections arose in the mid-1970s when the Court established for the first time that commercial speech was protected under the First Amendment.[58] Soon thereafter, the Court made clear that regulations seeking to limit advertising or other speech proposing a commercial transaction needed to meet a heightened standard of judicial scrutiny, though not as high as the compelling government interest needed to justify a regulation of political or social speech.[59]

Since that time, the Supreme Court has addressed commercial speech in the context of pharmaceutical advertising on three separate occasions, starting with *Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council, Inc.*[60] in 1976. More recently, the question of what restrictions can be imposed on commercial speech relating to

53. *Id.*
54. *See* Valentine v. Chrestensen, 316 U.S. 52, 54–55 (1942).
55. 316 U.S. 52 (1942).
56. *Id.* at 54.
57. *Id.*
58. *See* Bigelow v. Virginia, 421 U.S. 809, 826 (1975).
59. *See* Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n, 447 U.S. 557, 562–63 (1980).
60. 425 U.S. 748 (1976).

the use of prescription drugs was featured in the 2002 case of *Thompson v. Western States Medical Center*[61] and the 2011 case of *Sorrell v. IMS Health Inc.*[62] To help clarify the role that commercial speech jurisprudence plays in the future of off-label marketing regulations, we examine each of these cases in turn.

A. Virginia State Board of Pharmacy

The Supreme Court's first clear statement that commercial speech is protected under the First Amendment happened to arise in a case concerning prescription drugs.[63] The controversy stemmed from a Virginia statute that made pharmacists guilty of unprofessional conduct if they advertised or promoted any price, fee, or discount for prescription drugs.[64] A consumer group brought the challenge against the State Board of Pharmacy seeking a declaration that the statute was unconstitutional because it violated plaintiffs' First Amendment right to receive information about drug prices that pharmacists wished to communicate to them through advertising.[65]

In finding the statute unconstitutional, the Court held that speech proposing a commercial transaction was not so removed from an "exposition of ideas" that it lacked all protection, and economic interest alone does not disqualify speech from protection.[66] The decision to break new constitutional ground was made on the basis of the "keen" interest that consumers have in the pricing information being sought and that society has in the "free flow of commercial information."[67] As the Court explained, "So long as we preserve a predominantly free enterprise economy . . . [i]t is a matter of public interest that [private economic] decisions, in the aggregate, be intelligent and well informed."[68]

The *Virginia State Board* decision did not, however, place commercial speech entirely outside the sphere of proper regulation. The Court clearly stated that illegal commercial transactions would not be granted such protection, and "time, place, and manner" restrictions could be valid "provided that they are justified without reference to the content of the regulated speech, that they serve a

61. 535 U.S. 357 (2002).
62. 131 S. Ct. 2653 (2011).
63. Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, 425 U.S. 748 (1976).
64. *Id.* at 749–50.
65. *Id.* at 753 & n.10, 754.
66. *Id.* at 762 (quoting Chaplinsky v. New Hampshire, 315 U.S. 568, 572 (1942) (internal quotation marks omitted)).
67. *Id.* at 763.
68. *Id*. at 765.

significant governmental interest, and that in so doing they leave open ample alternative channels for communication of the information."[69] In a final footnote, the Court also limited its holding to commercial advertising by pharmacists, remarking that the considerations could be different in other professions such as the practice of medicine, which might be characterized by "enhanced possibility for confusion and deception if they were to undertake certain kinds of advertising."[70]

Although the *Virginia State Board* case garnered a seven-justice majority,[71] two justices penned concurrences in which they highlighted important limitations on the holding. The first concurrence, from Chief Justice Warren Burger, sought to emphasize the remark in the final footnote that the holding was limited to the question of whether pharmacists could publicly list the retail prices of drugs in their pharmacies and did not extend to commercial circumstances "in which professional judgment is a large component."[72] He specifically invoked the important state interest in regulating physicians,[73] distinguishing the limited price transparency sought in this case from regulation of commercial speech related to the practice of medicine on the basis that the latter would be less amenable to judicial review because it would be hard to determine "which claims of superiority are 'misleading' and which are justifiable."[74] In such cases, he argued, heightened judicial scrutiny may not be appropriate, or may be more easily met.[75]

The second concurrence, from Justice Potter Stewart, reinforced Chief Justice Burger's inclination to limit the scope of the majority's holding. Justice Stewart agreed with the majority that commercial speech merited some constitutional protection, but he wrote separately to emphasize that the only goal of extending such protection was to contribute to the "flow of accurate and reliable information" for consumers.[76] The drug prices at issue in this case met that standard in large part because unlike "ideological expression," "factual claims contained in commercial price or product advertisements relate to tangible goods or services" and "may be

69. *Id*. at 771 (citations omitted).
70. *Id.* at 773 n.25.
71. Justice John Paul Stevens recused himself from the case. *See id.* at 773.
72. *Id.* at 774 (Burger, C.J., concurring).
73. *Id.*
74. *Id.* at 775.
75. *See id.*
76. *Id*. at 781 (Stewart, J., concurring).

tested empirically and corrected to reflect the truth."[77] He was not willing to extend commercial speech protection to false, misleading, deceptive, or other types of commercial communication that could not be rigorously tested and verified.[78]

Justice William Rehnquist's dissenting opinion emphasized two points. First, he felt that the realm of commercial speech regulation and determination of what information was useful for the public interest was best handled by legislatures, not courts.[79] Second, he favored reviewing pharmaceutical advertising differently than advertising for other commercial products because, "while prescription drugs are a necessary and vital part of medical care and treatment," he noted, "there are sufficient dangers attending their widespread use that they simply may not be promoted in the same manner as hair creams, deodorants, and toothpaste."[80]

Given the special dangers of prescription drugs and the complexity of medical prescribing decisions, Justice Rehnquist felt that the distinction offered by the majority between "truthful" and "false and misleading" speech was too simplistic.[81] He pointed out the majority's decision allows pharmacists to disseminate irresponsible and potentially dangerous advertisements such as, "Can't shake the flu? Get a prescription for Tetracycline from your doctor today" and then puts the burden on the government to prove that the statement was "actually untruthful or misleading."[82] His warning against an "open door" policy that would undermine the "societal interest against the promotion of drug use for every ill, real or imaginary,"[83] presciently forecasted the current controversy over promotion of off-label drug use.

B. Western States

The next major Supreme Court decision concerning pharmaceutical-related speech came more than a quarter century later, in *Thompson v. Western States Medical Center*.[84] The source of controversy was a provision of section 503A of the Act that allowed pharmacies making compounded drugs to avoid the FDA's new-drug

77. *Id*. at 780.
78. *See id*. at 780–81.
79. *See id.* at 783 (Rehnquist, J., dissenting).
80. *Id.* at 788.
81. *Id.* at 787 (internal quotation marks omitted).
82. *Id.* at 788.
83. *Id.* at 790.
84. 535 U.S. 357 (2002).

registration process as long as they refrained from advertising their compounding services.[85] A compounded drug is a drug tailored to the needs of an individual patient that is custom-made by specially trained pharmacists in a small-scale facility.[86] Compounding can make important modifications to existing drugs for patients with particular needs—for example, turning a pill into a liquid for someone who is unable to swallow pills—or even create drugs not sold widely by manufacturers because the intended population is too small.[87] Compounding is usually regulated at the local or state level, although with the FDAMA, the FDA was poised to step in to help oversee the safety of compounded drugs.[88]

The FDA's rationale for the FDAMA provision at issue in *Western States* was to permit the traditional and useful practice of compounding in local communities to proceed without costly federal registration, while preventing compounding pharmacies from growing too big and emulating regular, brand-name manufacturers by selling drugs in large batches and across disparate geographic areas.[89] Compounding pharmacies challenged the speech-related provisions of section 503A on the basis that the pharmacies had a First Amendment right to disseminate truthful and non-misleading information about "the use and effectiveness of specific compounded drugs."[90]

In a 5-4 decision, the Court struck down the regulation as an impermissible imposition on commercial speech.[91] It applied the formal, four-part test for commercial speech restrictions that the

85. *Id.* at 365 ("[T]he Act [required] that they refrain from advertising and promoting their products if they wish to continue compounding . . . ." (citing Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 127(a), 111 Stat. 2296, 2328 (codified at 21 U.S.C. § 353a (2012)) (adding section 503A to the FDCA)).

86. LOYD V. ALLEN, JR., THE ART, SCIENCE, AND TECHNOLOGY OF PHARMACEUTICAL COMPOUNDING 2 (4th ed. 2012).

87. M. Dooms, H. Pincé & S. Simoens, *Do We Need Authorized Orphan Drugs When Compounded Medications Are Available?*, 38 J. CLINICAL PHARMACY & THERAPEUTICS 1, 1–2 (2013) (providing case studies showing how compounded drugs are used to treat rare diseases).

88. S. REP. No. 105-43, at 67 (1997) (noting that the goal of the statute was to "clarify the application of the [FDCA] to the professional practice of pharmacist compounding of drug products").

89. *Western States*, 535 U.S. at 369 ("The Government also has an important interest, however, in permitting the continuation of the practice of compounding so that patients with particular needs may obtain medications suited to those needs. And it would not make sense to require compounded drugs created to meet the unique needs of individual patients to undergo the testing required for the new drug approval process.").

90. *Id*. at 365.

91. *Id.* at 377.

Court announced in the 1980 case of *Central Hudson Gas & Electric Corporation v. Public Service Commission of New York*,[92] which became the framework for evaluating subsequent commercial speech restrictions. First, was the speech false or misleading, or did it concern unlawful activity?[93] If so, the speech deserves no protection.[94] Second, is the government's interest in regulating the speech substantial?[95] Third, does the regulation directly and materially advance the government's interest?[96] Finally, is the regulation narrowly tailored, meaning, no more extensive than necessary to serve that interest?[97]

Writing for the *Western States* majority, Justice Sandra Day O'Connor jumped quickly to the balancing-test components of *Central Hudson* because the truthfulness of advertisements for compounding pharmacies was not at issue.[98] Justice O'Connor opined that the government's stated interest in maintaining the integrity of the new drug approval system while at the same time permitting compounding for the needs of individual patients was substantial, and the scheme restricting advertising was "rationally calculated" and might indeed directly advance the government's interest in limiting the scale of compounding.[99] However, she struck down the regulation as being more extensive than necessary because she believed the Court's precedent held that "if the Government could achieve its interests in a manner that does not restrict speech, or that restricts less speech, the Government must do so."[100]

Justice O'Connor listed a number of ways that oversight of compounded pharmacies could be achieved with narrower

92. 447 U.S. 557 (1980). *Central Hudson* involved a challenge to a New York state energy conservation policy that prevented utility companies from promoting "use of electricity." *Id.* at 558 (citation omitted). The Court found the regulation to be unconstitutional because it also limited promotional activities that provided "information about electric devices or services that would cause no net increase in total energy use," *id.* at 570, while a narrower restriction would support conservation equally well, *id.* at 570–71.

93. *Western States*, 535 U.S. at 367 (citing *Central Hudson*, 447 U.S. at 566).

94. *Id.*

95. *Id.* (quoting *Central Hudson*, 447 U.S. at 566).

96. *Id.* (quoting *Central Hudson*, 447 U.S. at 566).

97. *Id.* (quoting *Central Hudson*, 447 U.S. at 566). *Central Hudson* held that the energy-conservation policy failed the fourth prong of the test. *Central Hudson*, 447 U.S. at 571. Although the Court recognized the state's important interest in promoting energy conservation and accepted that the regulation would directly further that interest, it deemed the regulation unconstitutionally broad because the regulation indiscriminately restricted all promotional advertisements regardless of their effect on electricity use. *Id.* at 568–71.

98. *See Western States*, 535 U.S. at 368.

99. *Id.* at 371.

100. *Id.*

restrictions on speech, such as limiting the amount of compounded drugs that could be sold or preventing compounding in anticipation of receiving a prescription.[101] Her opinion focused on the fact that there was "no hint" in the legislative history or briefs as to whether the government considered these non-speech-restricting possibilities and made a determination as to why they "would be insufficient to prevent compounding from occurring on such a scale as to undermine the new drug approval process."[102] The general principles she stressed were that restrictions on speech should be "necessary," not just "convenient," and that "regulating speech must be a last—not first—resort."[103]

Writing in vigorous dissent, Justice Stephen Breyer (joined by Chief Justice Rehnquist) argued that the majority had applied the *Central Hudson* test too strictly.[104] He argued that the regulation was reasonably related to the government's interests and offered the additional justification that a limit on compounding advertisements could promote public health goals by limiting prescribing of compounded drugs inspired by truthful but not necessarily fully descriptive advertisements.[105] He also evaluated each of the majority's so-called "less restrictive alternatives" and found them to be impractical or ineffective.[106] Conceding that a blanket ban on advertising may restrict circulation of some truthful information, he nonetheless found the regulation proportional to the government's goals and not deserving of the same close judicial scrutiny that would attach to regulations of individual self-expression or political speech.[107]

The dissent also argued that the Court should avoid interfering in a "democratically determined governmental decision to regulate a commercial venture in order to protect . . . the public health."[108] Invoking the ill-fated *Lochner*-era interference in economic legislation, when the Court often struck down economic regulations based on justices' disagreement with legislative decisions about commercial policies, they warned that "an overly rigid 'commercial speech' doctrine will transform what ought to be a legislative or

101. *Id.* at 372.
102. *Id.* at 373.
103. *Id.*
104. *See id.* at 389 (Breyer, J., dissenting).
105. *See id.* at 380, 382, 384–85.
106. *Id.* at 385–86.
107. *Id.* at 387–88.
108. *Id.* at 388 (citation omitted).

regulatory decision about the best way to protect the health and safety of the American public into a constitutional decision prohibiting the legislature from enacting necessary protections."[109]

In the majority opinion, Justice O'Connor dismissed the dissent's concerns about advertising giving rise to inappropriate prescribing.[110] She wrote that this goal rested "on the questionable assumption that doctors would prescribe unnecessary medications."[111] Even if that proved to be the case, she held, the Court's decision in *Virginia State Board* firmly established that government may not prevent "the dissemination of truthful commercial information in order to prevent members of the public from making bad decisions with the information."[112] If the concern was that physicians or the public might be confused by the advertisements and encouraged to prescribe compounded drugs inappropriately, such an outcome could be avoided "by the far less restrictive alternative of requiring each compounded drug to be labeled with a warning that the drug had not undergone FDA testing and that its risks were unknown."[113]

The Supreme Court thus ruled that the speech-related provisions were invalid, but it did not address the rest of the Ninth Circuit's decision, which found that these provisions were not severable from the rest of the section.[114] As a result, in the wake of the Court's decision, the FDA stated that "all of section 503A is now invalid."[115] Compounding pharmacies remained under primarily local or state control, although the FDA subsequently issued a Compliance Policy Guide that included some of Justice O'Connor's less restrictive alternatives intended to prevent them from expanding their reach outside the official new drug approval system.[116]

With weaker central regulation and variable local oversight, many compounding pharmacies grew to a national scale.[117] In 2012, a

109. *Id.* at 389.

110. *Id.* at 373–75 (majority opinion).

111. *Id.* at 374.

112. *Id.*

113. *Id.* at 376.

114. *See id.* at 377; W. States Med. Ctr. v. Shalala, 238 F.3d 1090, 1096–98 (9th Cir. 2001), *aff'd sub nom.* Thompson v. W. States Med. Ctr., 535 U.S. 357 (2002).

115. U.S. FOOD & DRUG ADMIN., DEP'T OF HEALTH & HUMAN SERVS., GUIDANCE FOR FDA STAFF AND INDUSTRY: COMPLIANCE POLICY GUIDES MANUAL § 460.200 PHARMACY COMPOUNDING 2 (2002), *available at* http://www.fda.gov/ohrms/dockets/98fr/02d-0242_gdl0001.pdf.

116. *See id.* at 3.

117. STAFF OF S. COMM. ON HEALTH, EDUC., LABOR & PENSIONS, 113TH CONG., THE CASE FOR CLARIFYING FDA AUTHORITY: LARGE-SCALE DRUG COMPOUNDING AND THE ONGOING RISK TO PUBLIC HEALTH 7 (Comm. Print 2013), *available at*

public health crisis related to compounded drugs struck as hundreds of people were sickened and dozens killed from fungal infections arising from unsafe compounded steroid injections made in a Massachusetts compounding pharmacy but sold nationwide.[118] These compounded drugs were extensively advertised, and they were often prescribed without supporting evidence of effectiveness.[119]

C. Sorrell

The next Supreme Court case concerning the relationship between commercial speech and pharmaceutical promotion arrived with the Court's 2011 decision in *Sorrell v. IMS Health Inc.*[120] The underlying dispute concerned a Vermont law that restricted the commercial sale, disclosure, and use of prescribing records revealing prescribers' identities without their consent and prohibited pharmaceutical manufacturers and marketers from using that information for marketing or promotion.[121] Though the statute's prohibitions appeared to relate to transfers of data and not speech, it was challenged as a violation of the First Amendment's protection of commercial speech because the Vermont legislature explicitly intended to rein in pharmaceutical sales representatives' "detailing" visits to prescribers, in which representatives made use of prescribing data to customize their marketing presentations to particular physicians.[122] Numerous studies show that pharmaceutical marketing through personal sales visits to physicians drives prescriptions in favor of the drugs being promoted, and sales representatives rely heavily on

http://www.help.senate.gov/imo/media/doc/Senate%20HELP%20Committee%20Staff%20Report%20-%20Large-Scale%20Drug%20Compounding%205%2022%2013.pdf ("Between 2006 and 2012, Ameridose grew rapidly and, by the time of the [New England Compounding Center]-caused meningitis crisis, Ameridose-compounded drugs were available to the 3,000 hospital members of Novation, the largest group purchasing organization in the country, in addition to 22,000 other providers and facilities." (citation omitted)).

118. *See* Kevin Outterson, *Regulating Compounding Pharmacies after NECC*, 367 NEW ENG. J. MED. 1969, 1971 (2012).

119. *Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients: Statement Before the S. Comm. on Health, Educ., Labor, and Pensions*, 108th Cong. 38–39 (2003) (statement of Steven K. Galston, Deputy Director of the Center for Drug Evaluation and Research at the FDA) ("Many compounding pharmacies have established Internet websites to promote and sell their products.").

120. 131 S. Ct. 2653 (2011).

121. VT. STAT. ANN. tit. 18, § 4631 (2010), *invalidated by* Sorrell v. IMS Health Inc., 131 S. Ct. 2653 (2011); *see also Sorrell*, 131 S. Ct. at 2659 (describing the provisions of the Vermont law).

122. *Sorrell*, 131 S. Ct. at 2663 ("Any doubt that § 4631(d) imposes an aimed, content-based burden on detailers is dispelled by the record and by formal legislative findings.").

prescriber-identified prescription data to enhance the effectiveness of their marketing message.[123]

In a 6-3 decision, the Supreme Court struck down the law.[124] Writing for the majority, Justice Anthony Kennedy observed that the statute was "content- and speaker-based" on its face, applying only to marketing content and pharmaceutical manufacturers.[125] Further, the Court found that Vermont had engaged in "viewpoint discrimination" by targeting the restriction to specific speakers with whose message—that expensive, branded drugs should be prescribed more often—it disagreed.[126] The Court seemed very troubled by the intent of the statute to "burden[] disfavored speech by disfavored speakers."[127]

Justice Kennedy began the majority opinion by considering whether the statute should be subject to "heightened scrutiny."[128] He concluded that heightened scrutiny, akin to that provided to government actions affecting political speech, may be appropriate in cases of blatant viewpoint discrimination even in the commercial arena because the "information can save lives."[129] However, Justice Kennedy ultimately did not evaluate the controversial statute at issue under the strict-scrutiny framework. Rather, he held that the statute did not meet even the lesser standard of *Central Hudson* because the restriction on the commercial sale of prescriber-identified data was not narrowly tailored to achieving any of the asserted interests.[130]

Quoting *Western States*, Justice Kennedy emphasized that "the 'fear that people would make bad decisions if given truthful information' " cannot justify content-based burdens on speech.[131] Two points were of principal importance to Justice Kennedy's reasoning. First, it was clear from the legislative history that the goal of the Vermont statute was to stifle speech in order to advance a policy agenda.[132] Second, physicians were sophisticated actors, and "[i]f pharmaceutical marketing affects treatment decisions, it does so because doctors find it persuasive."[133]

123. For a review of studies, see Puneet Manchanda & Elisabeth Honka, *The Effects and Role of Direct-to-Physician Marketing in the Pharmaceutical Industry: An Integrative Review*, 5 YALE J. HEALTH POL'Y L. & ETHICS 785, 788–808 (2005).

124. *Sorrell*, 131 S. Ct. at 2672.

125. *Id.* at 2663.

126. *Id.* (quoting R.A.V. v. St. Paul, 505 U.S. 377, 391 (1992)).

127. *Id.* at 2663.

128. *Id.* at 2664.

129. *Id.*

130. *Id.* at 2668.

131. *Id.* at 2670 (quoting Thompson v. W. States Med. Ctr., 535 U.S. 357, 374 (2002)).

132. *Id.* at 2672.

133. *Id.* at 2670.

As in *Western States*, Justice Breyer dissented.[134] He objected to the majority's seeming creation of a heightened standard of scrutiny and again invoked the specter of the Court's *Lochner* era.[135] Applying the *Central Hudson* test, Justice Breyer found the Vermont statute to satisfy constitutional standards—particularly the narrow-tailoring prong of the test—because it imposed only "modest harm" on commercial speech.[136] As a counterweight, the statute directly advanced the state's substantial interest in improving prescribing practices by focusing sales discussions on drugs' merits rather than a prescriber's prescribing habits.[137] Finally, he pointed out that the majority could not point to an "adequately supported," more narrowly tailored regulation that would achieve the same benefits.[138]

Notwithstanding Justice Breyer's disagreement, the *Sorrell* decision signaled that judicial unwillingness to countenance government restrictions on commercial speech had reached a new level. However, it remains unclear whether the nebulous "heightened scrutiny" standard suggested by the *Sorrell* majority is intended to put content- and speaker-based commercial speech restrictions on the same constitutional footing as limitations on non-commercial speech. It is an inherent characteristic of many, if not most, commercial speech regulations that only some speakers are restricted and that the restriction pertains to particular content.[139] Therefore, applying this principle would seem to elevate review of all commercial speech limitations to the non-commercial-speech plateau, an outcome that the *Sorrell* Court could hardly have intended. More likely, the *Sorrell* decision represents a move to implement a more stringent application of the *Central Hudson* test to restrictions on commercial speech that target a class of speakers expressing a particular viewpoint. Yet even this outcome represents a plain intensification of the judicial scrutiny applied to commercial-speech restrictions.[140]

134. *See id.* at 2673 (Breyer, J., dissenting); *Western States*, 535 U.S. at 378 (Breyer, J., dissenting).

135. *Sorrell*, 131 S. Ct. at 2679 (Breyer, J., dissenting).

136. *Id.* at 2680, 2684.

137. *Id.* at 2682.

138. *Id.* at 2683.

139. Michelle M. Mello & Noah A. Messing, *Restrictions on the Use of Prescribing Data for Drug Promotion*, 365 NEW ENG. J. MED. 1248, 1252 (2011).

140. The implications of this decision for the FDA's off-label marketing regulatory scheme are unmistakable. *See* John N. Joseph et al., *Is* Sorrell *the Death Knell for FDA's Off-Label Marketing Restrictions?*, 5 J. HEALTH & LIFE SCI. L. 1, 27 (2012) ("A fair reading of the *Sorrell* decision arguably presents serious hurdles to FDA's ban on off-label marketing, even under *Central Hudson*'s intermediate standard of First Amendment scrutiny of commercial speech restrictions.").

D. Summary

Several thematic threads connect the Supreme Court's decisions in the trio of cases concerning prescription-drug-related speech. First, it is clear that governmental restrictions on truthful statements about pharmaceuticals will be judged under an elevated level of scrutiny that is at least as stringent as the *Central Hudson* test, and perhaps higher. *Sorrell* opens up the door to evaluating such restrictions under an even more rigorous "heightened scrutiny" if they implicate discrimination against a particular viewpoint and suggests that many commercial-speech restrictions will be categorized as viewpoint discrimination.

Second, in the pharmaceutical market as in other markets, the Court has been very suspicious of restrictions on commercial speech that smack of "paternalism," or a governmental attempt to keep consumers in the dark for what the legislature has determined to be their own good. This perspective is seen in the *Virginia State Board* opinion where the majority expressed the goal of supporting consumers' ability to comparison shop among pharmacies based on price.[141] In *Western States* and *Sorrell*, the Court was concerned with supporting physician decision making by ensuring access to information about compounded drugs and informational meetings with pharmaceutical sales representatives. In each case, paternalistic incursions by government were characterized as blocking consumers' or physicians' ability to receive and weigh potentially useful, truthful information: the Court spoke of low-income patients who need to comparison shop among pharmacies,[142] pediatricians unaware of "a new development in compounding" allowing new administration of a previously unavailable drug,[143] and "some Vermont doctors" who enjoy receiving targeted detailing.[144]

The Court found the government's paternalistic overtures especially objectionable when they were directed at physicians, who it viewed as "sophisticated and experienced" consumers highly capable of performing a critical weighing of information provided by

141. *See* Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, 425 U.S. 748, 763 (1976). "These figures eloquently suggest the diminished capacity of the aged for the kind of active comparison shopping that a ban on advertising makes necessary or desirable." *Id.* at 764 n.18.

142. *Id.* at 764 n.18.

143. Thompson v. W. States Med. Ctr., 535 U.S. 357, 377 (2002).

144. Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2671 (2011).

pharmaceutical manufacturers and their marketing representatives.[145] For example, in *Western States*, Justice O'Connor rejected the "questionable assumption that doctors would prescribe unnecessary medications" as a rationale for finding advertising restrictions on compounded drugs improper.[146] Similarly, in *Sorrell*, Justice Kennedy stressed that antipaternalism concerns attached "with full force" because of the listeners' sophistication.[147]

Third, each Court decision emphasizes the trope of the "marketplace of ideas." Commercial-speech rights are characterized as supporting a vigorous exchange of ideas in the free market, leading to optimal economic decision making. In *Virginia State Board*, the majority opinion cited the "free flow" of commercial information as "indispensable" to ensuring that public economic decisions are intelligent and well-informed.[148] In *Sorrell*, the Court quoted a Vermont physician's belief that "information is power" and that more information leads to better decisions in medicine.[149] The principle that information is not "in itself harmful" motivated the Court in each case to strike down a restriction that somehow limits the contribution of pharmaceutical promotional information.[150] Further, the Court did not examine whether the marketplace of ideas actually functions well, except insofar as it judges that the market's functioning would be worse in a world where pharmaceutical-related speech is restricted.

Embedded within this affection for the marketplace-of-ideas concept is a fourth commonality: a presumption that the information at issue is true and, therefore, useful. Although Justice Stewart in his *Virginia State Board* concurrence would have restricted the commercial speech protection to empirically verifiable information,[151] the majority opinion required only that the information be "truthful

145. *Id.* at 2658 (quoting Edenfield v. Fane, 507 U.S. 761, 775 (1993) (internal quotation marks omitted)).

146. *Western States*, 535 U.S. at 374.

147. *Sorrell*, 131 S. Ct. at 2671.

148. Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, 425 U.S. 748, 765 (1976) ("To this end, the free flow of commercial information is indispensable.").

149. *Sorrell*, 131 S. Ct. at 2671 ("As one Vermont physician put it: 'We have a saying in medicine, information is power. And the more you know, or anyone knows, the better decisions can be made.' " (quoting Petition for a Writ of Certiorari Joint Appendix I at 279, *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653 (2011) (No. 10-779), 2011 WL 687134, at *279)).

150. *Sorrell*, 131 S. Ct. at 2671; *Va. State Bd. of Pharmacy*, 425 U.S. at 770 ("That alternative is to assume that this information is not in itself harmful, that people will perceive their own best interests if only they are well enough informed, and that the best means to that end is to open the channels of communication rather than to close them.").

151. *Id.* at 780–81 (Stewart, J., concurring).

and legitimate."[152] In all three cases, beyond announcing a cursory conclusion that the information conveyed in the commercial speech is not false or misleading, the Court declined to evaluate the quality of the information.[153]

III. COMMERCIAL-SPEECH CHALLENGES TO OFF-LABEL MARKETING

The steady expansion of judicial protection of commercial speech in the context of pharmaceuticals and other fields has collided with ramped-up federal enforcement of off-label marketing rules in the past decade. In the face of enforcement actions that have led to massive settlements,[154] some companies have evidently been encouraged by jurisprudential trends to challenge the FDA's prohibition on communications about the use of drugs for non-FDA approved indications. These challenges, culminating most notably in the recent *Caronia* decision, have chipped away at the FDA's ability to regulate off-label promotion.

One earlier example of such a challenge stemmed from a 2009 government investigation of the drug manufacturer Allergan[155] regarding onabotulinumtoxinA (Botox), a purified neurotoxin approved for therapeutic use in rare neuromuscular disorders of the eye and neck muscles and excessive underarm sweating (hyperhidrosis).[156] The Department of Justice investigated charges that Allergan promoted the drug for numerous other medical conditions ranging from bladder dysfunction to myofascial pain to certain types of headache without clear evidence at the time of efficacy in any of these conditions.[157] In response, Allergan initiated a lawsuit seeking a preliminary injunction that would find the labeling

152. *Id.* at 772 n.24 (majority opinion).

153. Of course, the Court's lack of attention to this detail has arisen in part because the government did not contest the quality of the information either in *Sorrell* or *Caronia*.

154. Michelle M. Mello, David M. Studdert & Troyen A. Brennan, *Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals*, 360 NEW ENG. J. MED. 1557, 1561–62 (2009).

155. Complaint at 1, United States *ex rel.* Lang v. Allergan, Inc., No. 1:07-CV-1288 (N.D. Ga. June 5, 2007), *available at* http://www.justice.gov/opa/documents/lang-rushin-complaint.pdf.

156. *See generally* John P. Ney & Kevin R. Joseph, *Neurologic Uses of Botulinum Neurotoxin Type A*, 3 NEUROPSYCHIATRIC DISEASE & TREATMENT 785 (2007) (summarizing clinical uses of the drug).

157. Complaint, *supra* note 155, at 54 ("Squillacote told Dr. Lang that another physician in Mississippi, Dr. Terry Millette, was using one of the covered codes (*i.e.*, ICD-9-CM code 723.5 for 'torticollis unspecified') for Botox injections treating myofascial pain, and Squillacote emphasized that 'Dr. Millette is getting paid for it.' ").

sections of the FDCA and the FDA's prohibitions on off-label advertising in the Code of Federal Regulations unconstitutional under the First Amendment as they applied to communications from Allergan discussing unapproved uses of Botox.[158] However, in 2010, Allergan pleaded guilty to illegal off-label marketing and agreed to settle the case by paying $600 million in criminal and civil fines[159] and dropping its lawsuit as part of a five-year corporate integrity agreement with the federal government.[160]

Similar circumstances arose in the case of Par Pharmaceuticals, a drug manufacturer that came under scrutiny from the Department of Justice for off-label marketing of its appetite-stimulating estrogen derivative, Megace ES.[161] The company allegedly promoted the drug to physicians caring for geriatric patients and cancer patients despite the fact that it had only been approved for use in HIV-positive patients with AIDS-related wasting syndrome.[162] In 2011, Par Pharmaceuticals filed a lawsuit claiming it had a First Amendment right to engage in off-label marketing of Megace ES, even though the drug had not been rigorously tested in non-HIV populations and had been associated with serious risks in clinical trials, including deep vein thrombosis, diabetes, and adrenal suppression.[163] Before its First Amendment claims could move ahead, though, the company abandoned the case, settling criminal and civil charges related to illegal off-label marketing for $45 million in March 2013.[164]

158. Complaint at 2, Allergan, Inc. v. United States, No. 1:09-cv-01879 (D.D.C. Oct. 1, 2009), 2009 WL 3187592.

159. Settlement Agreement at 5–7, *Allergan*, 1:07-cv-1288-WSD (N.D. Ga. Aug. 18, 2010), *available at* http://pdfserver.amlaw.com/cc/final_settlement090110.pdf.

160. Natasha Singer, *Maker of Botox Settles Inquiry on Off-Label Use: Unapproved Therapies*, N.Y. TIMES, Sept. 2, 2010, at A1 ("Allergan has also entered into a five-year corporate integrity agreement with the government under which the company will be required to publish information about its payments to doctors. The agreement also required Allergan to drop its First Amendment lawsuit against the F.D.A., in which it had claimed free speech protections when giving doctors information about unapproved uses of Botox.").

161. Complaint and Demand for Jury Trial at 1–2, United States *ex rel.* Doe v. Par Pharm. Cos., No. 08-3624-SRC (D.N.J. June 25, 2012), *available at* http://whistleblowerlegal.com/3-4.pdf.

162. *Id.* at 5 ("[T]heir sales goals are to flip a percentage of the LTC [long term care] business regardless of whether there are any HIV or indicated cancer patients.").

163. *Id.* at 8 ("In presenting to nursing staffs and dietitians in LTC facilities, questions arise regarding potential risks to the geriatric patient population, such as, for example, deep vein thrombosis, diabetes, and adrenal suppression (which are among the known and reported potential adverse effects of Megace ES).").

164. Press Release, U.S. Dep't of Justice Office of Pub. Affairs, Par Pharmaceuticals Pleads Guilty and Agrees to Pay $45 Million to Resolve Civil and Criminal Allegations

The first challenge to reach a court decision was the *Caronia* case, perhaps because it was initiated by a pharmaceutical sales representative, rather than a pharmaceutical company, and involved a criminal conviction.[165] Alfred Caronia, a sales representative for the brand-name drug company Orphan Medical, was assigned to promote the drug sodium oxybate (Xyrem) to physicians.[166] Sodium oxybate—also known as gamma hydroxybutyrate (GHB), a chemical that when used for recreational purposes has been associated with drug-assisted sexual assault—was approved by the FDA in 2002 for use in the rare clinical condition of narcolepsy with severe cataplexy, a condition marked by sudden onset of lethargy, sleepiness, and full loss of muscle tone.[167] Xyrem's approval was based on two randomized, controlled trials involving approximately 200 patients with the condition.[168] According to a sales representative who later initiated a qui tam action against the company, after a year of modest sales for the intended use, the company decided to start promoting the drug off-label to grow revenue and position for a lucrative acquisition.[169] To do so, Orphan Medical encouraged sales representatives to suggest alternative, non-FDA-approved uses for the product; to organize continuing medical education events featuring physicians known to prescribe the drug for off-label uses; and to market the drug using these tactics to physicians (such as geriatricians and pediatricians) who would not likely see patients with narcolepsy.[170]

Caronia was one of Orphan Medical's sales representatives at the time the Department of Justice started investigating the company for possible off-label marketing.[171] At the office of a target physician who

Related to Off-Label Marketing (Mar. 5, 2013), *available at* http://www.justice.gov/opa/pr/2013/March/13-civ-270.html.

165. *See* United States v. Caronia, 703 F.3d 149, 152 (2d Cir. 2012). Caronia, as an individual pharmaceutical sales representative facing a misdemeanor conviction, was in a better position to follow through on his case to a jury decision (and appeal) than a corporation such as Allergan or Orphan Medical, which would more likely be risk averse and settle for a financial penalty facing the possibility of substantially greater damages at trial and potentially exclusion from Medicare.

166. *Id.*

167. *Xyrem (sodium oxybate) Oral Solution*, U.S. FOOD & DRUG ADMIN. (May 2002), http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/21196lbl.pdf.

168. *Id.* at 5 ("The effectiveness of sodium oxybate as an anti-cataplectic agent was established in 2 randomized, double-blind, placebo-controlled trials (Trials 1 and 2) in patients with narcolepsy, 85% and 80%, respectively, of whom were also being treated with [Central Nervous System] stimulants.").

169. Second Amended Complaint and Demand for Jury Trial at 3–4, United States *ex rel*. Lauterbach v. Orphan Med. Inc., No. 05-CV-0387-SJF-KAM (E.D.N.Y. Feb. 17, 2006).

170. *Id.* at 3, 19, 25–26.

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

was wearing a wire, Caronia was recorded suggesting, unprompted, that sodium oxybate was effective for a constellation of conditions including insomnia, fibromyalgia, restless leg syndrome, chronic pain, Parkinson's disease, and multiple sclerosis.[172] He also claimed that the drug could safely be used in elderly and pediatric patients despite clear statements on the FDA-approved labeling that the drug had not been tested in those populations.[173] Along with his employer and a psychiatrist expert that the company had hired to facilitate the scheme, Caronia was prosecuted for conspiracy to introduce a misbranded drug into interstate commerce.[174]

In 2007, the manufacturer pled guilty to introducing a misbranded drug into interstate commerce with intent to defraud and mislead and paid criminal and civil fines of about $27 million.[175] However, unlike the *Allergan* and *Par Pharmaceutical* cases, the litigation continued because Caronia did not enter a plea. Instead, the government took him to trial, claiming that his communications were part of a conspiracy that effectively misbranded sodium oxybate because it was not FDA-approved for the purposes he discussed.[176]

The district court reviewed the First Amendment implications of Caronia's conviction under the *Central Hudson* test.[177] It considered the government's interest to be substantial in "subjecting off-label uses of a drug or medical device to the FDA's evaluation process" and found that a restriction on off-label promotion directly served those interests.[178] The district court pinned the constitutionality of the FDA's regulatory regime to the final *Central Hudson* criterion: whether the regime was more extensive than necessary to meet the government's legitimate interest.[179] It concluded that "constraining the marketing options of manufacturers is one of the 'few

172. *Id.*

173. *See id.* at 155–57.

174. *Id.* at 157. This charge is a misdemeanor under 21 U.S.C. §§ 331(a), 333(a)(1) (2012).

175. Press Release, U.S. Dep't of Justice U.S. Attorney's Office, E. Dist. N.Y., Jazz Pharmaceuticals, Inc. Agrees to Pay $20 Million to Resolve Criminal and Civil Allegations in "Off-label" Marketing Investigation (July 13, 2007), *available at* http://www.justice.gov/usao/nye/pr/2007/2007jul13a.html.

176. *See* United States v. Caronia, 576 F. Supp. 2d 385, 389–90 (E.D.N.Y. 2008), *vacated and remanded*, 703 F.3d 149 (2d Cir. 2012).

177. *Id.* at 396–403. As we will discuss in Part IV.B, the conclusion that Caronia's speech was even within the realm of the *Central Hudson* test was a controversial one, hotly contested by the dissent in the appeal to the Second Circuit. Speech that is used as evidence of intent to commit a crime is not protected by the First Amendment. *See* Wisconsin v. Mitchell, 508 U.S. 476, 489 (1993); *Caronia*, 576 F. Supp. 2d at 394.

178. *Caronia*, 576 F. Supp. 2d at 398.

179. *Id.* at 399.

mechanisms available' to the FDA to ensure that manufacturers will not seek approval only for certain limited uses of drugs, then promote that same drug for off-label uses, effectively circumventing the FDA's new drug requirements."[180] The district court concluded that it could not identify non-speech restrictions that would serve the same purpose of "ensuring the integrity of the new drug approval process while allowing patients to continue to have unfettered access to new and potentially life-saving uses for drugs and devices approved only for other purposes."[181] The district court, therefore, favored the rationale that restrictions on off-label promotion incentivized production of quality information about pharmaceutical products.[182]

Caronia appealed the district court's determination that the off-label promotion rules were allowable under the First Amendment, arguing that the government could not criminalize his speech.[183] "[T]he First Amendment does not," he claimed, "permit the government to prohibit and criminalize a pharmaceutical manufacturer's truthful and non-misleading promotion of an FDA-approved drug to physicians for off-label use where such use is not itself illegal and others are permitted to engage in such speech."[184] The government responded that it had merely used his speech as evidence of his (and the company's) intent concerning how they wanted physicians to use the drug, citing precedent establishing the permissibility of such use in criminal prosecutions.[185] A showing that they intended the drug to be used in unapproved ways—which were, of course, not described on the drug's labeling—would establish that the drug's labeling was inadequate, and thus that it was misbranded.[186]

On December 3, 2012, the Court of Appeals for the Second Circuit overturned Caronia's conviction.[187] Writing for the majority in a 2-1 split, Judge Denny Chin held that criminally prosecuting a

180. *Id.* at 401 (quoting Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 72 (D.D.C. 1998), *judgment vacated in part sub. nom.* Wash. Legal Found. v. Henney, 202 F.3d 331 (D.C. Cir. 2000)).

181. *Id.* at 401.

182. *Id.*

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

184. *Id.* at 160.

185. Brief and Special Appendix for United States at 53, *Caronia*, 703 F.3d 149 (No. 09-5006-cr(L)), 2010 WL 6351497. The government cited *Wisconsin v. Mitchell*, 508 U.S. 476, 489 (1993), in which a unanimous Supreme Court determined that "[t]he First Amendment . . . does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent." Brief and Special Appendix for the United States, *supra*, at 53 (quoting *Mitchell*, 508 U.S. at 489).

186. *See* Brief and Special Appendix for United States, *supra* note 185, at 55–56.

187. *Caronia*, 703 F.3d at 152.

pharmaceutical sales representative for conspiring to misbrand a drug by promoting off-label uses violated the representative's First Amendment right to free speech.[188] The three-judge panel accepted Caronia's view that he was being prosecuted for his speech, rejecting the government's alternative frame that the speech was merely used as evidence of intent and the prosecution that was based on his conduct.[189] In support of this conclusion, the court pointed to several factors: (1) the government repeatedly argued in its summation and rebuttal at trial that Caronia engaged in criminal conduct by promoting off-label uses of Xyrem; (2) during the trial, the government did not limit its use of Caronia's speech to proving intent; (3) the government never suggested that Caronia engaged in any conduct constituting misbranding other than his promotional statements (for example, by placing deficient labeling on the drug); and (4) the district court's jury instructions communicated to the jury that Caronia's speech itself was the illegal conduct.[190]

Judge Chin's opinion drew heavily from the *Sorrell* decision.[191] Following *Sorrell*, he found that the speech restriction was both content- and speaker-specific: the FDA regulations targeted only off-label promotion, as opposed to all promotion, and applied only to drugmakers, as opposed to all speakers.[192] Consequently, the court held that the restriction constituted viewpoint discrimination, triggering heightened judicial scrutiny.[193] As in *Sorrell*, the *Caronia* majority declined to state what level of scrutiny should be applied—the *Central Hudson* test or stricter scrutiny—and disposed of the case

188. *Id.* at 169.

189. *Id.* at 160–62. Judge Chin's majority opinion strongly criticizes the way the government framed Caronia's prosecution, including the closing argument and the jury instructions. For example, he quotes the "jury charge" at length to show that it relied solely on Caronia's promotional speech, rather than his conduct. *Id.* at 159. Future prosecutors in this area may learn from this decision to frame their cases better. *See infra* Part IV.A; *see also, e.g.*, Petition for a Writ of Certiorari at 27, Scruggs v. United States, 714 F.3d 258 (5th Cir.), *cert. denied*, 134 S. Ct. 336 (2013) (No. 13-206), 2013 U.S. S. Ct. Brief LEXIS 3349, at *41 ("The Second Circuit struck down the conviction, holding that the prosecutor's overt focus on the promotional speech itself, as if it were the actus reus of the crime, gave rise to First Amendment concerns."); Brief for the Respondents in Opposition at 23, Disc. Tobacco City & Lottery, Inc. v. United States, 674 F.3d 509 (6th Cir. 2012), *cert. denied sub nom.* Am. Snuff v. United States, 133 S. Ct. 1996 (2013) (No. 12-521), 2013 U.S. S. Ct. Briefs LEXIS 1641, at *41 ("holding prosecution erroneously rested on theory that promotional acts were themselves unlawful").

190. *Caronia*, 703 F.3d at 161.

191. *See, e.g.*, *id.* at 165 (citing various parts of Sorrell v. IMS Health Inc., 131 S. Ct. 2653 (2011)).

192. *Id.*

193. *Id.* at 165; *see* Mello & Messing, *supra* note 139, at 1250 (discussing the "heightened scrutiny" standard).

by concluding that even under the lower of the two possible standards, the speech restriction failed.[194]

In applying the *Central Hudson* test, Judge Chin first averred that the speech at issue in this case was not false or misleading because the government, in presenting its case, had not tried to paint Caronia's statements as such.[195] "Of course," Judge Chin wrote, "off-label promotion that is false or misleading is not entitled to First Amendment protection."[196] But since the government did not argue this claim at trial, Judge Chin did not engage the issue. Judge Chin also quickly agreed that the government had substantial interests at stake, which he identified as "preserving the efficacy and integrity of the FDA's drug approval process and reducing patient exposure to unsafe and ineffective drugs."[197]

The Second Circuit's decision turned on *Central Hudson*'s final two factors—whether the off-label promotion rules directly advance the government's interests and whether they are broader than necessary.[198] Judge Chin ruled that restricting off-label drug promotion failed on both points.[199] First, the restriction on off-label promotion did not directly advance the government's interest in reducing unsafe drug use because it "prohibits the free flow of information that would inform" the legal practice of off-label use.[200] Rather than advancing patient safety, "paternalistically" interfering with information dissemination about legal uses of a drug inhibited "informed and intelligent treatment decisions."[201] Judge Chin emphasized that physicians were a skilled and sophisticated audience, and it was their—not the government's—role to determine which information was useful.[202] Caronia's promotional information helped them do so, serving the public interest by ensuring "that decisions

194. *See Caronia*, 703 F.3d at 168–69 (rejecting the government's arguments); *see also* Petition for a Writ of Certiorari, *supra* note 189, at 27 (considering political speech to require "much stricter scrutiny" than the standard applied in *Caronia*); Brief for Pharm. Research & Mfrs. of Am. as Amicus Curiae Supporting Applicants at 19, Caldwell *ex rel.* State v. Janssen Pharm., No. 2012-C-2447 (La. 2014), 2013 LA S. Ct. Briefs LEXIS 57, at *34 (using *Sorrell* and *Caronia* to argue that "speaker-based discrimination is subject to 'heightened scrutiny' ").

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

196. *Id.* at 165 n.10 (citing Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n, 447 U.S. 557, 566 (1980)).

197. *Id.* at 166.

198. *Id.*

199. *Id.* at 167–68.

200. *Id.* at 167.

201. *Id.* at 166 (citation omitted).

202. *Id.* (quoting Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2670 (2011)).

about the use of prescription drugs, including off-label usage, are intelligent and well-informed."[203]

Second, the court held that restricting manufacturers' off-label promotion was too broad an intervention because other options could achieve the same goal without inhibiting speech.[204] The court proposed that the government could educate physicians and patients about how to distinguish between "misleading and false promotion, exaggerations and embellishments, and truthful or non-misleading information," require disclaimers for off-label uses, limit the number of off-label prescriptions a physician may write, or warn physicians and manufacturers about their potential exposure to malpractice claims from adverse outcomes resulting from off-label treatment decisions.[205]

Caronia's conviction was rejected over a dissent from Judge Debra Ann Livingston, who argued that the majority opinion "calls into question the very foundations of our century-old system of drug regulation."[206] She argued that the regulations were not about restricting speech, crediting the government's argument that Caronia's speech was merely being used as evidence of his intent to engage in misbranding.[207] She criticized the majority for departing from judicial precedent allowing the use of speech for purposes of establishing intent in criminal cases.[208]

Turning to the *Central Hudson* test, she found that the restrictions on off-label promotion were pivotal to the FDA's rigorous pre-market approval process, a cornerstone of the agency's strategy to protect the public from unsafe and nonefficacious drugs.[209] Without them, she argued, companies' incentive to establish the

203. *Id.* at 167. This language in particular raised the ire of the dissent and led to Judge Livingston's concern about undermining the FDCA. *See infra* note 206, 209–11 and accompanying text.

204. *Caronia*, 703 F.3d at 167–68.

205. *Id.* at 168.

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

207. *Id.* at 172.

208. *Id.* at 175 (citing cases relating to employment discrimination); *id.* at 176 (quoting the D.C. Circuit's conclusion in Whitaker v. Thompson, 353 F.3d 947, 953 (D.C. Cir. 2004), that "it is constitutionally permissible for the FDA to use speech, in the form of labeling, to infer intent for purposes of determining that [the plaintiff's] proposed sale of saw palmetto extract would constitute the forbidden sale of an unapproved drug"). Further, Judge Livingston noted, words themselves may constitutionally serve as the basis of some crimes. *Id.* at 175 (listing the crimes of attempt, conspiracy, and inducement as examples); *id.* at 175 n.5 (citing cases involving insider trading laws, antitrust laws, and laws prohibiting unlicensed laypersons from dispensing legal and medical advice).

209. *Id.* at 177–78.

safety and efficacy of new drug uses and obtain FDA approval for them would be undermined.[210] The majority's position would allow "any substance that may be legally sold for *some* purpose [to] be promoted by its manufacturer for *any* purpose—so long as the manufacturer's statements are merely unsubstantiated, rather than demonstrably false or misleading."[211] Judge Livingston also found no defect in the tailoring of the speech restriction.[212] She rejected as inadequate, impractical, or otherwise undesirable the majority's proffered alternative policies.[213]

Though the three-judge decision could have been subject to review by the full Second Circuit (as well as the Supreme Court), the FDA announced in January that it would not appeal.[214] The FDA averred that *Caronia* would not "significantly affect the agency's enforcement of the drug-misbranding provisions of the Food, Drug and Cosmetic Act," as it "does not strike down any provision of the . . . act or its implementing regulations, nor does it find a conflict between the act's misbranding provisions and the First Amendment or call into question the validity of the act's drug approval framework."[215] While the FDA's characterization of the scope of the opinion is correct—the *Caronia* court barred a particular avenue of criminal prosecution, rather than striking down any statutory or regulatory provision per se—its conclusion that its enforcement efforts will not be hampered is rather mystifying.[216] As Judge

210. *Id.* at 178.

211. *Id*.

212. *Id.* at 177.

213. *See id*. at 179–80 (arguing that measures such as funding physician educational programs and imposing disclaimers are unlikely to be effective in addressing the problems created by off-label promotion).

214. Thomas W. Burton, *FDA Won't Appeal Free-Speech Marketing Decision*, WALL ST. J. (Jan. 24, 2013, 8:20 PM), http://online.wsj.com/news/articles/SB10001424127887324539304578260323575925896.

215. David Sell, *U.S. Won't Pursue Case of Drug Representative and 'Off-Label' Promotion*, PHILA. INQUIRER (Jan. 26, 2013), http://articles.philly.com/2013-01-26/business/36550335_1_drug-companies-fda-misbranded-drug.

216. Notably, two off-label marketing cases have since settled in the Second Circuit, suggesting that *Caronia* certainly does not absolutely bar such cases being brought forward, even in that circuit. The first, in December 2012, involved Amgen pleading guilty to the charge that it "illegally sold [Aranesp, Enbrel, and Neulasta] with the intention that it be used at off-label doses that the FDA had specifically considered and rejected, and for an off-label treatment that the FDA had never approved" and agreeing to pay $762 million in civil and criminal fines. Press Release, U.S. Dep't of Justice, Amgen Inc. Pleads Guilty to Federal Charge in Brooklyn, NY.; Pays $762 Million to Resolve Criminal Liability and False Claims Act Allegations (Dec. 19, 2012), *available at* http://www.justice.gov/opa/pr/2012/December/12-civ-1523.html. The second, in May 2013, involved an anti-inflammatory ophthalmologic drop made by ISTA Pharmaceuticals

Livingston pointed out in her dissent, it is hard to see how the majority's reasoning would ever allow promotional statements about off-label uses of drugs to be used to support a conviction for misbranding.[217]

The decision not to appeal may have been more of a strategic calculation than a genuine conclusion that its effects will be minimal. With the Supreme Court and courts of appeals showing consistently strong support for commercial-speech rights, it is a treacherous time to pursue such an appeal. The outcome of an appeal could be the expansion of the Second Circuit panel's holding to the national stage.

Even absent appeal in *Caronia*, the Second Circuit's ruling may be tested. Targets of off-label promotion prosecutions may appeal in other circuits[218] or within the Second Circuit based on different facts. It is therefore worthwhile to consider both the merits of the *Caronia* ruling and what avenues it leaves open to the FDA to regulate off-label promotion in the future.

IV. THE FUTURE OF REGULATIONS RESTRICTING OFF-LABEL PROMOTION

The *Caronia* decision has been hailed by advocates of expanded commercial speech rights for the pharmaceutical and medical device industries.[219] These commentators have argued that the FDA's

approved for use in post-cataract pain but promoted widely for other pain relief indications related to the front of the eye as well as medical conditions in the back of the eye. Press Release, U.S. Dep't of Justice, ISTA Pharmaceuticals Inc. Pleads Guilty to Federal Felony Charges; Will Pay $33.5 Million to Resolve Criminal Liability and False Claims Act Allegations (May 24, 2013), *available at* http://www.justice.gov/opa/pr/2013/May/13-civ-606.html. ISTA pled guilty and agreed to $33.5 million in fines and exclusion from the federal health care programs. *Id.* Bausch+Lomb, which had recently acquired ISTA, agreed to institute a wide-ranging corporate integrity program. *Id.* It is likely, however, that these settlements were in the final planning stages long before the *Caronia* decision was issued, so we expect the impact of that decision to be felt much more acutely in the future.

217. *Caronia*, 703 F.3d at 172 (Livingston, J., dissenting). Commentators have also taken the view that *Caronia* portends a dim future for FDA prosecution of off-label promotion. *See, e.g.*, Christopher Robertson, *When Truth Cannot Be Presumed: The Regulation of Drug Promotion Under an Expanding First Amendment*, 94 B.U. L. REV. 545 (2014) (calling the decision "a severe blow" for the FDA's regulatory regime); John T. Bentivoglio et al., *How* Caronia *Could Reshape Government Investigations*, LAW360.COM (Jan. 2, 2013, 12:32 PM), http://www.law360.com/health/articles/403767/how-caronia-could-reshape-govemmentinvestigations ("The government's theory of off-label liability deployed for so long and so prominently as part of settlements rather than in litigation, now has been rejected by an appellate court.").

218. *See infra* note 235.

219. *See, e.g.*, Ralph F. Hall, Professor of Practice, Univ. of Minn. Law Sch., 1st Amendment Cases: Our Most Important Judicial Trend, Presentation to Food and Drug

restrictions on off-label promotion are too broad because they cover potentially truthful speech about off-label uses and because those off-label uses are lawful and can be clinically indicated.[220] They claim the combination of these factors "prevents promotion of valuable off-label uses of which doctors otherwise may well be unaware."[221] Advocates of this position also point to unfair "asymmetry" in the marketplace, in which parties other than the manufacturers are able to discuss these uses, including insurers, unaffiliated drug information vendors, and other physicians.[222]

However, the *Caronia* decision marks another setback (following on *Sorrell*) in the government's effort to limit dangerous public health outcomes from non-evidence-based industry marketing, and it adds another signal that the courts are intensifying their protection of commercial speech.[223] The *Caronia* court's application of the Supreme Court's line of commercial speech cases raises the question of what avenues remain for government regulation of the pharmaceutical

Law Institute Advertising and Promotion for the Pharmaceutical, Medical Device, Biological, and Veterinary Medicine Industries 6 (Sept. 17, 2013) (unpublished slideshow), *available at* http://www.fdli.org/docs/ap2013-slides/top-20-combined-final.pdf?sfvrsn=0 (pointing to the *Caronia* decision as part of the "most important judicial issue of our generation"); *see also* Respondent's Brief at 31, Coleman v. Medtronic Corp., 223 Cal. App. 4th (2014) (No. B243609), 2013 CA App. Ct. Briefs LEXIS 2784, at *52 (arguing that the FDA can no longer prohibit off-label promotion after *Caronia* since "deriving an indirect prohibition on off-label promotion from the FDCA's misbranding provision is precisely the position that was rejected in *Caronia*").

220. *See* Coleen Klasmeier & Martin H. Redish, *Off-Label Prescription Advertising, the FDA and the First Amendment: A Study in the Values of Commercial Speech Protection*, 37 AM. J.L. & MED. 315, 316, 344 (2011) (calling FDA regulation of off-label speech "paternalistic manipulation of consumer behavior"). Klasmeier and Redish go further to argue that the *Central Hudson* test is no longer applicable to pharmaceutical promotional speech but that "the Court would today apply a categorical standard which automatically invalidates suppression of truthful expression that advocates lawful consumer behavior." *Id*. at 344; *see also* Gregory Conko, *Hidden Truth: The Perils and Protection of Off-Label Drug and Medical Device Promotion*, 21 HEALTH MATRIX 149, 154–55 (2011) (citing a survey and American Medical Association position statement indicating that physicians believe the FDA has made it more difficult for them to learn about new uses for drugs and devices and that it should not regulate off-label promotion).

221. Klasmeier & Redish, *supra* note 220, at 316.

222. Tevi D. Troy, Senior Fellow, Hudson Inst., CER, FDA, and the Free Speech Challenge, Presentation at the National Pharmaceutical Council Conference: Asymmetry in the Ability to Communicate CER Findings (Feb. 9, 2012), *available at* http://www.npcnow.org/system/files/conferences/download/ttroy_asym12.pdf (calling out "unfair restrictions").

223. *See* Brief for Appellants at 28, Caldwell *ex rel.* State v. Janssen Pharm., No. 2012-C-2447 (La. 2014) (considering *Caronia* as standing for the proposition that "promotion that 'is not in and of itself false or misleading' cannot constitutionally be punished merely because it conveys information not authorized in FDA-approved labeling" (quoting United States v. Caronia, 703 F.3d 149, 165 (2d Cir. 2012)).

manufacturers' off-label promotional speech. We can see five ways forward for the FDA. The first three involve seizing on key technical issues invoked in the *Caronia* case: (1) ensuring that prosecutions are based on written rather than oral statements; (2) emphasizing that speech is being used as evidence of intent; and (3) focusing on the false or misleading nature of the promotional materials. In addition, in defending its policies against future claims of commercial speech infringement, the FDA could make a stronger case that its regulations meet the criteria of the *Central Hudson* test, with the principles enumerated by the Supreme Court in its prior pharmaceutical promotion cases in mind. Finally, the FDA could reconfigure its regulatory regime to adapt its restrictions on commercial speech in ways that still permit oversight of public safety.

A. Prosecutions Based on Written Statements

In stating its belief that *Caronia* would not significantly affect its ability to prosecute misbranding,[224] the FDA may have envisioned that it would rely more heavily on written materials as evidence in the future.[225] Printed materials produced by the drug manufacturer, such as brochures and PowerPoint slides that a sales representative would show during an office visit to a physician or the materials that a company's medical affairs office would send in response to a physician's direct inquiry about a potential off-label use, could be considered part of the labeling of a drug. Consequently, if these materials included statements about unapproved uses, this would constitute direct evidence of intent to misbrand the drug. By contrast, in *Caronia*, the government made no claim that Caronia's oral statements were part of the drug labeling.

This avenue of prosecution is clearly viable from a legal perspective. It is of limited practical utility, however, as any company with a competent compliance program will avoid making impermissible statements about off-label uses in printed materials, particularly those that could be considered part of the drug's labeling.

224. *See* Sell, *supra* note 215 and accompanying text.

225. A similar suggestion is made in Hyman, Phelps & McNamara, P.C., *A Deep Dive into the Second Circuit's* Caronia *Decision, Potential Next Steps, and Potential Enforcement Fallout*, FDA LAW BLOG (Dec. 12, 2012, 1:37 AM), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2012/12/a-deep-dive-into-the-second-circuits-caronia-decision-potential-next-steps-and-potential-enforcement.html ("We wonder if we will see FDA shift its focus to the 'unapproved new drug' charge to support off-label promotion cases against pharmaceutical manufacturers . . . . This shift would require evidence of labeling containing the drug's new intended use.").

B. Speech as Evidence of Intent

The government could seek to work within the confines of the *Caronia* decision by framing its future prosecutions so as to avoid a finding that it is prosecuting individuals because of their speech. The holding in *Caronia* turned on the majority's determination that the government was prosecuting Caronia *for* his speech, rather than merely using his speech as evidence of his intent to misbrand.[226] Judge Livingston dedicated the first half of her dissenting opinion to disputing this finding.[227] Both sides agreed that there was a real and constitutionally significant distinction between the two ways of using speech in a misbranding prosecution.

This raises the question whether the government might have prevailed against Caronia's First Amendment claim if prosecutors had chosen their words more carefully in arguing the case.[228] If so, it would be an absurd outcome: the same conduct should not be eligible or ineligible for criminal prosecution depending simply on how it is described in court.[229] Yet it may offer an avenue for distinguishing Caronia's prosecution from future prosecutions for misbranding.

FDA regulations make clear that the intended use of a drug, for purposes of making out a misbranding claim, may be established by reference to "the objective intent of the persons legally responsible for the labeling of drugs."[230] This may be shown through "oral or written statements by such persons or their representatives."[231] The *Caronia* majority assumed, without expressly deciding, that the government could "offer evidence of a defendant's off-label promotion to prove a drug's intended use and, thus, mislabeling for that intended use," citing precedent in support of this view.[232]

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

227. *Id.* at 169–77 (Livingston, J., dissenting).

228. *See* Kesselheim, Mello & Avorn, *supra* note 21, at 446; Allen Rostron, *Pragmatism, Paternalism, and the Constitutional Protection of Commercial Speech*, 37 VT. L. REV. 527, 562 (2013).

229. *See, e.g.*, Petition for a Writ of Certiorari at 19, Ring v. United States, 134 S. Ct. 175 (2013) (No. 12-1462), 2013 U.S. S. Ct. Briefs LEXIS 2667, at *31 ("[T]he line between criminalizing speech and permitting speech to be used as proof of intent is illusory, leading to disparate results in cases like . . . *Caronia* . . . where intent is an essential element of the crime.").

230. *Caronia*, 703 F.3d at 154 (quoting 21 C.F.R. § 201.128 (2012)).

231. *Id.* (quoting 21 C.F.R § 201.128 (2012)).

232. *Id.* at 161 (citing Wisconsin v. Mitchell, 508 U.S. 476, 489 (1993); Whitaker v. Thompson, 353 F.3d 947, 953 (D.C. Cir. 2004)); *see also Caronia*, at 172 (Livingston, J., dissenting) (stressing that these same precedents do clearly establish that the First Amendment does not preclude the use of speech as evidence to prove the elements of a crime); *id.* at 174–75 (discussing several additional precedents concerning the same point).

The court faulted the government, however, for failing to circumscribe its use of Caronia's statements in this way.[233] It noted that the government repeatedly referred to his promotional statements as the criminal conduct itself and did not argue that he engaged in any conduct constituting misbranding other than the oral statements (such as conspiracy to place deficient labeling on the drug).[234] The majority and dissenting opinions both suggested the court may have taken a different view of the applicability of First Amendment protection had the prosecutors emphasized that Caronia's promotional statements were being offered merely as proof that he intended the drug to be used for purposes not described in the labeling.

In future prosecutions, the government could be sure to emphasize the combination of promotional statements by sales representatives and other available evidence of intent—for example, training practices that encourage sales representatives to promote off-label uses and documentary evidence of a company's interest in promoting off-label uses[235]—to establish intent to misbrand. However, we are skeptical that the constitutional objections raised against off-label promotion rules in *Caronia* would be remedied merely by a change in prosecutorial language. For example, in *Sorrell*, the State of Vermont tried to defend its data-mining statute by arguing that the statute was being applied in such a way as to promote an interest in preserving the privacy of physician-identified prescription information.[236] Ultimately, however, the majority decision was unmoved by this change in linguistic approach and struck down the statute anyway because it found that the rules applied content- and speaker-based restrictions without appropriate justification.[237] In the context of *Caronia*, it may be hard for changes

The *Whitaker* case, though it does not emanate from the Supreme Court, is particularly relevant. There, the Court of Appeals for the District of Columbia held that the First Amendment did not protect the plaintiff's right to label saw palmetto extract with a drug claim about an unapproved use. Whitaker v. Thompson, 353 F.3d 947, 953 (D.C. Cir. 2004).

233. *Caronia*, 703 F.3d at 161–62.

234. *Id*.

235. *See* Ed Silverman, *Off-Label Marketing: Free Speech or Illegal Promotion?*, 346 BMJ f320, f320 (2013).

236. Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2682 (2011) (Breyer, J., dissenting) ("Vermont compiled a substantial legislative record to corroborate this line of reasoning.").

237. *See id.* at 2662 (majority opinion) ("At oral argument . . . the State for the first time advanced an alternative reading of § 4631(d)—namely, that pharmacies, health insurers, and similar entities may not sell prescriber-identifying information for any

in prosecutorial language to move a sufficiently motivated judge to look beyond the FDA's off-label marketing rules.

C. Off-Label Promotion As False or Misleading Speech

A third possibility for the government to avoid the reach of commercial speech protections in enforcing its off-label promotion rules is to prosecute off-label promotion as false or misleading speech.[238] The Supreme Court and lower courts have consistently stressed that commercial-speech protection under the First Amendment is limited to speech that is truthful and nonmisleading.[239]

Cases of false and misleading speech have been successfully prosecuted under the misbranding provisions of the FDCA. For example, in the 2008 case of *United States v. Caputo*,[240] the Court of Appeals for the Seventh Circuit adjudicated a dispute regarding promotional statements made by two principals of a small medical device company called AbTox, which made a medical instrument sterilizing device called the Plazlyte.[241] The FDA had cleared AbTox's application for a small-volume Plazlyte,[242] but expressly limited its

purpose, subject to the statutory exceptions set out at § 4631(e) .... In any event, § 4631(d) cannot be sustained even under the interpretation the State now adopts.").

238. *See* Silverman, *supra* note 235, at f321 (speculating that the government will now "focus only on those cases where [it] can prove that false or misleading information was knowingly conveyed to healthcare providers"); Bentivoglio, *supra* note 217 (predicting the same); Katie Thomas, *Ruling Is Victory for Drug Companies in Promoting Medicine for Other Uses*, N.Y. TIMES (Dec. 3, 2012), http:// www.nytimes.com/2012/12/04 /business/ruling-backs-drug-industry-on-off-label-marketing.html (same); *see also* Kesselheim, Mello & Avorn, *supra* note 21, at 446 (suggesting that this is a prosecutorial avenue left open by *Caronia*); Robertson, *supra* note 217, at 565 ("[T]he courts should decline to presume truthfulness, and decline to presume that [off-label promotional] claims are shielded by the First Amendment as protected commercial speech.").

239. *See* Appellant's Reply Brief at 21, Coleman v. Medtronic, Inc., 223 Cal. App. 4th 413 (2014) (No. B243609), 2013 WL 4050440, at *21 (arguing against defendant's contention that *Caronia* held that there was no federal prohibition against off-label promotion by stating that "the court essentially adopted a narrowing construction of the law so that it does not criminalize *truthful* speech").

240. 517 F.3d 935 (7th Cir. 2008).

241. *Id.* at 937–38.

242. *510(k) Premarket Notification: Plazlyte(TM)*, U.S. FOOD & DRUG ADMIN. (Dec. 22, 1994), http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K905119. Clearance for the small-volume Plazlyte came under the FDA's 510(k) pathway for review of medical devices that allows moderate-risk devices to be marketed based on a proof of substantial equivalence to prior-approved devices. *See id.*; *Premarket Notification (510k)*, U.S. FOOD & DRUG ADMIN. (Jan. 3, 2014), http://www.fda.gov/MedicalDevices /DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm. For the FDA's purposes, substantial equivalence can be adequately demonstrated without the need to conduct studies of the performance of the device; indeed, a manufacturer needs to demonstrate only substantial equivalence to a

clearance for use with stainless-steel instruments. Since such a limitation would have restricted the product's marketing potential, AbTox started offering for sale a large-volume Plazlyte (previously available only outside the United States) and promoting its use for general-purpose sterilization.[243] The controversy arose because the large-volume Plazlyte left a dangerous residue on brass instruments used in ophthalmologic surgery, leading to blindness in some patients.[244] In the ensuing criminal prosecution, AbTox's directors offered a First Amendment defense for their actions, claiming a commercial speech right to talk about off-label uses of their device.[245] However, the Seventh Circuit rejected this defense on the basis that AbTox lied to the FDA when seeking approval for the small-volume Plazlyte, and the large-volume Plazlyte could not lawfully be sold in the United States.[246] As a result, the speech of the AbTox directors was false and concerned unlawful activity. It was not protected as commercial speech.[247]

The *Caputo* case is an extreme example of false and misleading speech relating to medical products. A more familiar scenario occurred in the recent case of *United States v. Harkonen*.[248] The chief executive officer of the drug manufacturer InterMune, W. Scott Harkonen, was indicted for felony misbranding and wire fraud relating to his promotion of the immunomodulating drug interferon gamma-1b (Actimmune) as a treatment for idiopathic pulmonary fibrosis (IPF), a fatal lung inflammatory disease.[249] The controversy revolved around a 2002 company-sponsored clinical trial that showed that the drug was not effective in treating IPF based on the primary endpoints of the trial.[250] Harkonen ordered a post-hoc analysis of the

device that had previously been cleared. *See Premarket Notification (510k)*, *supra*. According to the Seventh Circuit, the FDA was wary of Plazlyte's safety and instructed the company that if it wanted approval of a larger device for use in a wider range of instruments, the company would have to submit under the Premarket Approval pathway reserved for high-risk devices, which requires submission of considerable data from safety and effectiveness testing. *See Caputo*, 517 F.3d at 937.

243. *Caputo*, 517 F.3d at 937.

244. *Id.* at 938.

245. *Id.*

246. *Id.* at 940 (describing the jury's findings); *id.* at 944 (affirming the district court).

247. *Id.* at 940 ("Unless the machine itself could be sold lawfully, there were no lawful off-label uses to promote.").

248. No. C 08-00164 MHP, 2010 WL 2985257 (N.D. Cal. July 27, 2010).

249. *Id.* at *1.

250. According to the court records, the trial failed on the primary endpoint of disease-progression-free survival as well as all nine predetermined secondary endpoints. *See* Joe Barber, *US Court Set to Rule on Former Intermune CEO Free-Speech Case*, FIRSTWORD PHARMA (Dec. 6, 2012),

data. According to later testimony at trial, Harkonen said he would "cut that data and slice it until [he] got the kind of results [he was] looking for,"[251] and indeed he did—he found that patients in the "mild to moderate" subgroup of IPF showed improvement in survival in the active treatment arm compared to placebo (5% versus 16%).[252] FDA medical officers informally reviewed the clinical-trial data and stated that they did not believe it would support the use of Actimmune for IPF.[253] Nonetheless, twelve days later, Harkonen organized a press release that claimed a "survival benefit" and said the drug "reduces mortality by 70% in patients with mild to moderate disease."[254] InterMune followed up this press release with other promotional materials regarding Actimmune's purported survival benefit, and Harkonen instructed his company's sales representatives to disseminate these materials to physicians.[255]

Sales of the drug increased nearly fivefold over the next three years due to increased use among IPF patients.[256] Of course, post-hoc subgroup analyses are controversial analytic tools because they generate multiple comparisons that raise the likelihood of finding erroneous statistical significance and may not adjust for imbalances across subgroups.[257] A follow-up study organized by InterMune

http://www.firstwordpharma.com/node/1039261?tsid=17#axzz2sPO45jJn; Thomas M. Burton, *Courts to Weigh Free Speech Rights in Pharmaceutical Marketing Cases*, WALL ST. J. (Dec. 5, 2012), http://online.wsj.com/news/articles/SB10001424127887323316804578161601385027858. However, one of those secondary endpoints was overall survival, and there the drug showed a slight difference from placebo (10% mortality versus 17% mortality in the placebo arm) that was not statistically significant (p=0.08). David Brown, *The Press-Release Conviction of a Biotech CEO and Its Impact on Scientific Research*, WASH. POST (Sept. 23, 2013), http://www.washingtonpost.com/national/health-science/the-press-release-crime-of-a-biotech-ceo-and-its-impact-on-scientific-research/2013/09/23/9b4a1a32-007a-11e3-9a3e-916de805f65d_story.html.

251. United States v. Harkonen, 510 F. App'x 633, 636 (9th Cir. 2013) (internal quotation marks omitted), *cert. denied*, Harkonen v. United States, 134 S. Ct. 824 (2013).

252. The difference appeared to be highly significant (p=0.004). Brown, *supra* note 250. However, because Intermune did not account for testing multiplicity in arriving at this p-value, the p-value was not very meaningful. *See infra* note 257 and accompanying text.

253. Brown, *supra* note 250.

254. Press Release, InterMune, InterMune Announces Phase III Data Demonstrating Survival Benefit of Actimmune in IPF (Aug. 28, 2002), *available at* http://www.sec.gov/Archives/edgar/data/1087432/000091205702033878/a2088367zex-99_1.htm.

255. Complaint at 6–7, United States *ex rel.* Gallagher v. InterMune, Inc., No. 04:CV-4323 (E.D. Pa. July 9, 2004), *available at* http://www.drugepi.org/downloads/downloads/Intermune_Complaint1.pdf.

256. *Id.* at 8 ("During the period 2001 through 2004, InterMune's sales of Actimmune grew from $35 million in 2001 to more than $140 million in 2003 . . . . In 2003, 96.5% of InterMune's sales of Actimmune were for off-label uses, primarily for treatment of IPF.").

257. *See* Kirkwood F. Adams, *Post Hoc Subgroup Analysis and the Truth of a Clinical Trial*, 136 AM. HEART J. 753 (1998).

sought to evaluate the efficacy of Actimmune in the mild- to moderate-disease subgroup.[258] The trial, which involved 826 patients in 81 centers across the world, showed no survival difference between patients receiving the drug and placebo (15% versus 13% mortality) and was prematurely stopped.[259] That study was published in 2009.[260]

Harkonen fought his prosecution by claiming that his speech was a protected opinion under the First Amendment because it was "scientific speech about 'medical practices in fields where knowledge has not yet been crystallized' " and "where there exists 'no exact standard of absolute truth.' "[261] The government replied that the free-speech argument was meant to distract from the fraudulent nature of his statements and emphasized that "neither the government nor the FDCA seeks to make criminal good-faith scientific debate."[262] The government's tactic in the *Harkonen* case, as distinct from the *Caronia* case, was to argue that it was not "seeking to restrict truthful, non-misleading promotion of the off-label uses of Actimmune" or regulate anyone's "ability to engage in a discourse on whether Actimmune might someday prove beneficial as a treatment for IPF."[263] Rather, it was prosecuting Harkonen because his speech was fraudulent.[264]

Siding with the government, the district court opined that Harkonen's statements should not be analyzed as opinions about a contested scientific matter, but as fraudulent speech.[265] Since it was "undisputed that the government has the right to regulate false and misleading statements made to doctors and patients about drug products in interstate commerce,"[266] the proper arbiter for the dispute over Harkonen's statements was a jury.

Harkonen argued to the jury that he genuinely believed his interpretation of the Actimmune trial data, and that at worst his press release constituted advertising "puffery," not fraud.[267] However, having examined an extensive record that showed substantial

258. *See* Talmadge E. King Jr. et al., *Effect of Interferon Gamma-1b on Survival in Patients with Idiopathic Pulmonary Fibrosis (INSPIRE): A Multicentre, Randomised, Placebo-Controlled Trial*, 374 LANCET 222, 222 (2009).

259. *Id.*

260. *Id.*

261. United States v. Harkonen, No. C 08-00164 MHP, 2009 WL 1578712, at *4 (N.D. Cal. June 4, 2009) (quoting Reilly v. Pinkus, 338 U.S. 269, 273–74 (1949)).

262. *Id.*

263. *Id.* at *8.

264. *Id.*

265. *Id.*

266. *Id*.

267. *Id.*

evidence that Harkonen knowingly employed improper tactics and strategies in promoting Actimmune, the jury convicted him of wire fraud.[268] He was sentenced to three years' probation and assessed a $20,000 fine.[269] Harkonen appealed his conviction, but in March 2013 was rebuffed.[270] In a relatively brief decision that did not recapitulate Harkonen's First Amendment claims, the Ninth Circuit affirmed the jury's finding of intentional fraud as reasonable.[271]

The *Harkonen* case thus illustrates one potential path for future government prosecution of off-label promotion: arguing that a pharmaceutical company representative is being prosecuted "not because he promoted [a drug] for an unapproved use . . . but because he made knowingly false and misleading statements in doing so."[272] For many statements that sales representatives make to promote off-label uses, the government could make a reasonable argument that the speech qualifies as misleading and deceptive. Among well-trained sales representatives, the tactic of communicating "non-demonstrably false information," to use Judge Livingston's term,[273] is probably common—and arguably deceptive. Most off-label uses of drugs have little or no scientific support,[274] but sales representatives may omit that material fact or misrepresent the strength of evidence.[275]

The existence of such behaviors has been supported by numerous published reports from pharmaceutical sales representatives. For example, psychiatrist Daniel Carlat, acting as a representative on behalf of a Wyeth antidepressant, addressed a physician's concern about a dangerous side effect of the drug

268. United States v. Harkonen, 510 F. App'x 633, 635 (9th Cir. 2013) (describing the lower court result). The jury's decision to acquit Harkonen on the misbranding charge is puzzling in light of its decision to convict him of wire fraud. *See* United States v. Harkonen, No. C 08-00164 MHP, 2010 WL 2985257, at *1 (N.D. Cal. July 27, 2010).

269. *Harkonen*, 510 F. App'x at 635.

270. *Id.*

271. *Id.* at 635–39. Harkonen filed a petition for certiorari to the Supreme Court. *See* Petition for Writ of Certiorari, *Harkonen*, 510 F. App'x. 633 (No. 13-180), 2013 WL 4027035. In December 2013, the Supreme Court denied certiorari. *Harkonen*, 510 F. App'x 633, *cert. denied*, 134 S. Ct. 824 (2013); *see* Lawrence Hurley, *U.S. Supreme Court Refuses to Hear Ex-InterMune CEO's Appeal*, REUTERS (Dec. 16, 2013, 2:52 PM), http://www.trust.org/item/20131216143706-v9uq8.

272. *Harkonen*, 2009 WL 1578712, at *6 (quotation omitted).

273. United States v. Caronia, 703 F.3d 149, 181 (2d Cir. 2012) (Livingston, J., dissenting).

274. *See* Radley, Finkelstein & Stafford, *supra* note 39, at 1023.

275. *Cf.* Robertson, *supra* note 217, at 566 (pointing out that drug sales representatives receive a contingent payment for every unit sold, creating "biases that likely skew the advice given").

(hypertension) by downplaying its significance.[276] He later reflected, "I knew I had not lied—I had reported the data exactly as they were reported in the paper. But still, I had spun the results of the study in the most positive way possible, and I had not talked about the limitations of the data."[277] Another ex-pharmaceutical sales representative also reported, "[E]very word, every courtesy, every gift, and every piece of information provided is carefully crafted, not to assist doctors or patients, but to increase market share for targeted drugs."[278] These are not isolated instances. Manufacturers have for decades provided inadequate information to enhance the sales of their products by boosting the drugs' efficacy and downplaying their side effects for unapproved uses.[279] Another strategy is the publication of partial data, leading to a publication that is true on its face but leaves out critical information that may undermine conclusions about its utility.[280] Numerous other factors contribute to marketed products having inaccurate risk-benefit profiles for off-label uses.[281]

276. Daniel Carlat, *Dr. Drug Rep.*, N.Y. TIMES (Nov. 25, 2007), http://www.nytimes.com/2007/11/25/magazine/25memoir-t.html?pagewanted=all&_r=0.

277. *Id.*

278. Adriane Fugh-Berman & Shahram Ahari, *Following the Script: How Drug Reps Make Friends and Influence Doctors*, 4 PLOS MED. 621, 625 (2007).

279. *See* JEREMY A. GREENE, PRESCRIBING BY NUMBERS: DRUGS AND THE DEFINITION OF DISEASE (2007).

280. *See* Joanna K. Sax, *Protecting Scientific Integrity: The Commercial Speech Doctrine Applied to Industry Publications*, 37 AM. J.L. & MED. 203, 208 (2011). Sax describes a hypothetical case study in which a pharmaceutical company has twelve months of data but publishes only six because the beneficial effect noted at six months becomes non-significant at the later time point. *Id.* Sax concludes that

> the publication may be accurate or truthful with respect to the data gathered at the six-month time-point, but the publication gives a false impression, via omission, that no other data was collected or that no other data exists to provide support for a contrary conclusion. Plus, the public, politicians, scientists, and clinicians have almost no way to confirm or deny the data.

Id. This hypothetical is based on a real case: the nonsteroidal anti-inflammatory drug and selective COX-2 inhibitor, celecoxib (Celebrex). *See* Katie Thomas, *In Documents on Pain Drug, Signs of Doubt and Deception*, N.Y. TIMES (June 24, 2012), http://www.nytimes.com/2012/06/25/health/in-documents-on-pain-drug-celebrex-signs-of-doubt-and-deception.html?pagewanted=all&_r=0.

281. Efthimios Parasidis, *Patients over Politics: Addressing Legislative Failure in the Regulation of Medical Products*, 2011 WIS. L. REV. 929, 975 ("Notably, the health risks posed by the current regulatory system are exacerbated by tactics employed by industry in the course of product research and development. These techniques, many of which have come into the public domain through litigation, undermine the claim that the current regulatory framework provides adequate safeguards."). *See generally* THE RISKS OF PRESCRIPTION DRUGS (Donald W. Light ed., 2010) (describing strategies used to promote

In this light, making conclusory, unsubstantiated claims of safety and efficacy for unapproved uses without reference to supporting evidence might reasonably be characterized as misleading. The FDA has pursued such an enforcement strategy in past cases involving unsubstantiated claims and minimization of risks in the context of off-label promotion,[282] and it is consistent with the agency's prior interpretations of the meaning of misleading speech.[283]

This approach has a few clear disadvantages, however. Establishing that off-label promotional statements are false or misleading requires, first, evidence in the record as to the specific words used by the defendant. Not all off-label promotion cases involve the pristine evidence available to the government in the *Caronia* case because of the willingness of a cooperating physician to audiotape conversations.

Second, even if the nature of the promotional statements can be clearly established, the government must prove that they are false or misleading, which requires a case-by-case evaluation.[284] The boundary line between protected speech and false speech in the area of off-label promotion is unclear and likely to be heavily contested if the government pursues this strategy. Few cases will be as clear-cut as Caputo's, which involved a completely unapproved product,[285] or

inaccurate perceptions that overstate the benefits and underestimate the risks of many approved prescription drugs).

282. For example, the FDA issued warning letters to Forest Laboratories concerning oral statements made by its sales representatives in promoting two of its drugs, Savella and Daliresp, for off-label uses. Marc J. Scheineson & Guillermo Cuevas, United States v. Caronia*: The Increasing Strength of Commercial Free Speech and Potential New Emphasis on Classifying Off-Label Promotion as "False and Misleading*," 68 FOOD & DRUG L.J. 201, 213–14 (2013).

283. *Id.* at 214.

284. *See* Robertson, *supra* note 217, at 559. "The many different claims that drug representatives make about a drug each raise distinct empirical questions. These claims are unlike the representations made in other domains, where the truthfulness is 'easily verifiable.' " *Id.* (quoting Zauderer v. Office of Disciplinary Counsel, 471 U.S. 626, 645 (1985)). Robertson proposes that courts shift the presumption so that the truthfulness of off-label promotional statements must be affirmatively shown, arguing that the truth or falsity of such claims is "unknown, largely because the drugmaker has declined to invest in making such a proof" by conducting the trials necessary to demonstrate the drug's effects. *Id.* at 575. This is a sensible suggestion, but one that seems unlikely to find traction. One reason is that it might mean the end of off-label promotion, since a manufacturer would have to "spend the time and money to prove to the FDA the truth of its promotional claims" before making them. *Id.* at 573. Depending on the level of proof required, the burden could be so heavy that the manufacturer either ceases making off-label claims or, having conducted the studies necessary to prove them, simply seeks FDA approval for the off-label use.

285. United States v. Caputo, 517 F.3d 935, 937–38 (7th Cir. 2008).

Harkonen's, whose patently false speech did not "trench anywhere near the outer bounds of speech deemed controversial."[286]

Third, the precise boundaries of this realm of speech, and what is required to establish that particular speech lies within them, are somewhat unclear. Though the *Central Hudson* test has been often described as excluding "unlawful or false or misleading" speech from protection, in actuality the *Central Hudson* opinion used different words, holding that the government may freely ban forms of commercial communication "more likely to deceive the public than to inform it" or that "do not accurately inform the public about lawful activity."[287] In other commercial-speech cases, the Supreme Court has described commercial speech unworthy of First Amendment protection as being "misleading, deceptive, or aggressive."[288] Unfortunately, in the past three decades, no judicial opinion in a commercial-speech case has taken up the call from the Stewart concurrence in *Virginia State Board* to better define the level of proof required to distinguish between misleading and truthful promotion.[289]

In the absence of "smoking gun" evidence that the speaker knew the statements to be false, establishing that promotional speech is false or misleading will require assessing the strength, validity, and appropriateness of evidence for each claim. This will require a considerable amount of complex expert testimony and pose heavy cognitive demands on lay jurors.[290] In light of these challenges, the misleading-speech strategy for prosecuting off-label promotion will be useful only in a narrow range of cases. Though an awareness that the FDA might pursue such an approach could motivate companies to take stronger steps to ensure that their representatives avoid the worst excesses of off-label promotion, because of the limitations of this approach, we next explore two broader alternatives.

D. Taking Another Run at the Central Hudson *Hurdle*

A fourth potential strategy for the FDA is simply to continue to prosecute off-label promotion on the theory that its regulatory approach satisfies the *Central Hudson* test notwithstanding the

286. United States v. Harkonen, No. C 08-00164 MHP, 2009 WL 1578712, at *6 (N.D. Cal. June 3, 2009).

287. Cent. Hudson Gas & Elec. Corp. v. Pub. Serv., 447 U.S. 557, 563 (1980).

288. 44 Liquormart, Inc. v. Rhode Island, 517 U.S. 484, 501 (1996).

289. Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, 425 U.S. 748, 780–81 (1976) (Stewart, J., concurring).

290. *See* Silverman, *supra* note 235, at f320 (predicting "haggling . . . over which activities, literature, and statements constitute false or misleading information" and "increased argument" over "complicated and intricate statistics").

Caronia decision. That is, the government could take the position that restricting off-label marketing is a proper exercise of government power even if it is not technically false or misleading. The reasoning in *Caronia* is vulnerable enough to criticism that the FDA might prevail under such a theory in other jurisdictions and thus be able to maintain its existing regulatory approach in most of the country.

This strategy would address a troubling potential effect of the *Caronia* rule: the decision appears to pave the way for medical product companies to conduct poor-quality studies for the purpose of showing products' utility for unapproved indications.[291] There is no need for companies to design these studies to meet the FDA's standards for methodological rigor if the companies have no intention of submitting an application for approval of the new use but rather intend to use the study findings only in marketing communications. Companies can design studies in ways that maximize the chances of obtaining a desired result and select which studies to emphasize in promotional communications, ignoring others that do not support their promotional message.[292] *Caronia* provides a fertile ground for such practices to grow by effectively erecting a First Amendment bulwark around the communications, so long as they do not rise to the level of false and misleading speech. Thus, the regulatory framework established by the *Caronia* decision is worth resisting.

To build a strong case for the permissibility of its regulatory approach to off-label promotion under the *Central Hudson* test, the government will need to respond to judicial pronouncements on each

291. Kesselheim, Mello & Avorn, *supra* note 21, at 446.

292. There is an extensive record demonstrating that funding of trials by the pharmaceutical industry leads to results that favor the financial interests of the company sponsoring the trial. For a brief review, see Christopher Robertson, Susannah Rose & Aaron S. Kesselheim, *Effect of Financial Relationships on the Behaviors of Health Care Professionals: A Review of the Evidence*, 40 J.L. MED. & ETHICS 452 (2012). Alternative solutions have been proposed "to allow industry support of science without allowing undue influence," such as a blinded intermediary between funding sources and the scientists who design and run the trial. Christopher T. Robertson, *The Money Blind: How to Stop Industry Bias in Biomedical Science, Without Violating the First Amendment*, 37 AM. J.L. & MED. 358, 373 (2011). Robertson describes an alternative reality in which

> [t]he funder would provide to the intermediary the product for testing and designate a testable hypothesis (i.e., that the product will be safe and/or effective for some specified clinical indication). The intermediary would then determine how much money would be necessary to properly test that hypothesis, and require such payment in advance.

Id. Such proposals might help reduce the likelihood of bias, but they would not prevent funders from proposing self-serving scientific studies in the first place or from cherry-picking the ones favorable to them for use in their promotional materials.

of the three main prongs: (1) substantiality of the government interest; (2) direct advancement; and (3) narrow tailoring. We discuss each in turn.

1. Substantial Government Interest

The first *Central Hudson* principle is whether the government interest that the regulation is intended to serve is substantial. All courts that have reviewed restrictions on pharmaceutical promotion have agreed that the government has offered some substantial interest, sufficient to satisfy this criterion, but not every interest claimed by the government has been accepted as substantial.[293] Attention to this criterion is important because how the government interests at issue are described will affect the rest of the balancing test. The broader the interests that courts accept as legitimate justifications for restricting off-label promotion, the broader the government's latitude will be in designing the regulatory scheme.

Courts have resisted governmental attempts to frame a substantial interest in preventing off-label promotion from reaching physicians. For example, in *Washington Legal Foundation v. Friedman*, the district court accepted the government's assertion of a substantial interest in "providing manufacturers with ample incentive to get previously unapproved uses on label" but rejected the government's contention that it also had a substantial interest in "ensuring that physicians receive accurate and unbiased information so that they may make informed prescription choices."[294] "To the extent that the FDA is endeavoring to keep information from physicians out of concern that they will misuse that information," the court wrote, "the regulation is wholly and completely unsupportable."[295] The government's attempt to reassert this interest in *Caronia*[296] was largely ignored by the majority opinion, which

293. *See, e.g.*, Bolger v. Youngs Drug Prods. Corp., 463 U.S. 60, 71–73 (1983) (finding a government interest in protecting postal patrons from offensive but not obscene materials did not qualify as substantial).

294. Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 69 (D.D.C. 1998), *judgment vacated in part sub. nom.* Wash. Legal Found. v. Henney, 202 F.3d 331 (D.C. Cir. 2000).

295. *Id.*

296. In its brief, the government wrote,

> Unlike *Sorrell*, this is not a case in which the government is animated by "fear that people would make bad decisions if given truthful information." The promotion of unapproved uses involves representations of safety and efficacy that are scientifically unproven and potentially false, and physicians and patients who rely on those representations may do so to the detriment of the patients' health and even their lives.

focused on the interests in safeguarding the integrity of the drug-approval system and reducing patient exposure to unsafe and ineffective drugs.[297]

Notwithstanding the district court's holding in *Washington Legal Foundation* and the strong anti-paternalism of the *Caronia* opinion, it is worth pressing the government's interest in ensuring that physicians receive accurate, unbiased information to support informed treatment choices as substantial in future cases. Prevailing on this point is likely to require more concerted effort to persuade courts of three realities about off-label communications. First, even when they do not rise to the level of what courts would define as false or misleading, off-label promotional statements may fall well short of accurate, unbiased information. It will be difficult to make this case for some forms of off-label communication, such as dissemination of articles from reputable, peer-reviewed journals. But, as the transcripts from Caronia's conversation with the cooperating physician show, oral conversations in the confines of physician offices have fewer mechanisms of accountability.[298] It is not unreasonable to argue that the government has a substantial interest in preventing the communication of unsubstantiated information in such settings and to

Supplemental Brief for United States at 10, United States v. Caronia, 703 F.3d 149 (2d Cir. 2012) (No. 09-5006-cr(L)) (quoting Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2658 (2011)), *available at* http://www.hpm.com/pdf/blog/US%20Caronia%20Supp%20Brief.pdf.

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

298. *See id.* at 156–57. Indeed, the *Washington Legal Foundation* court's reasoning in rejecting the government's asserted interest has much more applicability to communications about off-label uses made in journal articles or other written forms than to oral communications from sales representatives. *See Wash. Legal Found.*, 13 F. Supp. 2d at 69–70. The court had in mind companies' efforts to distribute "scientific research product[s]" such as "an article . . . in the *New England Journal of Medicine*," textbook reprints, and continuing medical education presentations. *Id.* at 70. The court judged physicians clearly capable of evaluating the credibility of scientific claims in these media. *Id.* It may have had in mind the fact that written communications can be scrutinized, digested, and verified at the physician's leisure. It may also have in mind the other mechanisms of accountability that inhere in the publication process. For journal articles and book chapters, the involvement of editors and peer reviewers and the venue of publication provide physicians with markers of the scientific rigor and importance of a set of study findings. The semi-public nature of continuing medical education presentations, the memorialization of presentations in written form (such as slides), and the attestations that presenters are required to make all provide incentives for speakers to avoid unsubstantiated claims. The *Washington Legal Foundation* court was not asked to, and did not, consider the very different circumstances surrounding private conversations between sales representatives and physicians during physician-office visits. *See* Mello, Studdert & Brennan, *supra* note 154, at 1557–58 (discussing the degree of transparency around different forms of off-label promotion).

push back on courts' seemingly consistent assumption that off-label communications are always wholly accurate.

Second, courts have had greater confidence than is warranted in physicians' ability to evaluate claims about off-label uses. When promotional claims are made without the representative offering supporting evidence, such as published study findings, the impossibility of critically evaluating the credibility of the claims is obvious. Physicians must rely on their judgments of representatives' personal credibility. Some promotional claims may be inherently impossible for physicians to verify, such as a claim that other physicians are already widely prescribing the drug for a particular off-label use and have encountered no serious safety problems.

Third, even when a journal article or other document supporting a claim about the safety or effectiveness of an off-label use is offered, it may convey only a slice of the full empirical picture. There may be countervailing study findings or important study limitations that were omitted from the write-up in the article. The FDA approval process serves as a bulwark against such problems by deploying highly skilled scientists to analyze all of the available information about a drug's use, verify analyses conducted by the drug's sponsor independently, and scrutinize the design of the studies offered to support the new use. Individual physicians cannot approach this level of evaluation; even if they had the time and inclination to explore the veracity of claims made in off-label promotional communications, they lack access to the information necessary to do so thoroughly.[299] These same considerations led Congress to require drug manufacturers to submit proof of efficacy to the FDA prior to marketing,[300] and they

299. Kesselheim, Mello & Avorn, *supra* note 21, at 446 ("[I]t is not 'paternalistic' to recognize the obstacles that prevent physicians from [sorting through marketing claims and making sound decisions on their own] when it comes to off-label prescribing. FDA approval involves numerous highly skilled scientists reviewing a great deal of data for months. It is not possible for individual prescribers to conduct the same rigorous evaluation, even if such data are available to them (which they often are not) or to expect that sales representatives' presentations will effectively meet this need.").

300. *See* Waxman, *supra* note 10, at 306–07. In a particularly trenchant anecdote, U.S. Representative Henry Waxman recalled that

> the Secretary of the Department of Health Education and Welfare (HEW) testified in 1962 [that] it is meaningless to say that a physician should have the right to decide for himself whether a drug is effective, unless "truthful and complete information" about the effectiveness of a drug is available to any physician in the ordinary course of practice. The marketplace as it existed before there was an effectiveness requirement provided neither. For most physicians, "truthful" information was impossible to separate from misleading information, and "complete information" almost was never available.

apply with equal force to off-label promotional statements fifty years later.

For these reasons, it is worthwhile for the government to continue to assert an interest in imposing reasonable restrictions on off-label communications for the purpose of ensuring that the information communicated to physicians is accurate and unbiased. It is a reasonable, and non-paternalistic, exercise of government power to encourage the private creation of new, high quality information about drugs that could then be communicated fully without restriction once it appeared on the drugs' labeling. It should also, of course, assert the other interests that courts have had less difficulty accepting as substantial, such as protecting the integrity of the drug approval process and protecting the public from unsafe prescribing.[301]

2. Direct Advancement

The second component of a reinvigorated defense of restrictions on off-label promotion under *Central Hudson* is establishing that the regulation directly advances the asserted government interest(s).[302] A three-pronged argument is needed to overcome this hurdle to regulation.

First, the government should underscore the ways in which unfettered off-label promotion destabilizes its long-accepted drug-approval system. Judge Livingston argued this position in her dissenting opinion in *Caronia*,[303] and the argument has considerable force. If companies are free to promote their products for any use or any population, once the product has been approved for one use or population, their incentive to invest in the clinical studies required to

Id. at 307 (citation omitted).

301. *Cf.* Robertson, *supra* note 217, at 565 ("[E]xpenditures on marketing are zero sum; they simply redistribute wealth. Expenditures on research are, on the other hand, positive sum, creating greater welfare. Without such a requirement that manufacturers prove efficacy and safety prior to promotion, that proof will not be secured, and zero-sum marketing predominates. The epistemic and economic motive for the FDCA, tying investments to market rewards, is much different than the paternalistic one caricatured by the courts and commentators."). A recent review bolsters the case for the government interest in avoiding unsafe prescribing by compiling a number of studies showing a statistical association between physicians' exposure to pharmaceutical company promotional information and lower quality of prescribing decisions, though it also references several studies that did not detect such an association. *See* Geoffrey K. Spurling et al., *Information from Pharmaceutical Companies and the Quality, Quantity, and Cost of Physicians' Prescribing: A Systematic Review*, 7 PLOS MED. e1000352 (2010).

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

303. *See supra* text accompanying notes 210–11.

secure FDA approval for new uses is dramatically undercut. A world in which off-label promotion is unregulated is likely to be one in which poorly substantiated marketing claims about unapproved uses proliferate,[304] with attendant effects on prescribing decisions and patients' health and safety. It is hard to overstate the public health importance of this point. Promotional statements strongly drive prescribing behavior in ways that do not match evidence-based practice guidelines or the medical literature, and they have been empirically demonstrated to lead to use of targeted prescriptions increases after sales representative visits as well as increases in requests by physicians to add drugs to their hospital formularies.[305] The literature is clear that there is a strong, consistent, specific, and independent association between physician prescribing and exposure to pharmaceutical marketing messages.

Second, the government must address the *Caronia* majority's assertion that there is a logical inconsistency between the decision not to prohibit off-label prescribing and the FDA's attempt to regulate promotion of off-label uses.[306] If prescribing is to be allowed, the majority reasoned, it should be as informed as possible, and obstructing the free flow of information about off-label uses works against this goal.[307]

As with most of the majority's reasoning, this argument is premised on the unchallenged assumption that off-label promotional communications are sufficiently accurate and unbiased to support "intelligent and well-informed" decision making.[308] Because there is reason to doubt this assumption, based on decades of experience with off-label promotion, regulating off-label promotional communications is by no means incompatible with the decision to permit off-label prescribing. To the contrary, the government has a strong interest in seeing that promotional communications are accurate and unbiased

304. Kesselheim, Mello & Avorn, *supra* note 21, at 446 ("Because costly products would carry the highest incentive for such activity, evidence-poor prescribing would result in runaway costs.").

305. *See, e.g.*, Jerry Avorn, Milton Chen & Robert Hartley, *Scientific Versus Commercial Sources of Influence on the Prescribing Behavior of Physicians*, 73 AM. J. MED. 4, 6 (1982); Mary-Margaret Chren & C. Seth Landefeld, *Physicians' Behavior and Their Interactions with Drug Companies: A Controlled Study of Physicians Who Requested Additions to a Hospital Drug Formulary*, 271 JAMA 684, 688 (1994).

306. *See* Reply Brief for Petitioners at 7, Am. Snuff Co. v. United States, 133 S. Ct. 1996 (2013) (No. 12-521), 2013 U.S. S. Ct. Briefs LEXIS 1764, at *7 ("Where, however, FDA *regulates speech* about products that may otherwise be *lawfully sold*, the First Amendment applies with full force.").

307. United States v. Caronia, 703 F.3d 149, 167 (2d Cir. 2012).

308. *Id.*

to ensure that physicians make clinically sound prescribing decisions. For this reason, there is a strong argument that some regulation of off-label promotion—though not all forms, and certainly not a blanket prohibition on off-label communication—would meet the direct-advancement criterion.

In the context of this argument, it is worth recalling that the FDA's current regulatory approach does not impose a blanket prohibition on off-label promotion, but instead focuses on those forms of communication that are most amenable to corruption.[309] Unprompted oral communications from sales representatives in the personal confines of a physician's office, such as the tactics at issue in the *Caronia* case, are not permitted.[310] In contrast, peer-reviewed journal articles and independent continuing medical education programs are permitted to discuss off-label uses, and manufacturers can respond to physician-initiated questions about off-label uses.[311]

Third, the government will need to refute the argument that regulating off-label promotional communications constitutes constitutionally impermissible paternalism. The optimal approach is again to focus on the government's interest in ensuring accurate, unbiased communications. Of course, the FDA's regulatory framework does not keep physicians "in the dark" about off-label uses, as the *Caronia* majority insinuated.[312] As the majority recognized, the FDA openly permits some forms of company communications about off-label uses that are reasonably designed to hold companies accountable for their communications.[313] The majority actually criticized the FDA for taking an inconsistent position about the utility of communications about off-label uses because of these allowances, but the existence of these safe harbors arguably shows that the FDA's intent is to permit the flow of truthful information while preventing companies from disseminating unsubstantiated claims through nontransparent mechanisms. That approach is hard to square with the anti-paternalism trope of the *Caronia* decision. The risk against which the FDA is trying to guard is

309. *See supra* notes 22–41 and accompanying text.

310. *See supra* notes 32–35 and accompanying text.

311. *See supra* notes 42–53 and accompanying text.

312. *Caronia*, 703 F.3d at 166 ("The First Amendment directs us to be especially skeptical of regulations that seek to keep people in the dark for what the government perceives to be their own good."(quoting 44 Liquormart, Inc. v. Rhode Island, 517 U.S. 484, 503 (1996))).

313. *See id.* at 166–67; Mello, Studdert & Brennan, *supra* note 154, at 1559–60.

not that "the public will respond 'irrationally' to the truth,"[314] but that it will not be told the whole truth.

It is also worth noting a distinction between the factual circumstances surrounding off-label prescribing and those in other cases, such as *Virginia State Board*, that formed the genesis of anti-paternalism objections to commercial-speech restrictions. In *Virginia State Board*, the restriction on pharmacy advertising was intended to influence shoppers' choice of pharmacy.[315] By contrast, we would argue, in seeking to curb the excesses of off-label promotion of medical products to physicians, the FDA seeks to protect not the recipients of the promotion, but their patients. When physicians decide to prescribe a drug for an unapproved use based on a biased presentation of the evidence concerning that use, they put a third party at risk of physical harm. Congress has tasked the FDA with the responsibility to protect the public from unsafe and ineffective drugs.[316] It is not paternalism for the agency to discharge its responsibility in this way.

3. Narrow Tailoring

The final component of the *Central Hudson* test is the requirement that the restriction on commercial speech be no broader than necessary to advance the government's objective.[317] The Supreme Court in *Sorrell* threw down a difficult gauntlet for the government with respect to simultaneously satisfying this part of the test and the third prong.[318] On the one hand, commercial-speech restrictions must be very narrowly drawn to meet the tailoring requirement, but on the other, the Court took such a stringent view of what directly and materially advances the government's interest that it seems that nothing but a very broad speech restriction would have a great enough impact to satisfy the third prong. The government is further hamstrung by the requirement that the restriction be as narrowly tailored as possible coupled with the requirement that it avoid discriminating against a particular class of speakers. These

314. *Caronia*, 703 F.3d at 166 (quoting 44 Liquormart, Inc. v. Rhode Island, 517 U.S. 484, 503 (1996)).

315. Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, 425 U.S. 748, 752 (1976).

316. *See* 21 U.S.C. § 355(d) (2012).

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

318. *See* Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2670–71 (2011); Mello & Messing, *supra* note 139, at 1253 (noting the potential for states to be "whipsawed" between the narrow-tailoring and direct-advancement prongs when attempting to regulate the sale of prescriber data to protect physician privacy).

tensions are real, but several arguments may help the government prevail on the tailoring prong in future cases involving off-label promotion regulation.

a. The FDA's Existing Approach Allows Some Forms of Off-Label Promotional Speech

First, as discussed above, the FDA's regulatory regime for off-label promotion is already limited and tailored.[319] Through regulatory guidance setting out safe harbors, the FDA has carefully identified forms of off-label promotional communications that are permitted because they are less likely than other forms to contain misleading information. These safe harbors demonstrate the FDA's commitment to tailoring its regulations to the objective of ensuring that communications with physicians about drug uses convey accurate and unbiased information. Companies are also free to engage in other forms of truthful communication about potential new uses of their drugs that do not fall within the category of promotional speech, such as press releases, disclosures in SEC filings, and publication of clinical study results in medical journals.[320]

b. Non-Speech-Restricting Alternatives Are Inadequate

Second, the policy approaches proposed by the *Caronia* majority as alternatives to speech restrictions fall well short of the mark. Far from working "equally well" as the FDA's chosen approach, as the majority asserted,[321] they range from ineffectual to impracticable to just plain ridiculous. The first of five policies proposed by the majority was to "guide physicians and patients in differentiating between misleading and false promotion, exaggerations and embellishments, and truthful or non-misleading information."[322] The nation's experience prior to the 1962 FDCA amendments amply demonstrated that physicians could not distinguish between truthful and misleading claims of drug efficacy, in part because of misleading promotional statements.[323] Even if didactic strategies for distinguishing among the types of claims made in off-label promotion and understanding the evidence base underlying them could be identified, along with strategies for effectively reaching every physician with this information, it is inconceivable that the

319. *See supra* notes 42–53 and accompanying text.
320. *See supra* notes 42–53 and accompanying text.
321. United States v. Caronia, 703 F.3d 149, 168 (2d Cir. 2012).
322. *Id*.
323. Waxman, *supra* note 10, at 306–07.

government would appropriate funding at a level sufficient to create an effective counterweight to the $50 billion that pharmaceutical companies spend each year on promotion to physicians.[324]

The second proposed policy was for the FDA to "develop its warning or disclaimer systems or develop safety tiers within the off-label market."[325] Experience in the field of "nutraceuticals" has sufficiently demonstrated the ineffectiveness of warning labels that alert consumers that the FDA has not validated the health claims made about the product.[326] Consumers spend billions on vitamins and minerals with such labels that have no proof of efficacy.[327] Disclaimers were also deemed an inadequate remedy for the proliferation of unsubstantiated claims of efficacy prior to the 1962 amendments to the FDCA that required manufacturers to demonstrate effectiveness as well as safety.[328] It defies understanding how the FDA could develop "safety tiers" for off-label uses of drugs since by very definition these are uses for which all of the data that manufacturers purport to have amassed are not provided to the FDA for review. Even if the FDA developed a tiering system based on publicly available data, sales representatives could argue (probably correctly) that the ratings were not based on all of the available information known to the manufacturer. Finally, because disclaimers have little

324. Kesselheim, Mello & Avorn, *supra* note 21, at 446 (citation omitted).

325. *Caronia*, 703 F.3d at 168.

326. *See* Tonya Dodge, Dana Litt & Annette Kaufman, *Influence of the Dietary Supplement Health and Education Act on Consumer Beliefs About the Safety and Effectiveness of Dietary Supplements*, 16 J. HEALTH COMM. 230, 230 (2011) ("[I]nformation about FDA approval failed to have a statistically significant effect on beliefs about safety or effectiveness of the dietary supplement."). *See generally* Marlys J. Mason & Debra L. Scammon, *Health Claims and Disclaimers: Extended Boundaries and Research Opportunities in Consumer Interpretation*, 19 J. PUB. POL'Y & MARKETING 144 (2000) (finding no evidence to support the effectiveness of disclaimers related to health claims).

327. *See* Eliseo Guallar et al., *Enough Is Enough: Stop Wasting Money on Vitamin and Mineral Supplements*, 159 ANNALS INTERNAL MED. 850, 850 (2013) ("[S]ales of multivitamins and other supplements have not been affected by major studies with null results, and the U.S. supplement industry continues to grow, reaching $28 billion in annual sales in 2010.").

328. Waxman, *supra* note 10, at 300 ("[D]isclaimers disclosing the state of the evidence supporting a claim . . . were inadequate to stop deceptive and dangerous products . . . . Disclaimers cannot in any way address the grave harm to patients caused by a marketplace in which no one is sure which products work and which do not . . . ."). Disclaimers were judged inadequate even when directed at physicians rather than less sophisticated consumers. *See id.* at 311 (arguing persuasively that both a required statement that the FDA has not reviewed the claim and a required statement disclosing evidence sufficient for consumers to gauge the truth of the claim would provide little useful information to prescribers).

effect on consumers' purchasing decisions, having to put a disclaimer on the labeling probably would not provide sufficient incentive for manufacturers to seek FDA approval for new drug uses.[329]

The court's third proposal was that the government require manufacturers to "list all applicable or intended indications when they first apply for FDA approval, enabling physicians, the government, and patients to track a drug's development."[330] This information would indeed be helpful in creating a roadmap for tracking the course of a drug's diffusion into clinical practice, particularly if it was incorporated into a living document that was updated over the drug's lifecycle as new uses emerge in clinical practice or are investigated by the manufacturer.[331] It is not clear, however, why the *Caronia* majority thought this would advance the government's interests in safeguarding the integrity of its drug-approval process or protecting patients from unsafe and ineffective drugs. Requiring companies to go on record as to other potential uses of their drug does nothing to eliminate the incentive problem that is created when they are not required to seek FDA approval for those uses in order to promote them without restriction. Nor does it give physicians useful information with which to evaluate off-label uses or promotional communications about off-label uses, or create any mechanisms to protect patients from unsafe prescribing.

The court's fourth suggestion was that the FDA impose "ceilings or caps on off-label prescriptions" or other mechanisms to restrict the amount of off-label prescribing directly—or to prohibit off-label prescribing entirely.[332] Such suggestions are nonstarters for two reasons. First, direct regulation of the practice of medicine is outside the FDA's jurisdiction.[333] Second, the FDA recognizes that off-label

329. Conko, *supra* note 220, at 180–81.

330. *Caronia*, 703 F.3d at 168.

331. *Cf.* COMM. ON ETHICAL AND SCIENTIFIC ISSUES IN STUDYING THE SAFETY OF APPROVED DRUGS, INST. OF MED., ETHICAL AND SCIENTIFIC ISSUES IN STUDYING THE SAFETY OF APPROVED DRUGS 110–11 (2012) (proposing that all newly approved drugs, as well as already approved drugs about which there are lingering concerns regarding safety or efficacy, have a Benefit-Risk Assessment and Management Plan outlining what is known about the drug and what plans exist for reducing uncertainty about safety and effectiveness).

332. *Caronia*, 703 F.3d at 168.

333. *See Promotion of Unapproved Drugs and Medical Devices*, *Testimony Before the S. Comm. on Labor and Human Res.*, 104th Cong. (1996) (statement of William B. Schultz, Deputy Comm'r for Policy, Food & Drug Admin.), *available at* http://www.fda.gov/NewsEvents/Testimony/ucm115098.htm ("Thus, once a drug is approved for marketing, FDA does not generally regulate how, and for what uses, physicians prescribe that drug.").

prescribing can be helpful, and indeed, lifesaving in some clinical situations,[334] and has no apparent wish to deprive the public of those benefits. It is ludicrous to suggest it would ban off-label prescribing even if it had legal authority to do so and equally nonsensical to propose that physicians be allowed to write only a certain number of prescriptions off label. A blunt cap of that nature would do nothing to distinguish between appropriate and inappropriate off-label prescribing.[335] Such a policy arrow is not in the FDA's quiver, and it would land nowhere near the FDA's target of preventing harm from inappropriate prescribing while preserving physicians' discretion to determine when off-label use is clinically appropriate and ensuring that they have accurate information with which to do so.

Finally, the court suggested that the government could "remind physicians and manufacturers of, and even perhaps further regulate, the legal liability surrounding off-label promotion and treatment decisions."[336] This proposal springs from a demonstrably wrong notion that physicians and drug companies are unaware that they operate under a substantial risk of being sued in tort. Much of the most perverse behavior in medicine, such as "defensive medicine" and secrecy concerning medical errors, springs from physicians' perceptions that they practice every day under the threat of potentially catastrophic malpractice litigation.[337] Similarly, drug companies are acutely aware of the threat of product-liability suits and have threatened action against the public interest, including discontinuation of essential products like vaccines, in response.[338] Ratcheting up their perceived liability pressure is highly unlikely to produce a socially desirable response. Because no non-speech-restricting alternative policy could achieve the government's interest even marginally and because the FDA has taken reasonable steps to allow companies to communicate truthful information about off-label uses in a responsible way, the FDA's regulatory scheme for off-label

334. *See id.* ("FDA knows that there are important off label uses of approved drugs.").

335. *See Caronia*, 703 F.3d at 179–80 (Livingston, J., dissenting) ("A ceiling on off-label prescriptions . . . could needlessly (and simultaneously) result in the denial of some effective treatments and the over-prescription of ineffective and even dangerous ones. Finally, a ban on off-label prescriptions would be no better. Indeed, it would constitute an unprecedented intrusion into the practice of medicine . . . .").

336. *Id.* at 168 (majority opinion).

337. *See* Michelle M. Mello et al., *"Health Courts" and Accountability for Patient Safety*, 84 MILBANK Q. 459, 472 (2006).

338. Aaron S. Kesselheim, *Safety, Supply, and Suits: Litigation and the Vaccine Industry*, 364 NEW ENG. J. MED. 1485, 1485 (2011).

promotion should be considered narrowly tailored under *Central Hudson*.

E. Expanded Use of "Safe Harbors" For Off-Label Promotion

A final strategy that the FDA could take to maintain oversight of off-label marketing in an era of expanding commercial speech protection is to adjust its current regulatory approach concerning off-label promotion "safe harbors." The goal of this strategy would be to provide a broader set of pathways for off-label promotion while providing mechanisms to help ensure the reliability of the communications. As discussed above, the FDA already offers meaningful pathways for off-label communications that meet certain quality standards—for example, by permitting distribution of peer-reviewed journal articles discussing off-label uses.[339] Providing additional opportunities for speech about off-label uses may help bolster the argument that the FDA's regulatory scheme is narrowly tailored to advancing the goal of protecting the public from unsafe prescribing.

Below, we discuss two potential mechanisms that the FDA could use for this purpose, both of which represent new applications of evidentiary standards already articulated in FDA regulations. The regulations set forth three alternative forms of evidence that can form the basis for a manufacturer to advertise a use of the drug that is described in the drug's labeling.[340] Advertisements are permitted for uses "for which the drug is generally recognized as safe and effective among experts," "for which there exists substantial evidence of safety and effectiveness" from "well-controlled investigations," and for uses "for which there exists substantial clinical experience" that is "adequately documented in medical literature or by other data."[341] Any one of these forms of evidence is sufficient to support advertisements. This regulation does not apply to promotion of off-label uses—but it could be expanded to encompass them. Specifically, we suggest expansion of the "substantial clinical experience" and "substantial evidence" standards. This move would provide a way for the FDA to permit speech about off-label uses while ensuring that promotional communications hew closely to the evidence about a drug's safety and efficacy.

339. *See supra* notes 42–45.
340. *See* 21 C.F.R. § 202.1 (2013).
341. *Id.* § 202.1(e)(4)(ii).

1. Use of the "Substantial Clinical Experience" Standard

The first approach is to permit off-label communications in circumstances in which the manufacturer can document that the statements reflect substantial clinical experience. When evaluating data that manufacturers submit regarding a drug's efficacy, the FDA usually applies a "substantial evidence" standard, but FDA rules stipulate that advertisements about a drug's efficacy for uses described in the labeling may instead rest on documentation of "substantial clinical experience."[342] Substantial clinical experience is defined as "substantial clinical experience adequately documented in medical literature or by other data (to be supplied to the Food and Drug Administration, if requested . . .), on the basis of which it can fairly and responsibly be concluded by qualified experts that the drug is safe and effective for such uses . . . ."[343]

The FDA has already made limited use of this standard. For instance, a 2011 guidance document permitted manufacturers to promote antihypertensive drugs as efficacious in producing health outcomes not specifically tested in clinical trials based on a "substantial clinical experience" rationale.[344] Usually, manufacturers promoting their drug must make their advertising claims strictly relate to the outcomes of the studies that they used to get the drug approved, and these are the studies that are described in the labeling.[345] For most manufacturers of antihypertensive drugs, those outcomes are reduction in patients' blood pressures or in the incidence of clinical hypertension. However, these are intermediate outcomes, and such manufacturers would naturally prefer to claim in their marketing materials that regular use of their drugs in patients with hypertension can prevent death due to cardiovascular events.

For a manufacturer that used only intermediate outcomes in getting its new antihypertensive medication approved, such a claim would be considered off-label promotion because the mortality endpoint was not included in the trials or mentioned in the labeling. In its 2011 guidance, however, the FDA announced that based on the accumulated literature, it would allow manufacturers of approved

342. *Id.* § 202.1(e)(4)(ii)(c).

343. *Id.*

344. U.S. FOOD & DRUG ADMIN., DEP'T OF HEALTH & HUMAN SERVS., OMB CONTROL NO. 0910-0670, GUIDANCE FOR INDUSTRY: HYPERTENSION INDICATION: DRUG LABELING FOR CARDIOVASCULAR OUTCOME CLAIMS 3, 5 (2011) [hereinafter HYPERTENSION INDICATION], *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075072.pdf.

345. § 202.1(e)(4)(i)(b).

antihypertensives to make claims about improved cardiovascular outcomes even if those outcomes were not tested in their randomized trials.[346] The FDA's stated rationale was that "blood pressure control is well established as beneficial in preventing serious cardiovascular events."[347] Going forward, the FDA's guidance means that manufacturers of newer antihypertensive drugs like aliskerin (Tekturna), which was approved based on clinical trials showing that it lowered patients' blood pressure, can promote their drugs as effective in reducing cardiovascular mortality even though aliskerin's labeling explicitly states that there are "no controlled trials demonstrating risk reduction" of fatal and nonfatal cardiovascular events with the drug.[348]

Application of the "substantial clinical experience" standard in this antihypertensive drug scenario had two distinguishing features. First, the decision was based on decades of clinical experience with hypertension, antihypertensive drugs, and patient outcomes.[349] Second, the announcement that off-label marketing would be permitted came in an official, prospective FDA guidance document, rather than in an ad hoc response to an individual manufacturer's request.[350] Creation of such a guidance document involves substantial internal deliberation and may involve input from outside experts.[351] These two features should undergird broader applications of the "substantial clinical experience" pathway as well. They increase the likelihood that the information disseminated through off-label promotion will be evidence-based and reliable.

Thus, we suggest that the FDA could modify this regulation to apply the same standard to advertisements of off-label uses and take steps to publicize the availability of this avenue of off-label promotion—for example, in a guidance document. The main

346. HYPERTENSION INDICATION, *supra* note 344, at 1; Aaron S. Kesselheim & Jerry Avorn, *The Food and Drug Administration Has the Legal Basis to Restrict Promotion of Flawed Comparative Effectiveness Research*, 31 HEALTH AFF. 2200, 2201 (2012).

347. HYPERTENSION INDICATION, *supra* note 344, at 1.

348. U.S. FOOD & DRUG ADMIN., HIGHLIGHTS OF PRESCRIBING INFORMATION: TEKTURNA 2 (2012), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021985s023lbl.pdf.

349. *See* NAT'L INSTS. OF HEALTH & NAT'L HEART, LUNG, & BLOOD INST., DEP'T OF HEALTH & HUMAN SERVS., THE SEVENTH REPORT OF THE JOINT NATIONAL COMMITTEE ON PREVENTION, DETECTION, EVALUATION, AND TREATMENT OF HIGH BLOOD PRESSURE 1 (2004), *available at* http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf.

350. *See* HYPERTENSION INDICATION, *supra* note 344, at 1.

351. Eric Colman, *Food and Drug Administration's Obesity Drug Guidance Document: A Short History*, 125 CIRCULATION 2156, 2156 (2012).

advantage of the process is that it would be less rigid—and less expensive—than a formal supplemental NDA,[352] the traditional route through which the FDA would have required antihypertensive drug manufacturers to change their labeling to include patient mortality as a reasonably predicted outcome.

A limitation of this arrangement is that the substantial clinical experience standard has to this point been rarely invoked by FDA, meaning that this proposal will not expand off-label marketing opportunities for manufacturers far beyond the current precepts. It may also take some time for the FDA to formally consider a request for expanded marketing made under this principle. The 2011 hypertension guidance, for example, originally arose out of an FDA Advisory Committee that reviewed class labeling for antihypertensive drugs in June 2005.[353] But as the FDA and its constituencies become more comfortable with this pathway, bureaucratic adjustments could make it more efficient and systematic.

2. Application of the "Substantial Evidence" Standard to Observational Research on Drug Safety

In addition to expanded use of the "substantial clinical experience" standard, the FDA might be able to provide additional accommodations beyond its current flexibilities to evidence-based off-label marketing in certain cases by expanding its view of what constitutes "substantial evidence." Specifically, it could recognize the possibility that manufacturers could submit well-controlled observational research supporting a claimed safety benefit of their drug.[354]

The advertising regulations define "substantial evidence" by reference to any "adequate and well-controlled" investigation,[355] but the FDA's current posture appears to militate against the view that observational studies can satisfy the standard—even though observational studies can be designed to include comparators and

352. *See* 21 C.F.R. § 314.50(d)(5) (2013) (summarizing the new drug application process).

353. HYPERTENSION INDICATION, *supra* note 344, at 2 ("On June 15, 2005, the Cardiovascular and Renal Drugs Advisory Committee met in open public session to discuss class labeling for cardiovascular outcome claims for drugs that are indicated to treat hypertension.").

354. *See* Stuart L. Silverman, *From Randomized Controlled Trials to Observational Studies*, 122 AM. J. MED. 114 (2009).

355. § 202.1(e)(4)(ii)(b).

strong controls for confounding.[356] For example, the pharmaceutical manufacturer Hoffman-La Roche received a warning letter in 2010 regarding promotional materials for saquinavir (Invirase), a protease inhibitor for treatment of human immunodeficiency virus that it advertised as posing a lower risk of myocardial infarction than other drugs in its class.[357] The communications at issue represented off-label marketing because the manufacturer was promoting its drug as providing benefits—greater safety than a competitor—that were not in the drug's approved labeling.[358] The warning letter arose because the off-label marketing was based on a "retrospective nested case-control study," which the FDA claimed was unreliable because it was an observational study from which "[f]irm conclusions about the risks of specific antiretroviral agents cannot be drawn."[359] Rather, the FDA asserted, "A randomized, controlled trial would need to be conducted to determine the comparative effects of different treatments."[360]

Though the FDA may have been right about the strength of observational evidence in this particular case,[361] the absolutist language in its warning letter seems to preclude the possibility that observational research could ever be used to support a claim of comparative advantage. To the contrary, large-scale observational studies are particularly well-suited for detecting and quantifying drug safety problems.[362] Randomized trials have several weaknesses as a mechanism of detecting safety problems, chief among them that their small sample sizes mean they are often inadequately powered to

356. The FDA's regulations generally consider that the adequate and well-controlled investigation standard should be met with trials that compare treatment with the test drug to an active or inactive comparator. *Id.* § 314.126(b)(2). However, these regulations permit flexibility in the level of evidence that the FDA may accept in making judgments. *Id.* For example, the FDA's regulation permits historical controls, with the caveat that "[b]ecause historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances." *Id.* § 314.126(b)(2)(v).

357. Letter from Lynn Panholzer, Regulatory Review Officer, U.S. Food & Drug Admin., to Inna Kissen, Dir., Dep't of Regulatory Affairs, Hoffman-La Roche, Inc. (Apr. 8, 2010), *available at* http://www.fda.gov/downloads/drugs/guidancecompliance regulatoryinformation/enforcementactivitiesbyfda/warninglettersandnoticeofviolationlette rstopharmaceuticalcompanies/ucm209517.pdf (discussing NDA numbers 20-628, 21-785 (Invirase (saquinavir mesylate) capsules and tablets)).

358. *Id.* at 2.

359. *Id.* at 3.

360. *Id.*

361. *See* Kesselheim & Avorn, *supra* note 346, at 2202.

362. *See, e.g.*, Jerry Avorn, *In Defense of Pharmacoepidemiology—Embracing the Yin and Yang of Drug Research*, 357 NEW ENG. J. MED. 2219, 2220 (2007); COMM. ON ETHICAL AND SCIENTIFIC ISSUES IN STUDYING THE SAFETY OF APPROVED DRUGS, *supra* note 331, at 181–84.

measure uncommon adverse events.[363] A strong argument can be made that rigorous and well-controlled observational studies can provide "substantial evidence" to support marketing statements about a drug's safety profile. Indeed, the FDA has often used observational studies as the basis for changing drug labeling to better warn about possible adverse events, including adding black box warnings, which are the strongest safety warning available. For example, in 2008, the FDA added a black box warning to conventional antipsychotic drugs such as haloperidol (Haldol) describing increased risk of death for elderly patients with dementia-related psychosis taking the drug.[364] The warning was added on the basis of two government-funded observational research trials that evaluated the risk of conventional antipsychotics like haloperidol compared against the risk of more recent "atypical" antipsychotics, which already had a black box warning about death in elderly patients.[365]

If the FDA showed greater openness to the view that comparative observational research could provide support for manufacturers' safety-related promotional statements, that could provide another pathway—short of formal supplemental new drug applications—through which manufacturers could receive prospective approval for some kinds of off-label marketing about their products. There is already flexibility within the FDCA to permit the FDA to consider observational studies or other evidence short of prospective randomized trials as offering "substantial evidence" for a given finding because the FDCA does not specify that substantial evidence needs to be supported by randomized controlled trials, only "adequate and well-controlled investigations."[366] However, because of the risk that such studies can yield unreliable results if not carefully designed and conducted, the FDA's current wariness about authorizing off-label marketing based on them is understandable.[367]

363. *See* COMM. ON ETHICAL AND SCIENTIFIC ISSUES IN STUDYING THE SAFETY OF APPROVED DRUGS, *supra* note 331, at 173–77; Avorn, *supra* note 362, at 2220.

364. U.S. FOOD & DRUG ADMIN., INFORMATION FOR HEALTHCARE PROFESSIONALS: CONVENTIONAL ANTIPSYCHOTICS (2008), *available at* www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm124830.htm.

365. Sudeep S. Gill et al., *Antipsychotic Drug Use and Mortality in Older Adults with Dementia*, 146 ANNALS INTERNAL MED. 775, 775, 784 (2007); Sebastian Schneeweiss et al., *Risk of Death Associated with the Use of Conventional Versus Atypical Antipsychotic Drugs Among Elderly Patients*, 176 CANADIAN MED. ASS'N J. 627, 627 (2007).

366. 21 U.S.C. § 355(d) (2012).

367. *See* Kesselheim and Avorn, *supra* note 346, at 2202.

To clarify its expectations, the FDA could issue a formal guidance document describing the features of high-quality observational research and the circumstances under which it might be sufficient (for example, defining adverse event rates or clarifying randomized trial findings) to support off-label marketing claims.[368] This approach would permit manufacturers to engage in truthful, evidence-based communications about off-label uses while helping to assure that unsubstantiated marketing claims do not provoke inappropriate, unsafe prescribing.

CONCLUSION

The Second Circuit's decision in *Caronia* is the latest in a stream of high-profile cases enunciating an expanding scope of judicial recognition of commercial-speech rights. Decisions by the Supreme Court and courts of appeals evince particular judicial distaste for attempts to regulate pharmaceutical promotion, based in part on the claimed public health importance of the free flow of truthful information about medical products and in part from the role that physicians, as sophisticated intermediaries, play as receptors of pharmaceutical promotional communications. However, in the case of off-label promotion, neither of these assumptions stands up to closer scrutiny, and years of experience with industry marketing practices leading to dangerous, non-evidence-based off-label uses of medical products justify the need for regulation in this arena.

The immediate effect of *Caronia* on the FDA's efforts to police off-label promotion are unclear: the FDA has voiced the opinion that its enforcement efforts can proceed unhindered, but the decision would appear to preclude some of its traditional enforcement practices, at least in the Second Circuit states. Significant retrenchment in the agency's enforcement activity would likely lead to adverse health consequences. Companies would likely feel emboldened to engage in more promotional communications with fewer incentives to ensure that promotional statements have an evidentiary basis, and they would find less reason to seek FDA

368. A recent report by an Institute of Medicine committee also came to the conclusion that formal guidance on the appropriate design and use of observational studies for assessing drug safety is needed. *See* COMM. ON ETHICAL AND SCIENTIFIC ISSUES IN STUDYING THE SAFETY OF APPROVED DRUGS, *supra* note 331, at 159 (recommending that the FDA issue a guidance document on the use of Bayesian methods); *id.* at 160 (recommending "guidance and review processes that ensure that observational studies with high internal validity are given appropriate weight in the evaluation of drug harms"); *id.* at 162 (recommending that the FDA develop guidance on use of noninferiority designs to assess drug safety).

approval for new uses of their products. Such moves would heighten the prevalence of prescribing decisions that put patients at undue risk without offsetting benefits.

To help avoid such consequences, we suggest several avenues along which the FDA might continue to prosecute off-label promotion and defend its existing regulatory framework against future challenges. Although the courts' commercial-speech jurisprudence over the last three decades is dispiriting for advocates of restrictions on off-label promotion, fighting to ensure that a regulatory regime is in place to promote accurate and unbiased promotional communications is a public health imperative.