# RECENT CASES

FIRST AMENDMENT — COMMERCIAL SPEECH — SECOND CIRCUIT HOLDS THAT PROHIBITING TRUTHFUL OFF-LABEL PROMOTION OF FDA-APPROVED DRUGS BY PHARMACEUTICAL REPRESENTATIVES VIOLATES FIRST AMENDMENT. — *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012).

Government regulation of pharmaceutical marketing has recently emerged as an important First Amendment issue. The Food and Drug Administration (FDA), pursuant to the Federal Food, Drug, and Cosmetic Act[1] (FDCA), approves all new drugs and drug labeling before commercial distribution. The labeling must set forth approved uses, and any unapproved use is considered "off-label."[2] Despite the fact that physicians can prescribe, and patients can use, drugs for off-label purposes, the government has construed the FDCA to prohibit off-label promotion[3] and frequently prosecutes pharmaceutical companies and their representatives for such activity.[4] Recently, in *United States v. Caronia*,[5] the Second Circuit held that the prohibition and criminalization of truthful off-label promotional speech by pharmaceutical companies and their representatives violates the First Amendment.[6] The *Caronia* ruling is consistent with the evolution of the commercial speech doctrine; however, the holding is undesirable from a policy perspective because it undermines substantial regulatory and public health interests.

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[1] 21 U.S.C. §§ 301–399f (2012).

[2] Joseph J. Leghorn et al., *The First Amendment and FDA Restrictions on Off-Label Uses: The Call for a New Approach*, 63 FOOD & DRUG L.J. 391, 392 (2008).

[3] The FDCA does not explicitly prohibit manufacturers from promoting FDA-approved drugs for off-label purposes, but two related statutory provisions — on labeling and misbranding, respectively — have operated to that effect. *See* 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, 1558 (2009). First, pharmaceutical manufacturers must obtain FDA approval before introducing new drugs and drug labels into interstate commerce. 21 U.S.C. § 355(a), *amended by* Pandemic and All-Hazards Preparedness Reauthorization Act of 2013, Pub. L. No. 113-5, § 301, 127 Stat. 161, 179. Marketing a drug for uses not specified on the label violates this provision. 21 C.F.R. §§ 202.1(e)(4), 310.3(h) (2013). Second, pharmaceutical manufacturers are prohibited from introducing "misbranded" drugs into interstate commerce. 21 U.S.C. § 331(a). A drug is "misbranded" if, inter alia, its labeling does not contain "adequate directions for use," *id.* § 352(f)(1), or "directions under which the layman can use a drug safely and for the purposes for which it is intended," 21 C.F.R. § 201.5. "Intended uses" encompasses all uses objectively intended by the manufacturer, as reflected in labeling, advertisements, and statements by representatives. *Id.* § 201.128.

[4] *See* Aaron S. Kesselheim, *Off-Label Drug Use and Promotion: Balancing Public Health Goals and Commercial Speech*, 37 AM. J.L. & MED. 225, 240–42 (2011) (identifying Department of Justice settlements for illegal off-label marketing totaling approximately $8 billion over the past decade).

[5] 703 F.3d 149 (2d Cir. 2012).

[6] *See id.* at 168–69.

In July 2002, Orphan Medical, Inc. received FDA approval to market Xyrem, a central nervous system depressant, to treat cataplexy in narcolepsy patients.[7] Xyrem has severe side effects and, if abused, can cause depression, seizures, coma, and death.[8] To protect against these safety risks, the FDA mandated "black box" labeling — the most serious warning on prescription medication — and national distribution from a single pharmacy.[9] In March 2005, Orphan hired Alfred Caronia as a sales consultant to promote Xyrem.[10] Shortly thereafter, the federal government began a criminal investigation into alleged off-label promotion of Xyrem by Orphan, Caronia, and Dr. Peter Gleason, a physician hired by the company to promote Xyrem through its "speaker programs."[11] In audio-recorded conversations with prospective physician customers, Caronia promoted Xyrem for unapproved uses, including unapproved indications (such as fibromyalgia, insomnia, and chronic pain) and unapproved populations (namely, patients under sixteen).[12] The government charged Caronia with two misdemeanor offenses under the FDCA: conspiracy to misbrand a drug and introduction of a misbranded drug into interstate commerce.[13] Caronia filed a motion to dismiss, arguing, inter alia, that the government's construction of the FDCA misbranding provisions violated his right to free speech under the First Amendment.[14]

The federal district court denied Caronia's motion.[15] The court first determined that off-label promotion constitutes commercial speech.[16] The court then applied the four-prong analysis set forth in *Central Hudson Gas & Electric Corp. v. Public Service Commission*[17] to determine whether the commercial speech regulation was consistent with the First Amendment.[18] First, as a threshold matter, to qualify for First Amendment protection, the speech must concern lawful activity and not be mis-

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[7] *Id.* at 155. In November 2005, the FDA also approved Xyrem to treat excessive daytime sleepiness in narcolepsy patients. *Id.*

[8] *Id.*

[9] *Id.* Xyrem's black box labeling stated, inter alia, that safety and efficacy were not established in patients under sixteen, and that experience in elderly patients was limited. *Id.*

[10] *Id.* at 155–56.

[11] *Id.* at 156. Speaker programs enlist physicians, for pay, to discuss FDA-approved drug uses with other physicians. *Id.*

[12] *See id.* at 156–57.

[13] *Id.* at 157.

[14] *Id.* at 158.

[15] United States v. Caronia, 576 F. Supp. 2d 385, 403 (E.D.N.Y. 2008).

[16] *Id.* at 396. Promotional activity is protectable as "commercial speech" if (1) it is an advertisement, (2) it refers to a specific product, and (3) the speaker has an economic motivation. *See id.* (citing Bolger v. Youngs Drug Prods. Corp., 463 U.S. 60, 66–68 (1983)).

[17] 447 U.S. 557 (1980).

[18] *See Caronia*, 576 F. Supp. 2d at 396 (citing Thompson v. W. States Med. Ctr., 535 U.S. 357, 367 (2002)).

leading.[19] Second, the asserted government interest must be substantial.[20] Third, the regulation must directly advance that interest.[21] Fourth, the regulation must be narrowly drawn and not more extensive than necessary.[22] Applying *Central Hudson*, the court upheld the constitutionality of the FDA regime.[23] A federal jury ultimately convicted Caronia for conspiracy to introduce a misbranded drug into interstate commerce.[24]

The Second Circuit vacated the conviction and remanded.[25] Writing for a divided panel, Judge Chin[26] first determined that Caronia was prosecuted for his speech, not for his conduct: off-label promotion did not merely serve as "evidence of intent" to introduce a misbranded drug into interstate commerce but, instead, constituted the actus reus of the crime.[27] The court then engaged in a two-part inquiry, mirroring the Supreme Court's approach in *Sorrell v. IMS Health Inc.*[28] (which was decided after Caronia's conviction), to determine whether the government's construction of the FDCA misbranding provisions was constitutional.[29]

First, the court observed that the ban on off-label promotion targeted speech with a particular content (truthful off-label marketing) when expressed by particular speakers (drug manufacturers).[30] Such content- and speaker-based restrictions warrant heightened scrutiny.[31]

Second, rather than determine the precise level of heightened scrutiny, the court concluded that the criminal prohibition would fail under even the less onerous *Central Hudson* test.[32] The first two prongs were "easily satisfied": off-label speech concerns lawful activity and is not inherently misleading, and the government has substantial inter-

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[19] *Cent. Hudson*, 447 U.S. at 566.

[20] *Id.*

[21] *Id.*

[22] *Id.* at 565–66.

[23] *See Caronia*, 576 F. Supp. 2d at 402.

[24] *Caronia*, 703 F.3d at 152.

[25] *Id.* at 169. On appeal, the court had two avenues to affirm the conviction: by determining that Caronia's off-label promotion served as evidence of intent, or by upholding the constitutionality of the FDA regime under *Central Hudson*. This comment focuses on the latter.

[26] Judge Chin was joined by Judge Raggi.

[27] *Caronia*, 703 F.3d at 160–62.

[28] 131 S. Ct. 2653 (2011). In *Sorrell*, the Supreme Court invalidated a Vermont statute on First Amendment grounds. *See id.* at 2672. The statute prohibited "detailing," a pharmaceutical marketing practice by which pharmaceutical companies use prescriber-identifying information to refine marketing practices and increase drug sales. *See id.* at 2659–60.

[29] *Caronia*, 703 F.3d at 164. Caronia also challenged his conviction on the basis of improper jury instructions; however, the court decided the case on First Amendment grounds alone. *Id.* at 160 n.7.

[30] *See id.* at 164–65.

[31] *See id.* at 163, 165 (citing *Sorrell*, 131 S. Ct. at 2667).

[32] *Id.* at 164. Heightened scrutiny includes strict and intermediate scrutiny. *Id.*

ests in drug safety and public health.[33] However, the third prong was not satisfied: since off-label use itself is legal, restricting off-label promotion does not directly advance the government's interests and instead "'paternalistically' interferes with the ability of physicians and patients to receive potentially relevant treatment information."[34] The government's construction of the FDCA "legalizes the outcome — off-label use — but prohibits the free flow of information that would inform that outcome."[35] Finally, under the fourth prong, the court determined that a complete and criminal ban was more extensive than necessary, as less restrictive alternatives — including off-label disclaimers and limits on off-label prescriptions — were available.[36]

Judge Livingston dissented.[37] She first argued that the government properly used speech as evidence of Caronia's intent to introduce a misbranded drug into interstate commerce.[38] However, even if Caronia was prosecuted for his speech, the government's construction of the FDCA misbranding provisions survives scrutiny under *Central Hudson* and *Sorrell* because it directly advances a substantial government interest and is narrowly drawn.[39] Finally, Judge Livingston warned that the decision "extends heightened scrutiny further than the Supreme Court ever has, and calls into question a fundamental regime of federal regulation that has existed for more than a century."[40]

The Second Circuit ruling is consistent with the Supreme Court's modern commercial speech jurisprudence, which may in part explain why the government decided not to appeal.[41] However, the case illustrates the dangers of applying an increasingly stringent commercial speech inquiry to prescription drug regulations. These dangers arise from the confluence of three factors: (1) the financial incentives of pharmaceutical companies and their representatives, (2) the limited in-

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[33] *Id.* at 165–66.

[34] *Id.* at 166 (citing Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc., 425 U.S. 748, 770 (1976)).

[35] *Id.* at 167.

[36] *Id.* at 167–68.

[37] *Id.* at 169 (Livingston, J., dissenting).

[38] *See id.* at 171–72.

[39] *See id.* at 177.

[40] *Id.* at 182. Judge Livingston identified a troubling extension of the majority's reasoning: "[I]f drug manufacturers have a First Amendment right to distribute drugs for any use to physicians or even directly to patients, then the entire FDCA may well be unconstitutional." *Id.* at 179.

[41] The FDA said in a statement that it does not believe *Caronia* will significantly affect its ability to enforce the FDCA misbranding provisions. Thomas M. Burton, *FDA Won't Appeal Free-Speech Marketing Decision*, WALL ST. J. (Jan. 23, 2013, 8:20 PM), http://online.wsj.com/article/SB10001424127887324539304578260323575925896.html. The Second Circuit ruling is binding only in three states and is limited to *truthful* speech about *legal* off-label uses. Sara A. Poulos & Mitha V. Rao, *What's Left for Plaintiffs in Off-Label Pharmaceutical Promotion Cases After* United States v. Caronia*?*, FED. LAW., May 2013, at 42, 46. Historically, most government settlements have alleged fraudulent or misleading statements. *Id.*

formational value of off-label promotion, and (3) the influence of pharmaceutical marketing on physician prescribing behaviors.

Over the past two decades, the Court has "markedly transformed" the *Central Hudson* doctrine.[42] As originally conceived, *Central Hudson* was an intermediate standard of review; the Court deferred to legislative and administrative judgments and upheld reasonable restraints on commercial speech tailored to further legitimate government interests.[43] More recently, the Court has applied *Central Hudson* to invalidate commercial speech restrictions that do not advance government interests in a material way,[44] that have less restrictive alternatives,[45] and that keep consumers "in the dark for what the government perceives to be their own good."[46] In *Sorrell*, the Court relied on this "unforgiving brand of 'intermediate' scrutiny"[47] to strike down a content- and speaker-based pharmaceutical marketing regulation.[48] The Court also suggested that content-based burdens demand even stricter scrutiny,[49]

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[42] David C. Vladeck, *Lessons from a Story Untold:* Nike v. Kasky *Reconsidered*, 54 CASE W. RES. L. REV. 1049, 1059 (2004). *See generally* Allen Rostron, *Pragmatism, Paternalism, and the Constitutional Protection of Commercial Speech*, 37 VT. L. REV. 527, 532–53 (2013) (describing the ideological dimensions of the Court's commercial speech jurisprudence).

[43] *See* Vladeck, *supra* note 42, at 1055–56, 1059; *see also* Posadas de P.R. Assocs. v. Tourism Co. of P.R., 478 U.S. 328, 331, 342 (1986) (deferring to the "reasonable" judgment of the legislature, *id.* at 342, in upholding a statute that prohibited casino advertising directed at Puerto Rican residents but permitted such advertising directed at nonresidents); Zauderer v. Office of Disciplinary Counsel, 471 U.S. 626, 651 (1985) (upholding disclosure requirements in attorney advertisements as "reasonably related" to the government interest in preventing consumer deception).

[44] *See* 44 Liquormart, Inc. v. Rhode Island, 517 U.S. 484, 505 (1996) (plurality opinion) (invalidating a state ban on liquor price advertising as a means of promoting temperance absent evidence to suggest the restriction would "*significantly* reduce alcohol consumption"); Edenfield v. Fane, 507 U.S. 761, 767–71 (1993) (invalidating a Florida ban on in-person solicitation by accountants).

[45] *See* Thompson v. W. States Med. Ctr., 535 U.S. 357, 371–73 (2002) (invalidating a federal law authorizing pharmacists to compound drugs but prohibiting pharmacists from advertising that service); Lorillard Tobacco Co. v. Reilly, 533 U.S. 525, 562–66 (2001) (invalidating a state regulation restricting outdoor advertising of tobacco products near schools and playgrounds); Rubin v. Coors Brewing Co., 514 U.S. 476, 490–91 (1995) (invaliding a law prohibiting alcohol content labeling citing "less intrusive" alternatives, *id.* at 491). In earlier cases, the Court merely required a "reasonable fit" between the regulation and interest served. *See* Fla. Bar v. Went For It, Inc., 515 U.S. 618, 632 (1995); Bd. of Trs. v. Fox, 492 U.S. 469, 480 (1989); Vladeck, *supra* note 42, at 1058.

[46] *Liquormart*, 517 U.S. at 503 (plurality opinion); *see also Lorillard*, 533 U.S. at 564 (noting that the tobacco industry has an interest in communicating truthful information about its products, and that adult consumers have an interest in receiving that information).

[47] Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2679 (2011) (Breyer, J., dissenting).

[48] *See id.* at 2667, 2672 (majority opinion).

[49] *See id.* at 2664. This language may signal a doctrinal shift; in prior cases, the Court evaluated all commercial speech regulations under *Central Hudson* and reserved stricter scrutiny for content-based *noncommercial* speech regulations. *See id.* at 2677 (Breyer, J., dissenting) (noting that "a standard yet stricter than *Central Hudson*" is unprecedented in the commercial speech context); Samantha Rauer, *When the First Amendment and Public Health Collide: The Court's Increasingly Strict Constitutional Scrutiny of Health Regulations that Restrict Commercial Speech*, 38 AM. J.L. & MED. 690, 705–06 (2012); Richard A. Samp, Sorrell v. IMS Health*: Protecting Free Speech or Resurrecting* Lochner*?*, 2010–2011 CATO SUP. CT. REV. 129, 133–35 (2011).

but ultimately applied the lesser *Central Hudson* test because intermediate scrutiny yielded "the [same] outcome."[50]

Although *Caronia* is defensible as a matter of constitutional doctrine, it is undesirable as a matter of policy. Three factors highlight the adverse regulatory and public health effects of applying a more demanding commercial speech inquiry to prescription drug regulations.

First, drug manufacturers have an incentive to circumvent the FDA approval process — which takes approximately fifteen years and costs an estimated $880 million[51] — by obtaining approval for a small number of on-label uses and then promoting additional off-label uses.[52] Sales representatives have a similar incentive to promote off-label uses, particularly if on-label sales fall below annual targets.[53] For example, Caronia was under pressure to sell his annual quota of 520 bottles of Xyrem when he engaged in several conversations about off-label uses.[54] Such behavior undermines the FDA's status as "gatekeeper"[55] for new drugs and contributes to rising healthcare costs.[56] The prohibition against off-label promotion by pharmaceutical companies and their representatives is "'one of the few mechanisms available' to encourage participation in the approval process."[57]

Second, off-label promotion does not fit neatly within the category of truthful and nonmisleading commercial speech protected by the First

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[50] *Sorrell*, 131 S. Ct. at 2667.

[51] Mitchell Oates, Note, *Facilitating Informed Medical Treatment Through Production and Disclosure of Research into Off-Label Uses of Pharmaceuticals*, 80 N.Y.U. L. REV. 1272, 1278–79 (2005); James O'Reilly & Amy Dalal, *Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, 12 ANNALS HEALTH L. 295, 304 (2003).

[52] *See, e.g.*, Katherine A. Helm, Note, *Protecting Public Health from Outside the Physician's Office: A Century of FDA Regulation from Drug Safety Labeling to Off-Label Drug Promotion*, 18 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 117, 164 (2007); Margaret Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, 58 HASTINGS L.J. 967, 979–80 (2007); Oates, *supra* note 51, at 1280.

[53] For some drugs, off-label uses account for the majority of sales. Johns, *supra* note 52, at 981; *see also* Allison D. Burroughs et al., *Off-Label Promotion: Government Theories of Prosecution and Facts that Drive Them*, 65 FOOD & DRUG L.J. 555, 574 (2010) (noting that off-label sales of Neurontin increased from 1.5% of total Neurontin sales in 1994 to 94% in 2002).

[54] *Caronia*, 703 F.3d at 172 n.3 (Livingston, J., dissenting).

[55] James T. O'Reilly, *Losing Deference in the FDA's Second Century: Judicial Review, Politics, and a Diminished Legacy of Expertise*, 93 CORNELL L. REV. 939, 949 (2008); *see also Caronia*, 703 F.3d at 178 (Livingston, J., dissenting) ("The [FDCA's] 'most substantial innovation' was to require approval of a drug's safety before it could enter the market." (quoting Wyeth v. Levine, 129 S. Ct. 1187, 1195 (2009))).

[56] *See* Kesselheim, *supra* note 4, at 227 (arguing that off-label use can raise drug costs for government payers); RS Stafford, *Off-Label Use of Drugs and Medical Devices: A Review of Policy Implications*, 91 CLINICAL PHARMACOLOGY & THERAPEUTICS 920, 922 (2012) (identifying civil and criminal suits alleging higher state Medicaid program costs due to off-label marketing).

[57] *Caronia*, 703 F.3d at 178 (Livingston, J., dissenting) (quoting Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 72 (D.D.C. 1998), *vacated in part sub nom.* Wash. Legal Found. v. Henney, 202 F.3d 331 (D.C. Cir. 2000)).

Amendment. Drug company research, financed with the expectation of future profits and conducted outside of the FDA oversight process, tends to emphasize the benefits of off-label uses while omitting information about possible risks and contraindications.[58] Thus, off-label promotion may be selective or inadequately supported, rather than demonstrably false or misleading.[59] Caronia, for example, made "truthful" representations to prospective physician customers that Xyrem was a "very safe drug" (despite its black box warning), could treat daytime fatigue (an unapproved use), and had been tested in patients under sixteen (an unapproved patient population).[60] While there is clearly a need for accurate and unbiased information about off-label uses,[61] promotional speech should not be equated with informational or educational speech.[62] The latter can be readily and more reliably obtained outside the marketing context.[63]

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[58] *See* Johns, *supra* note 52, at 981; *see also* Rebecca Dresser & Joel Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37 J.L. MED. & ETHICS 476, 479 (2009); Tamara R. Piety, *Market Failure in the Marketplace of Ideas: Commercial Speech and the Problem that Won't Go Away*, 41 LOY. L.A. L. REV. 181, 212–13 (2007); 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, 311–12 (2003).

[59] *See Caronia*, 703 F.3d at 178 (Livingston, J., dissenting); *see also* 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, 212 (2013) (explaining that inherently misleading speech is not protected by the First Amendment, but "only potentially misleading" speech may be protected). Oral statements made by company representatives are "notoriously difficult to track," further complicating the government's ability to determine whether sales content about off-label uses is "truthful." Mello, Studdert & Brennan, *supra* note 3, at 1558.

[60] *See Caronia*, 703 F.3d at 155–57, 160. Although the "truthful" categorization is dubious, the government did not argue that Caronia's promotion was false or misleading. *See id.* at 166 n.10. Such an argument would "require[] assessing the strength, validity, and appropriateness of evidence for each claim, which is not a simple task." Aaron S. Kesselheim, Michelle M. Mello & Jerry Avorn, *FDA Regulation of Off-Label Drug Promotion Under Attack*, 309 JAMA 445, 446 (2013).

[61] *See* Robert Post, *The Constitutional Status of Commercial Speech*, 48 UCLA L. REV. 1, 56 (2000) (noting that the First Amendment protects the "informational function" of commercial speech).

[62] *Cf.* Piety, *supra* note 58, at 224 ("For First Amendment purposes, the question is, does the evidence of existing incentive structures offer a basis for thinking that more truth would be produced by more protection for commercial speech? It would seem not.").

[63] Although pharmaceutical companies cannot engage in off-label promotional speech under the government's construction of the FDCA, they can communicate about off-label uses in two meaningful ways. First, pharmaceutical companies can respond to unsolicited questions from healthcare professionals about off-label uses. *See* 21 C.F.R. § 99.1 (2013). Second, they can disseminate reprints of scientific or medical journal articles or reference books discussing off-label uses of drugs and devices under certain circumstances. *See 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*, U.S. FOOD & DRUG ADMIN. (Jan. 2009), http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm [hereinafter *Good Reprint Practices*].

Third, pharmaceutical marketing can distort prescribing behaviors, exposing patients to concomitant risks.[64] Physicians tend to prescribe drugs more frequently and nonrationally in response to pharmaceutical promotions.[65] The risks of such practices are heightened for off-label prescribing, which often lacks the scientific support necessary to ensure that doctors make fully informed decisions.[66] This is not to say that off-label drug use should be banned altogether — both the Court and the FDA have recognized that off-label treatments are common, important, and sometimes necessary[67] — but the government has a substantial interest in "minimizing those occasions on which patients use drugs that have not been shown to be safe and effective."[68]

Thus, while *Caronia* is consistent with the contemporary commercial speech doctrine, the decision raises fundamental questions about applying that doctrine in the prescription drug context.[69] A pharmaceutical company's interests in minimizing regulatory costs and in maximizing drug sales are counter to the government's interests in reducing patient exposure to potentially unsafe or ineffective drugs and in preserving the integrity of the FDA drug approval process. The First Amendment can, and should, accommodate reasonable restraints on off-label promotion in support of legitimate regulatory objectives, particularly when those regulations still leave ample room for speech.

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[64] *See generally* David Blumenthal, *Doctors and Drug Companies*, 351 NEW ENG. J. MED. 1885, 1885–88 (2004) (documenting theoretical and empirical literature on the nature, extent, and consequences of industry-physician interactions).

[65] *See* Ashley Wazana, *Physicians and the Pharmaceutical Industry — Is a Gift Ever Just a Gift?*, 283 JAMA 373, 378 (2000) (finding that physician-industry interactions are associated with an inability to identify erroneous claims, a preference for newer and more expensive drugs, and higher prescription rates).

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

[67] *See, e.g.*, Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 350 (2001) (stating that off-label use is an "accepted and necessary corollary of the FDA's mission"); *Good Reprint Practices*, *supra* note 63 (noting that off-label treatment regimens may constitute the "medically recognized standard of care"). An estimated 40% to 60% of prescriptions are for unapproved uses. Johns, *supra* note 52, at 968.

[68] *Caronia*, 703 F.3d at 177 (Livingston, J., dissenting); *see also* Thompson v. W. States Med. Ctr., 535 U.S. 357, 369 (2002) (acknowledging that "the Government has every reason to want as many drugs as possible to be subject to [the FDA] approval process").

[69] Beyond prescription drugs, there is a question of whether the modern commercial speech doctrine threatens other long-established regulatory regimes. *See* Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2685 (2011) (Breyer, J., dissenting) (arguing that the Court may be "open[ing] a Pandora's Box of First Amendment challenges to many ordinary regulatory practices"); Jennifer L. Pomeranz, *No Need to Break New Ground: A Response to the Supreme Court's Threat to Overhaul the Commercial Speech Doctrine*, 45 LOY. L.A. L. REV. 389, 411, 416–17 (2012) (discussing implications for consumer protection and securities regulations).