
DEBATE

OFF-LABEL DRUG PROMOTION AND THE FIRST AMENDMENT

Off-label promotion—pharmaceutical manufacturers’ marketing of FDA-approved drugs for unapproved uses—is considered a First Amendment right by some, a threat to the safety and effectiveness of pharmaceutical drugs by others. Although off-label prescription is legal and often beneficial, the Federal Food, Drug, and Cosmetic Act (FDCA) and corresponding FDA regulations effectively prohibit off-label promotion. The FDA can look to statements by pharmaceutical representatives as evidence of a drug’s intended use, thereby placing manufacturers that promote off-label in a Catch-22: the drug will be subject to the FDCA’s misbranding provisions if manufacturers add labeling instructions for that intended use, but also if they fail to add those instructions. To legally promote a new intended use, pharmaceutical companies must satisfy the FDA’s rigorous approval process. In *United States v. Caronia*, the Second Circuit Court of Appeals ruled that the FDCA could not be interpreted to prohibit truthful, off-label promotion.

Professors Stephanie Greene and Lars Noah debate the constitutionality of the FDA’s prohibitions in light of *Caronia* and the Supreme Court’s increased deference to commercial speakers’ First Amendment rights. Professor Greene argues that *Caronia* was wrongly decided because the court failed to scrutinize the nature of off-label promotion. Greene contends that the truthfulness of off-label information is “speculative, unknown, or inaccessible,” and that the FDA’s restrictions on off-label promotion serve two substantial interests: ensuring that both doctors and consumers receive accurate, scientifically based information, and assuring that drugs have been proven safe and effective. Professor Noah questions Greene’s assumption that promotion of off-label drug uses is presumptively untruthful or misleading. He argues that Supreme Court precedent cuts against Greene’s position, and that the FDA’s restrictions on off-label promotion are unconstitutionally broad because they prevent drug manufacturers from disseminating even truthful and nonmisleading information, and because the FDA could accomplish its goals through less-speech-restrictive means.

OPENING STATEMENT

*FDA Prohibitions on Off-Label Marketing Do Not Violate
Drug Manufacturers' First Amendment Rights*STEPHANIE M. GREENE[†]

Pharmaceutical manufacturers maintain that truthful and nonmisleading promotion of drugs for off-label uses is protected by the First Amendment right to free speech and that regulations that restrict such speech are unconstitutional. This argument ignores the very purpose of the Federal Food, Drug, and Cosmetic Act (FDCA), which seeks to protect the public by ensuring that pharmaceutical drugs are safe and effective for their intended uses. 21 U.S.C. § 393(b) (2012). The truth about the risks and benefits of off-label uses is frequently known only by the manufacturer, whose motivation is to generate sales. In evaluating off-label promotion as commercial speech, courts must recognize that the current regulatory scheme is a response to the tragedies that occurred under prior regimes, when drugs could be freely promoted without proof of their safety or efficacy. Given the government's strong interest in protecting the public health through the approval process for new drugs, restrictions on off-label promotion should withstand constitutional scrutiny, even in the current climate of expanded protection for commercial speech.

Under the FDCA, each new drug must undergo a rigorous approval process to show that it does what it purports to do and that, with respect to its intended uses, the benefits of the drug outweigh the risks. *Id.* § 355. The U.S. Food and Drug Administration (FDA) is charged with overseeing the approval process for new drugs. Part of that process includes reviewing all of the manufacturer's clinical studies, both positive and negative, and approving a label that includes the indications, dosage, precautions, warnings, and contraindications. 21 C.F.R. § 314.50 (2013). The FDA ensures that the labeling is not "false or misleading in any particular." 21 U.S.C. § 355(d). Introducing a drug into interstate commerce without proper labeling constitutes the crime of "misbranding." *Id.* §§ 331(a), 352(a). Although FDA regulations do not directly prohibit off-label promotion,

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such promotion is tantamount to misbranding. Oral statements by pharmaceutical representatives may be used as evidence of a manufacturer's intended use for a drug, 21 C.F.R. § 201.128, thus rendering the drug's labeling subject to scrutiny under the misbranding provisions if it does not contain "adequate directions for [that] use." See 21 U.S.C. § 352(f); 21 C.F.R. § 201.5.

Although misbranding is a crime, off-label prescription is common, with perhaps more than twenty percent of prescriptions written for off-label uses. See David C. Radley et al., *Off-label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1023 (2006). It is not illegal for doctors to prescribe off-label and the FDCA clearly states that it should not be construed to interfere with the practice of medicine. 21 U.S.C. § 396. Off-label prescriptions may have important benefits, especially in cases where there are no other treatment options available. The United States Supreme Court has recognized that off-label prescribing "is an accepted and necessary corollary of the FDA's mission to regulate." *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001). But pharmaceutical companies take advantage of the doctor's right to prescribe off-label, targeting doctors in order to reach new markets for unapproved uses, and thereby avoiding the time and expense required by the FDA approval process.

Detailing, the practice of sales representatives visiting doctors in their offices to promote drugs, is especially effective for off-label promotion. Not only do companies spend substantially more money on marketing than on research, but a substantial proportion of the marketing budget is allocated to detailing. See Puneet Manchanda & Elisabeth Honka, *The Effects and Role of Direct-to-Physician Marketing in the Pharmaceutical Industry: An Integrative Review*, 2 YALE J. HEALTH POL'Y L. & ETHICS 785, 785-86 (2005). Evidence shows that doctors are susceptible to these marketing techniques and that their prescribing habits are impacted. See Adriane Fugh-Berman & Shahram Ahari, *Following the Script: How Drug Reps Make Friends and Influence Doctors*, 4 PLOS MED. 621, 623-24 (2007). The practice of detailing raises ethical issues as it may persuade doctors to prescribe unnecessary or more expensive drugs; these concerns are compounded when sales representatives promote off-label uses that have not been proven safe and effective.

The government has had considerable success in prosecuting drug manufacturers for off-label promotion. See, e.g., Erika Kelton, *Off-Label Pharma Prosecutions Won't Be Silenced by First Amendment Decision*, FORBES (Jan. 4, 2013), <http://www.forbes.com/sites/erikakelton/2013/01/04/off-label-pharma-prosecutions-wont-be-silenced-by-first-amendment-decision>. Increasingly, however, pharmaceutical manufacturers have raised the First Amendment as a defense to (or even in anticipation of) such charges. This defense,

however, rests on manufacturers' unsubstantiated claims that the information they provide is in fact truthful and not misleading. Furthermore, in promoting drugs for off-label use, manufacturers bypass the FDA's approval process, upsetting a system that seeks to assess the risks and benefits of drugs for a particular, intended use. Seizing on language in recent Supreme Court cases that struck down restraints on commercial speech, the industry recently convinced the U.S. Court of Appeals for the Second Circuit that its First Amendment argument has merit. *See United States v. Caronia*, 703 F.3d 149, 152 (2d Cir. 2012). The *Caronia* decision, however, is fraught with flaws. First, the decision fails to recognize that the defendant's off-label promotion was evidence of his intent to misbrand the drug in question. Second, in applying commercial free speech principles, the court gave inadequate consideration to the importance of the FDA's premarket approval process, which is designed to protect the public health.

The pharmaceutical industry's first successful First Amendment challenge involved provisions of the Food and Drug Administration Modernization Act (FDAMA) that restricted the dissemination of information about off-label uses in printed materials such as medical journals. *See Wash. Legal Found. v. Henney*, 56 F. Supp. 2d 81, 83, 87 (D.D.C. 1999), *vacated in part*, 202 F.3d 331 (D.C. Cir. 2000). As a result of that challenge, the FDA altered its interpretation of FDAMA, characterizing it as providing a "safe harbor" for drug manufacturers rather than authorizing the FDA to prohibit or sanction speech. *See Wash. Legal Found.*, 202 F.3d at 335. When the FDAMA "safe harbor" provisions, 65 Fed. Reg. 14,286 (Mar. 16, 2000), expired, the FDA issued a new guidance document that loosened restrictions on drug manufacturers' distribution of medical or scientific journal articles about off-label uses, but still required the information disseminated to be reliable and scientific. *See FDA, 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 2-3* (2009), *available at* <http://www.fda.gov/oc/op/goodreprint.html>.

The early success of the *Washington Legal Foundation* litigation, as well as a series of Supreme Court decisions expanding the scope of First Amendment protection for commercial speech, further emboldened the industry to seek protection for off-label promotion in other arenas, such as the practice of detailing. Recent Supreme Court decisions expanding protection of commercial speech have demonstrated concern with promoting the free flow of factual, verifiable commercial information to help consumers make

informed decisions. In *Sorrell v. IMS Health Inc.*, the Court held that a Vermont statute that prohibited pharmaceutical companies from using prescriber-identifying information for marketing purposes violated the First Amendment. 131 S. Ct. 2653, 2659 (2011). And in *Thompson v. Western States Medical Center*, the Court held that a law that prohibited pharmacies from advertising specific compounded drugs also violated the First Amendment. 535 U.S. 357, 360 (2002). Unlike the factual, verifiable information involved in these cases, claims regarding off-label promotion through detailing are not verifiable because only the manufacturer has access to all of the positive and negative scientific evidence about the drug. Because meetings between doctors and sales representatives occur in the doctor's office and are not open to public scrutiny, it is impossible to know whether the communicated content is truthful or misleading. See Michelle M. Mello et al., *Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals*, 360 NEW ENG. J. MED. 1557, 1558 (2009), available at http://www.hsph.harvard.edu/michelle-mello/files/2012/10/Off-label_PDF.pdf. More importantly, by choosing to promote off-label, manufacturers succeed in evading the FDA approval process, which would require submission of all clinical trial evidence—both positive and negative. This process is in place specifically to provide doctors and the public as much truthful and reliable information as possible.

The Supreme Court's concern that consumers have the information they need to make informed decisions also dictates against protecting off-label marketing. Courts have mistakenly assumed that doctors are able to discern misleading from nonmisleading information provided by drug manufacturers. In *IMS Health*, the Court referred to doctors as "sophisticated and experienced" consumers. 131 S. Ct. at 2671 (citation omitted). The medical literature, however, demonstrates that doctors are not able to distinguish between valid and misleading information. Doctors learn about new products primarily from the pharmaceutical industry and it is rare for them to read in depth about new drugs. JEROME GROOPMAN, HOW DOCTORS THINK 221 (2007).

In *United States v. Caronia*, a panel of the Second Circuit held in a 2–1 decision that provisions of the FDCA could not be interpreted to prohibit truthful, off-label promotion. 703 F.3d at 162. In so holding, the court improperly applied the Supreme Court's analysis in *Western States* and *IMS Health*. Perhaps most importantly, the court did not have the opportunity to consider whether the defendant's statements were truthful and not misleading. If it had, the First Amendment defense would not have succeeded.

The government charged Alfred Caronia, a pharmaceutical sales representative, with misbranding when he promoted the drug Xyrem® for off-label use. *Id.* at 152. Xyrem is a powerful depressant that the FDA approved for

two indications associated with narcolepsy, a serious sleep disorder. *Id.* at 155. Xyrem contains a black box warning, the most serious warning the FDA issues, because its side effects include seizures, coma, and death. *Id.* According to the government, Caronia conspired to misbrand the drug because he promoted it for unapproved uses such as insomnia, fibromyalgia, muscle disorders, and chronic pain. *Id.* at 156-57. Caronia was under substantial pressure to sell the drug for off-label uses as representatives were required to meet an annual sales quota and Caronia was near the bottom of his company's national sales force. *Id.* at 172 n.3 (Livingston, J., dissenting).

Caronia maintained that he was prosecuted for truthful, nonmisleading speech. *See id.* at 160 (majority opinion). The truthfulness of his speech, however, was never an issue at trial since the government believed it needed to show only that he promoted the drug for an off-label use. *Id.* Thus, the court never considered whether Xyrem was safe or effective for the uses that Caronia proposed. Had the truthfulness or misleading nature of Caronia's claims been at the heart of the case, the court's analysis would have been quite different. The Supreme Court has held that the government is "free to prevent the dissemination of commercial speech that is false, deceptive, or misleading, or that proposes an illegal transaction." *Zauderer v. Office of Disciplinary Counsel*, 471 U.S. 626, 638 (1985) (citations omitted). More recently, the Court identified the threshold inquiry in commercial speech cases as whether the speech is misleading: misleading speech, the Court stated, "is not protected by the First Amendment." *Western States*, 535 U.S. at 367.

In prosecuting Caronia, the government could have emphasized the false and misleading nature of the off-label promotion, particularly because Caronia promoted the drug as "very safe." *Caronia*, 703 F.3d at 157. Instead, the government emphasized only the off-label nature of the promotion and the defendant's intent to misbrand the drug by introducing it into commerce. *Id.* at 158-59. A divided panel concluded that Caronia had been improperly convicted for his speech. Although the jury instructions included explanations about the elements of misbranding and conspiring to misbrand, the court found that the government's summation, together with the jury instructions, gave the impression that the off-label promotion itself was prohibited. *See id.* To avoid conflict with the First Amendment, the court concluded that the FDCA should not be construed as criminalizing the simple promotion of a drug's off-label use. *Id.* at 160.

The court should have considered Caronia's speech as evidence of his intent to introduce a misbranded drug into interstate commerce. In *Wisconsin v. Mitchell*, the Supreme Court held that the First Amendment "does not

prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent.” 508 U.S. 476, 489 (1993). Thus, the problem the government encountered in *Caronia* may be rectified by a change in emphasis from off-label speech to intent to misbrand.

Because it considered *Caronia*’s statements truthful, nonmisleading speech, the Second Circuit used *IMS Health* as a template for its First Amendment analysis. *Caronia*, 703 F.3d at 164. In *IMS Health*, the Court offered two different standards for assessing the constitutionality of commercial speech. In addition to citing the traditional *Central Hudson* test for commercial speech restrictions, *IMS Health*, 131 S. Ct. at 2667-68, the Court found that “heightened judicial scrutiny” was required because the speech involved “viewpoint discrimination,” with both content- and speaker-based restrictions. *Id.* at 2663-64. The Court found that the law disfavored speech with a particular content (marketing), when expressed by certain disfavored speakers (pharmaceutical manufacturers). *Id.* at 2663. According to the Court, the Vermont legislature designed the law—which prohibited pharmaceutical companies from using prescriber-identifying information to market their drugs—to prevent marketers from more effectively selling high-cost, brand-name drugs, rather than the lower priced, generic drugs favored by the state. *Id.* at 2661. Heightened scrutiny is required, the Court stated, “whenever the government creates ‘a regulation of speech because of disagreement with the message it conveys.’” *Id.* at 2664 (citing *Ward v. Rock Against Racism*, 491 U.S. 781, 791 (1989)).

The *Caronia* court determined that heightened scrutiny was required to assess the constitutionality of restrictions on off-label promotion because the restrictions are content-based in that they distinguish between favored speech (uses that are FDA-approved) and disfavored speech (uses that are not FDA-approved). 703 F.3d at 165. Further, prohibiting off-label promotion is speaker-based, the court reasoned, because it targets one kind of speaker (pharmaceutical manufacturers and their representatives) while allowing others (such as doctors and academics) to speak freely about off-label uses. *Id.*

In applying heightened scrutiny, the Second Circuit suggested that an agency seeking to uphold its own regulatory system is viewpoint discriminatory. This analysis simply makes no sense. The purpose of prohibiting off-label promotion is to protect the public health by ensuring that both doctors and consumers receive accurate, scientifically based information—a mission accomplished through the FDA approval process. The court’s analysis leads to the conclusion that distinguishing between approved and unapproved drugs is viewpoint discriminatory, a conclusion that would make the entire FDA approval process unconstitutional.

The Second Circuit also made fatal errors in applying the *Central Hudson* test. To survive *Central Hudson*, the government must prove that its regulation of nonmisleading speech regarding a lawful activity: (1) stems from a substantial government interest; (2) directly advances that interest; and (3) is not more extensive than necessary. *Cent. Hudson Gas & Electric Corp. v. Pub. Serv. Comm'n*, 447 U.S. 557, 564 (1980). The district court in *Caronia* found that each element was satisfied: (1) the government has a substantial interest in the health and safety of its citizens, as well as in subjecting drugs to the FDA premarket approval process; (2) prohibiting off-label promotion directly advances that interest; and (3) the misbranding provisions are no more extensive than necessary because restricting marketing behavior is one of the few methods by which the FDA can encourage manufacturers to seek FDA approval for new uses of a drug. *See United States v. Caronia*, 576 F. Supp. 2d 385, 398-402 (E.D.N.Y. 2008), *rev'd*, 703 F.3d 149.

The Second Circuit's focus on the lawfulness of prescribing off-label, and on the fact that the FDA anticipated some off-label use, *Caronia*, 703 F.3d at 166, ignores the fundamental nature of the speech involved. The doctor's decision to prescribe is not commercial speech; it is the off-label promotion that must be scrutinized. The Second Circuit also concluded that restrictions on off-label promotion interfere "paternalistically" with both doctors' and patients' access to information about off-label use. *Id.* Restricting off-label promotion, however, is not a paternalistic effort by the FDA to keep doctors and patients in the dark about new treatments. It is, on the contrary, a corollary of the very core of the FDA's mission to assure doctors and the public that drugs have been proven safe and effective.

In *IMS Health* and *Western States*, the Supreme Court expressed concern about paternalistic regulation, but its concern centered on ensuring that the public received truthful, nonmisleading information. How can the truthfulness of off-label information be assessed? Access to all of the manufacturer's in-house clinical trial protocols and research reports—both positive and negative—as well as its marketing strategy, might be a starting point, although it is unlikely that manufacturers would be willing to disclose such information. The truthfulness of off-label information is speculative, unknown, or inaccessible. One author has wisely suggested that when manufacturers raise truthfulness as a defense, the manufacturer should bear the burden of proving the truthfulness of its off-label claims. *See Christopher Robertson, When Truth Cannot Be Presumed: The Regulation of Drug Promotion Under an Expanding First Amendment*, 94 B.U. L. REV. (forthcoming 2014) (manuscript at 127-31), available at <http://papers.ssrn.com/id=2318618>. Because the truth of off-label promotion cannot be presumed or proven

without access to all of the manufacturer's research, restricting its use is consistent with Supreme Court decisions that place a premium on ensuring that consumers receive truthful, nonmisleading information.

FDA regulations reflect the policy—supported by extensive evidence—that drugs should be promoted based on scientific proof that they are safe and effective, not on anecdotal information, conjecture, or profit motives. In *Western States*, the Supreme Court recognized that “[p]reserving the effectiveness and integrity of the FDCA’s new drug approval process is clearly an important governmental interest, and the Government has every reason to want as many drugs as possible to be subject to that approval process.” 535 U.S. at 369. To that end, the government should continue to prosecute drug manufacturers for off-label promotion. With a focus on the false and misleading nature of off-label claims, as well as the intent to misbrand, the problems the government encountered in *Caronia* are easily overcome. Furthermore, Supreme Court precedent, while expansive in its protection of commercial speech, does not support protecting speech that bypasses the truth-seeking mission of the FDA’s approval process. The First Amendment should not be manipulated to protect information that has the potential to unleash unknown risks and dangers on an unsuspecting public.

REBUTTAL

*Permission to Speak Freely?*LARS NOAH[†]

*If the law is against you, argue the facts.
If the law and the facts are against you, pound the table and yell like hell.*

Carl Sandburg (1936)

Professor Greene essentially concedes that all of the recent decisional law cuts against her position, so instead she relies on generalizations about overeager sales representatives, gullible doctors, and untested off-label uses. Her focus on the admittedly garbled decision in *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012), fundamentally misconceives what's at stake in this debate, and she fails to mention that the Department of Justice decided not to file a petition for certiorari in that case. See David Sell, *U.S. Won't Pursue Case of Pharma Salesman*, PHILA. INQUIRER, Jan. 25, 2013, at A23. Perhaps the government feared that the Supreme Court might take the occasion to put another nail in the coffin of FDA speech regulation.

No one doubts that, several times in recent years, pharmaceutical companies have promoted off-label uses in genuinely misleading ways. For instance, Warner-Lambert's campaign for the anticonvulsant Neurontin® (gabapentin) attracted plenty of justified criticism. See Stephanie Greene, *False Claims Act Liability for Off-Label Promotion of Pharmaceutical Products*, 110 PENN ST. L. REV. 41, 59-60 (2005); Michael A. Steinman et al., Narrative Review, *The Promotion of Gabapentin: An Analysis of Internal Industry Documents*, 145 ANNALS INTERNAL MED. 284, 290 (2006); see also *In re Neurontin Mktg. & Sales Practices Litig.*, 712 F.3d 21, 51 (1st Cir.) (affirming a \$142 million judgment in favor of health insurers), *cert. denied*, 134 S. Ct. 786 (2013). Whether the controversy involved Neurontin or the narcolepsy drug Xyrem® (at issue in *Caronia*), the fact that the promoted uses happened not to appear in the approved labeling struck me as entirely beside the point—the companies would have found themselves in equally

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hot water had they made the same unfounded claims of safety and effectiveness about the on-label uses of their drugs, *see* 21 C.F.R. § 202.1(e) (2013), and the First Amendment does not stand in the way of sanctioning such advertising.

Professor Greene criticizes the federal prosecutors in *Caronia* for failing to emphasize the misleading nature of the defendant's statements (e.g., calling Xyrem "very safe," 703 F.3d at 157, even for its approved uses seems entirely outrageous given the black box warning), but why would they go to that trouble when off-label promotion alone, which requires far less proof, runs afoul of federal law? If the FDA's flat prohibition on any mention of such uses fails constitutional scrutiny, then the government would have to shoulder the greater burden of proving in what respect a drug advertisement included a false or misleading claim. The First Amendment demands no less, and it represents sheer hyperbole to suggest that a contrary conclusion would somehow imperil the FDA's entire system of pharmaceutical regulation. Even without the current advertising prohibitions, drug manufacturers would have incentives to seek agency approval for new indications because, for instance, health insurers often restrict reimbursement for off-label uses. *See* Joshua Cohen et al., *Off-Label Use Reimbursement*, 64 FOOD & DRUG L.J. 391, 397-98 (2009).

To put the constitutional issue in stark relief, assume that a seller can adequately substantiate an appropriately limited claim of safety and effectiveness for an off-label use and also makes clear (by a prominent disclaimer or otherwise) that the use has not received the FDA's blessing. Imagine that Pharmerica Inc. has developed a novel anticoagulant. As required by federal law, it cannot begin selling this new drug without first securing a license from the Agency based on substantial testing conducted first in preclinical (animal) studies and then in clinical (human) trials. *See* LARS NOAH, LAW, MEDICINE, AND MEDICAL TECHNOLOGY 260-64, 270-71 (3d ed. 2012) [hereinafter NOAH, MEDICAL TECHNOLOGY]. By all accounts, the process of testing an investigational compound and then securing approval of a new drug application (NDA) requires a substantial investment of time and resources, averaging on the order of a dozen years and over \$1 billion. *See id.* at 261. Assume that this investigational drug beats the odds, *see id.* at 158, and receives FDA approval for use in guarding against blood clots in patients at a heightened risk of stroke.

A few years after Pharmerica introduces its prescription drug under the fanciful brand name Ridaclot, independent researchers using an unimpeachable study design and applying conventions for statistical significance discover that the drug also slows cognitive decline in the earliest stages of Alzheimer's disease. The results of their work appear in the *Archives of Geriatric*

Neurology, a respected but somewhat obscure peer-reviewed journal, and the popular press fails to report these findings to a much wider audience. Wholly apart from opening a potentially lucrative new market, Pharmerica believes that it has a public responsibility to ensure that these results get disseminated more broadly to physicians; after all, Alzheimer's patients currently have few promising treatment options, and nothing would prevent physicians from prescribing Ridaclot for this purpose.

Under FDA regulations that go back almost half a century, however, Pharmerica cannot share any information about such an off-label use with doctors. See 21 C.F.R. § 202.1(e)(4)(i)(a) (advertising may not "recommend or suggest any use that is not in the labeling accepted in such approved new-drug application or supplement"); *id.* § 202.1(e)(6)(i), (xi) (same); see also 21 U.S.C. § 352(n)(3) (2012) (providing that a prescription drug shall be deemed to be misbranded unless its seller includes in all advertisements a true statement of "such other information . . . as shall be required in regulations"). But see *Caronia*, 703 F.3d at 160 (concluding inaccurately that the "regulations do not expressly prohibit or criminalize off-label promotion"). No matter how carefully it structures the communication to avoid overstating the results or implying that the Agency has approved the indication, the company could not mention use in treating Alzheimer's disease anywhere in its labeling or advertising (in print or other medium) for the drug. Pharmerica first would have to file a supplemental new drug application (SNDA) and await the Agency's imprimatur. See Lars Noah, *Constraints on the Off-Label Uses of Prescription Drug Products*, 16 J. PROD. & TOXICS LIAB. 139, 144 & n.22 (1994). Although such "efficacy supplements" require far less effort than the original NDA, they are neither cheap nor fast (nor invariably successful). See *id.* at 145 & n.26. Even in the unlikely event that the sponsor could submit the previously published research rather than undertake its own expensive trials to satisfy the FDA's demanding standards, the application fee itself would cost over \$1 million. See Notice, Prescription Drug User Fee Rates for Fiscal Year 2014, 78 Fed. Reg. 46,980, 46,984 tbl.7 (Aug. 2, 2013).

If the Agency rejects the SNDA because it remains unpersuaded about the utility of the drug for Alzheimer's patients, Pharmerica would have to remain silent about this use. If approved, the SNDA would authorize the company to add a line or two to the list of indications in the package insert, which in turn would allow the company to advertise this now on-label use, but in all other respects the product would remain identical to the one originally introduced. In short, Pharmerica needed the FDA's permission to speak, in this hypothetical, by expending millions of extra dollars (and

waiting several more years) to secure a license that would authorize it to communicate truthful information about an entirely permissible use of an already lawfully marketed product. Indeed, the FDA regularly (if belatedly) approves off-label uses, *see* NOAH, *MEDICAL TECHNOLOGY*, *supra*, at 272-73, which suggests that the earlier evidence favoring such uses had some justification after all, even before the Agency officially concurred. Perhaps I am just seeing the proverbial glass as (almost) half full, but the oft-cited survey that Professor Greene references concluded that more than a quarter of identified off-label uses “were supported by strong scientific evidence” (even Neurontin hit nearly 20%) and some unspecified additional fraction presumably had at least limited scientific support. *See* David C. Radley et al., *Off-label Prescribing Among Office-Based Physicians*, 166 *ARCHIVES INTERNAL MED.* 1021, 1023 (2006).

Pharmerica might skip the SNDA step by finding indirect methods of getting the word out about the off-label use of Ridaclot. It could purchase thousands of reprints of the published article and mail these to physicians around the country, and it could sponsor continuing medical education (CME) programs where the authors of the study could discuss their results. Although at present no regulations specifically address such quasi-promotional campaigns, the FDA has issued nonbinding guidance documents that indicate it would permit these sorts of efforts only under the narrowest of circumstances. The FDA recently revoked the 2009 guidance cited by Professor Greene that had addressed the mailing of reprints, replacing it with a draft guidance document that specifies when manufacturer involvement in the dissemination of such materials would not draw the Agency’s ire. *See* Notice of Availability, Revised Draft Guidance for Industry on Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices, 79 Fed. Reg. 11,793 (Mar. 3, 2014); *see also* Notice, Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64,074 (Dec. 3, 1997) (focusing on CME events).

Unlike other FDA advertising regulations that aim to guard against particular types of potentially false or misleading claims, the blanket prohibition on any statements concerning off-label uses sweeps broadly to prevent the dissemination of information even if it is presented in an entirely truthful and nonmisleading way. Surely this arrangement would strike First Amendment scholars as at least mildly perplexing, if not blatantly unconstitutional. Many academics think that the Supreme Court’s increasing solicitude for “commercial speech” is profoundly misguided, but that represents another debate altogether. For purposes of resolving the question at hand, we need to take as given the commercial speech doctrine as presently configured, particularly

as set forth in *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002), which invalidated a federal prohibition on advertising by pharmacists about compounded drugs. In contrast, *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653 (2011), which invalidated a state prohibition on prescription data mining used by drug companies to facilitate more targeted pitches to individual physicians, strikes me as an outlier. The court in *Caronia* may very well have given that peculiar decision undue emphasis, as Professor Greene suggests, but prohibitions on off-label advertising fail heightened scrutiny even without *IMS Health*.

In previous work, I have recounted the skirmishing in the lower courts over the FDA's limited allowance for indirect advertising of off-label drug uses to physicians. See Lars Noah, *What's Wrong with "Constitutionalizing Food and Drug Law"?*, 75 TUL. L. REV. 137 (2000); see also Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 67 (D.D.C. 1998) (quoting my earlier work for the proposition that "the FDA is not a peer review mechanism for the scientific community"). More recently, I have explained that, when one fully appreciates the potentially radical aspects of *Western States*, even the Agency's prohibitions on direct advertising may fail a constitutional challenge. See Lars Noah, *Truth or Consequences?: Commercial Free Speech vs. Public Health Promotion (at the FDA)*, 21 HEALTH MATRIX 31, 72-75 (2011); see also *id.* at 76-84 (questioning the constitutionality of restrictions on indirect promotion); *id.* at 85-89 (same, for efforts directed at patients). *Western States* has gotten remarkably little attention from commentators. See *id.* at 64 & n.147. Indeed, Professor Greene's 2005 article on off-label promotion included a First Amendment analysis that never once cited this decision, and her selective references to it here entirely fail to do this important decision justice.

To my mind, the Supreme Court's evident deployment of the "unconstitutional conditions" doctrine in the context of commercial speech represents the most striking aspect of *Western States*. For purposes of this debate, it means that the FDA cannot pursue its ends through the back door either. Let us say that the Agency had not directly prohibited the advertising of off-label uses; under the statute, the FDA still could prosecute a company for selling an approved drug, if it lacked approval for some of its "intended uses," by pointing to the company's advertising of those off-label uses (or, as the government had charged in *Caronia*, for "misbranding" the drug in failing to provide "adequate directions" for these additional intended uses). *Western States* apparently prevents even that maneuver, however, because the threat of sanctioning conduct in this manner unduly burdens commercial speech. See *id.* at 54-57 & nn.110-12.

More generally, the Supreme Court seems to have effectively barred advertising restrictions that serve any purpose other than guarding against potentially false or misleading claims. *See id.* at 67-68. Whenever government seeks to pursue collateral purposes such as dampening consumer demand, non-speech-restrictive alternatives (e.g., barring the underlying conduct) invariably exist for accomplishing such goals. Or, if the government wants to encourage drug companies to seek FDA approval of off-label uses, then it can offer incentives such as extended market exclusivity periods. *See id.* at 74-75 & n.186. Furthermore, in guarding against potentially false or misleading claims, the Court routinely suggests disclaimer requirements as less-speech-restrictive alternatives, even if audiences routinely fail to read the small print. In the context of prescription drug advertising, health care professionals remain the primary audience, which makes a preference for disclaimers over flat prohibitions easier to swallow. Surely physicians comprehend what it means to say that a particular use qualifies as off-label, even if in other respects their information-processing skills are not nearly as good as people assume. *See id.* at 65-66, 72-73 & nn.178-79.

Indeed, making prophylactic rules seems inevitably less carefully tailored for this purpose than case-by-case enforcement to squelch particular instances of false or misleading advertising. The FDA's preference to control drug advertising by issuing broad regulations dates back to an era before commercial speech enjoyed any constitutional protection. Once that changed in the mid-1970s, the Federal Trade Commission's adjudicatory approach—and demand that sellers be able to substantiate whatever claims they wish to make—represents the more acceptable procedural choice. Professor Greene explains that the FDA cannot easily discover what transpires in doctors' offices during visits from sales reps, and she also suspects that the purported evidentiary support for off-label uses will remain hidden at company headquarters. Successful recent prosecutions seemingly belie such practical concerns, but, even if they have some force, ease of enforcement alone would never justify an overbroad restriction on commercial speech. *See id.* at 60 n.132. Is Professor Greene suggesting that the First Amendment would allow the Agency to go still further than it has already and forbid detailing altogether in order to guard against the possibility that drug reps might pitch unfounded off-label claims to unsuspecting doctors?

Lastly, the FDA's increasingly popular practice of issuing technically nonbinding guidance documents while counting on its power to cajole—a cagey if not always successful effort to shield its dubious policies from judicial scrutiny and avoid other forms of accountability—seems to represent the least defensible method of all when First Amendment rights hang in the balance. *See* Lars Noah, *The Little Agency That Could (Act with Indifference*

to *Constitutional and Statutory Strictures*), 93 CORNELL L. REV. 901, 905-06 (2008); *id.* at 921 (“The FDA formulated its [indirect] off-label promotion policies in a manner designed to evade normal administrative law constraints.”). See generally Lars Noah, *Governance by the Backdoor: Administrative Law(lessness?) at the FDA*, 93 NEB. L. REV. (forthcoming Aug. 2014). The Agency’s unambiguous regulations, noncommittal guidance documents, and threats of prosecution (or adverse action on pending license applications) make companies understandably hesitant to engage in constitutionally protected communications about off-label uses of their products (or even dare mount judicial challenges to the FDA’s policies). In contrast, a regime of case-by-case scrutiny to screen out false or misleading claims would pose a far reduced risk of chilling legitimate communications about off-label drug uses.

Let me close by quoting what struck me as Professor Greene’s most cringeworthy statement: “by choosing to promote off-label, manufacturers succeed in evading the FDA approval process, which . . . is in place specifically to provide doctors and the public as much truthful and reliable information as possible.” As the judge in the previously cited *Washington Legal Foundation* litigation put it: “In asserting that any and all scientific claims about . . . prescription drugs are presumptively untruthful or misleading until the FDA has had the opportunity to evaluate them, FDA exaggerates its overall place in the universe.” 13 F. Supp. 2d at 67. The Agency’s rules barring any and all direct claims about off-label uses of pharmaceutical products unmistakably operate to keep truthful information from doctors in ways that the Supreme Court no longer allows. Then again, insofar as Professor Greene urges prosecutors to target false or misleading aspects of particular off-label promotional efforts (and favors academic proposals to demand that companies substantiate claims), our positions on the constitutional question may not be so far apart after all.

CLOSING STATEMENT

The Whole Truth and Nothing But the Truth

STEPHANIE M. GREENE

The history of pharmaceutical marketing practices and concern for the public health support restrictions on off-label promotion of drugs. Although the pharmaceutical industry has had some success with First Amendment challenges to restrictions on off-label promotion, the case law is hardly decisive. The Second Circuit's decision in *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012), is but one decision, and not a unanimous or well-reasoned one at that. In *Washington Legal Foundation v. Friedman*, the court limited its holding to "a very narrow form of manufacturer communication." 13 F. Supp. 2d 51, 73 (D.D.C. 1998) (emphasis in original), *vacated in part*, 202 F.3d 331 (D.C. Cir. 2000). Although the court found that FDA Guidance on dissemination of certain promotional materials was more restrictive than necessary, it did not dispute that many restrictions on off-label promotion are necessary to incentivize manufacturers to seek FDA approval. The court recognized that there are "enormous differences between the permitted marketing of on-label as opposed to off-label uses" and that many other types of communication regarding off-label uses, including "person-to-person contact with a physician," were still prohibited. *Id.* Its decision to allow dissemination of some materials about off-label uses was premised on the fact that the remaining restrictions were adequate to safeguard the FDA approval process and the public health. The court noted that "[w]ere manufacturers permitted to engage in *all* [other] forms of marketing of off-label treatments, a different result might be compelled." *Id.* Furthermore, although the Supreme Court has clearly broadened protection for commercial speech, I believe that the Court would find restrictions on off-label promotion constitutional.

Referring to the Court's decision in *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002), Professor Noah maintains that "the Supreme Court seems to have effectively barred advertising restrictions that serve any purpose other than guarding against potentially false or misleading claims." Even if the Court insists on expanding protection of commercial speech to that limit, the case can be made that promotion of unapproved uses is "potentially false or misleading." Further, restrictions on off-label promotion survive constitutional scrutiny because they are no more restrictive of speech than necessary to maintain the integrity of the FDA premarket

approval process and to protect the public health. *Cf. id.* at 371-73 (striking down restrictions on advertising specific compounding practices because less-speech-restrictive alternatives could have protected the government's substantial interest in preserving the integrity of the FDA's new drug approval process while ensuring the availability of certain unapproved compounded drugs).

As the Court specifically recognized in *Western States*, preserving the FDA's new drug approval process is an important government interest and "the Government has every reason to want as many drugs as possible to be subject to that approval process." *Id.* at 369. Professor Noah does not dispute the importance of this interest, but suggests that disclaimers and postmarket enforcement of false and misleading claims are preferable to "prophylactic rules." Prophylactic rules, however, are at the very core of the FDCA. Decades of congressional hearings (in the 1950s and 1960s) that considered pharmaceutical marketing practices "showed that the pharmaceutical marketplace was filled with misleading promotional material on which physicians relied." 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, 301-02 (2003). The hearings also amassed "abundant evidence to support the conclusion that alternatives, such as disclaimers disclosing the state of the evidence supporting a claim, and postmarket enforcement actions, were inadequate to stop deceptive and dangerous products." *Id.* at 300. Postmarket enforcement takes months or even years, during which time a drug remains on the market, exposing patients to dangerous or ineffective treatment. Disclaimers are a poor method of controlling off-label promotion because evidence shows that they have a limited impact on physicians and that consumers frequently misinterpret or ignore them. *See* Aaron S. Kesselheim, *Off-Label Drug Use and Promotion: Balancing Public Health Goals and Commercial Speech*, 37 AM. J.L. & MED. 225, 250-51 (2011) [hereinafter Kesselheim, *Off-Label Drug Use and Promotion*].

While pharmaceutical companies assert that doctors are the target audience of off-label promotion, the risks and consequences associated with unapproved drugs are passed on to patients who are frequently unaware of a drug's unapproved status and receive no information with which to assess the risks and benefits of a disclaimer. Recognizing the influence that marketing has on physicians' prescribing habits and the risks inherent in off-label promotion, Dr. Kesselheim and others have stated that physicians themselves will need to be the "bulwark against off-label promotion." *See* Aaron S. Kesselheim et al., *Strategies and Practices in Off-Label Marketing of*

Pharmaceuticals: A Retrospective Analysis of Whistleblower Complaints, PLOS MED., Apr. 2011, at 7 [hereinafter Kesselheim et al., *Strategies and Practices*]. While physicians play a critical role in assessing the merits of off-label promotion, the legal system must also fulfill its role in appropriately balancing First Amendment concerns with the risks of such promotion.

In addition to disclaimers and postmarket enforcement, other less-speech-restrictive policies have been proposed as alternatives to prohibiting off-label promotion, including taxing off-label use, requiring FDA review of off-label use that reaches a certain threshold, and extending market exclusivity for manufacturers who seek approval for off-label use. These alternatives place inadequate emphasis on patient safety and assume the ability to monitor expanding off-label use. See Kesselheim, *Off-Label Drug Use and Promotion*, *supra*, at 251-52. Reducing the financial incentive to introduce unapproved uses to the market may be a more direct way to control off-label promotion. See Marc A. Rodwin, *Rooting Out Institutional Corruption to Manage Inappropriate Off-Label Drug Use*, 41 J.L. MED. & ETHICS 654, 659-60 (2013).

In considering whether less-speech-restrictive alternatives are sufficient to maintain the integrity of the FDA premarket approval process and to protect the public health, courts should be mindful that Congress considered and rejected alternatives such as disclaimers and postmarket enforcement as insufficient safeguards. After extensive examination of the pharmaceutical industry, the battle for a drug preapproval process based on safety and efficacy was won in 1962 with the passage of the Kefauver-Harris Amendments. See Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780. The industry will undoubtedly continue to push for changes that provide new opportunities to promote off-label. Legislators and regulators must recognize that powerful industries have the ability to shape legislative and administrative rules to protect their interests. See Malcolm S. Salter, *Lawful but Corrupt: Gaming and the Problem of Institutional Corruption in the Private Sector* (Harvard Bus. Sch., Working Paper No. 11-060, 2010) (manuscript at 14-25), available at <http://www.hbs.edu/faculty/Publication%20Files/11-060.pdf>.

In addition to withstanding First Amendment scrutiny under *Central Hudson* analysis, there are strong arguments that off-label promotion is “inherently misleading” and therefore not deserving of First Amendment protection at all. See Waxman, *supra*, at 306-10. Because manufacturers are adept at disguising promotional speech as truthful, nonmisleading, and unbiased discourse, it is difficult to distinguish between “off-label promotion” and “non-promotional speech.” See Kesselheim, *Off-Label Drug Use and Promotion*, *supra*, at 251. Professor Noah’s hypothetical about “truthful and nonmisleading” off-label promotion demonstrates the many conditions that

must be satisfied to ensure that off-label promotion is not misleading. The Pharmera hypothetical assumes that a drug study yielding positive results for the treatment of Alzheimer's is conducted by "independent researchers using an unimpeachable study design." Given these qualifications, the information from the study might well be "truthful" but still we must ask: does it represent the whole truth? Doctors and patients should be informed whether the study can be replicated and whether any other studies yielded negative results. Research indicates that pharmaceutical companies are less likely to publish unfavorable results and even threaten researchers who intend to expose negative studies. See Donald W. Light et al., *Institutional Corruption of Pharmaceuticals and the Myth of Safe and Effective Drugs*, 41 J.L. MED. & ETHICS 590, 595 (2013).

Professor Noah's hypothetical poses the rare case in which off-label marketing is purportedly needed to address a heartbreaking disease that has few, if any, effective approved treatments. It posits that the manufacturer believes it has a "public responsibility" to broadly disseminate information about this study to physicians. Research indicates, however, that the goal of off-label marketing schemes is to generate more revenue than FDA-approved indications could. See Kesselheim et al., *Strategies and Practices*, *supra*, at 3. Many real-world examples illustrate this point. Pfizer's drug Bextra®, approved to treat arthritis and menstrual cramps, was widely promoted for off-label use in treating acute and surgical pain, in dosages well above those approved by the FDA. Gardiner Harris, *Pfizer Pays \$2.3 Billion to Settle Marketing Case*, N.Y. TIMES (Sept. 3, 2009), <http://www.nytimes.com/2009/09/03/business/03health.html>. Risks to the kidney, heart, and skin were associated with increased dosages of the drug and it was eventually withdrawn because of these risks. *Id.* Although Pfizer paid \$2.3 billion to settle claims associated with the off-label promotion of Bextra and three other drugs, the \$16.8 billion in revenues that it earned from those drugs demonstrates not only how effective off-label marketing can be, but also how dearly patients and the healthcare system pay. See Rodwin, *supra*, at 658.

When projected sales are high enough, the risk of paying fines for off-label promotion is apparently worth taking. For example, profits from the sale of Neurontin® for its FDA-approved use (treating epilepsy) were projected at approximately \$500 million. See *In re Neurontin Mktg. & Sales Practices Litig.*, No. 04-10739, 2011 WL 3852254, at *6 (D. Mass. Aug. 31, 2011), *aff'd*, 712 F.3d 21 (1st Cir. 2013). An off-label marketing strategy, commenced in 1995, catapulted sales from \$97.5 million to \$2.7 billion by 2003, with nearly 90% of Neurontin prescriptions written for off-label uses. See *id.* at *8; P.A. Francis, *Pfizer Inc. Guilty*, PHARMABIZ (May 19, 2004),

<http://saffron.pharmabiz.com/article/detnews.asp?articleid=21919§ionid=47&cz=y>. Neurontin's manufacturer ultimately paid \$430 million to settle civil and criminal charges associated with off-label promotion—a fraction of its increased profits from the drug's off-label sales. Press Release, Dep't of Justice, Warner-Lambert to Pay \$430 Million to Resolve Criminal & Civil Health Care Liability Relating to Off-Label Promotion (May 13, 2004), *available at* http://www.justice.gov/opa/pr/2004/May/04_civ_322.htm.

The oft-cited study concluding that “[a]mong off-label mentions, most (73%) lacked evidence of clinical efficacy, and less than one third (27%) were supported by strong scientific evidence,” David C. Radley et al., *Off-label Prescribing Among Office-Based Physicians*, 166 ARCHIVES INTERNAL MED. 1021, 1023 (2006), underscores this problem. The fact that some off-label uses are ultimately proven safe and effective is little comfort to the patients and payers who have been subjected to the risks and costs of unsafe and ineffective uses.

Assuming the facts that Professor Noah proposes, however, we would surely want the medical community to receive information about a promising treatment for Alzheimer's. The most recent FDA guidelines indicate that the FDA would not view dissemination of a scientific or medical journal article about such a study as evidence of intent that the product be put to an unapproved use. *See* Notice of Availability, Revised Draft Guidance for Industry on Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices, 79 Fed. Reg. 11,793, 11,794-95 (Mar. 3, 2014). In fact, the hypothetical assumes several of the safeguards that the FDA recommends: the study is conducted by independent researchers; there is adequate substantiation for claims of safety and efficacy; and the study appears in a peer-reviewed journal. *See id.* The FDA's guidelines further suggest that the article be disseminated with the approved labeling; a comprehensive bibliography; publications that reach contrary results; and prominent disclosures of the drug's unapproved status, as well as potential conflicts of interest (including financial interests) of the study's authors. *Id.* These requirements are surely essential in assessing the reliability of the study. The FDA's thinking on dissemination of peer-reviewed journal articles is based on evidence that disseminated material does not always accurately or fairly reflect the current state of knowledge about the use in question and that manufacturers have little incentive to publish information that discredits the use of their drug. Thus the guidelines that the FDA provides support the dissemination of information in a manner that should inform recipients of its reliability, a goal that is consistent with First Amendment jurisprudence.

It should also be noted that the FDA specifically recognizes the importance of making new treatments available to patients, especially when there are few, if any, existing treatments. The FDA has created several processes to help accelerate availability of new treatments: Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review. *See For Consumers: Fast Track, Breakthrough Therapy, Accelerated Approval and Priority Review: Expediting Availability of New Drugs for Patients with Serious Conditions*, FDA (June 26, 2013), <http://www.fda.gov/ForConsumersByAudience/ForPatientAdvocates/SpeedingAccessToImportantNewTherapies/ucm128291.htm>. The Fast Track process recognizes Alzheimer's as a "serious condition[]" that merits expedited review. *Id.*

Professor Noah and I seem to disagree most fundamentally on the trustworthiness of the industry's marketing practices. Professor Noah points out that the FDA's regulations controlling drug advertisements date back to an era before commercial speech enjoyed any constitutional protection. The current expansive protection for commercial speech, however, is not without limits. Erosion of restrictions turns the clock back to the days when manufacturers could sell their products with no proof of safety and efficacy. In 1999, in the midst of its campaign to promote gabapentin (Neurontin) for off-label uses, a Pfizer executive proclaimed the drug to be "the 'snake oil' of the twentieth century." *See* Jim Edwards, *Lesson From Pfizer: Don't Describe Your Product as "Snake Oil" in Internal Email*, CBS MONEYWATCH (Mar. 26, 2010), <http://www.cbsnews.com/news/lesson-from-pfizer-dont-describe-your-product-as-snake-oil-in-internal-email>. In today's climate of sophisticated marketing strategies, prophylactic rules restricting off-label promotion in order to protect the public health may be more justifiable than ever.

CLOSING STATEMENT

The Whole “Truthiness”

LARS NOAH

*No government agency has jurisdiction over the truth.**The X-Files* (1993)

Professor Greene makes a powerful argument in favor of strong federal regulation over off-label drug claims, but her constitutional defense remains terribly flimsy. Notwithstanding Professor Greene’s suggestion to the contrary, I harbor no illusions about the capacity of physicians or the ethics of the pharmaceutical industry when it comes to marketing. See Lars Noah, *Medicine’s Epistemology: Mapping the Haphazard Diffusion of Knowledge in the Biomedical Community*, 44 ARIZ. L. REV. 373, 391-95, 402-06, 430-49 (2002). Unlike her, however, I do not regard the First Amendment as merely an afterthought or a bothersome obstacle to skirt. Again Professor Greene expresses concerns about making government enforcement more difficult, but isn’t that precisely the point of the Constitution? After studying this Agency for the last quarter century, I do not share her evident faith in the good sense of the FDA.

More remarkably, Professor Greene now suggests that off-label promotion may fail *Central Hudson’s* first prong as “inherently misleading.” The sole support offered for this astonishing proposition: an article by a distinguished member of the House of Representatives. Promotional claims about off-label (as well as on-label) uses of pharmaceutical products certainly have the *potential* to mislead, and the government may impose restrictions to guard against this possibility so long as it can satisfy the Court’s demanding form of heightened scrutiny, but to call such claims inherently misleading—and therefore completely unprotected by the First Amendment—boggles the mind. See, e.g., *Pearson v. Shalala*, 164 F.3d 650, 655 (D.C. Cir. 1999) (calling “almost frivolous” the FDA’s suggestion that health claims for dietary supplements were inherently misleading); see also *United States v. Caronia*, 703 F.3d 149, 165 n.10 (2d Cir. 2012) (“The government does not contend that off-label promotion is in and of itself false or misleading.”).

Professor Greene notes that, during the 1960s, Congress rejected the option of disclaimers. Interestingly, in spite of legislative findings of

promotional abuses in the field, it also failed to give the FDA full authority to regulate detailing. See Lars Noah, *Death of a Salesman: To What Extent Can the FDA Regulate the Promotional Statements of Pharmaceutical Sales Representatives?*, 47 FOOD & DRUG L.J. 309, 312-15, 323-26 (1992). Twenty years ago, by contrast, Congress endorsed the use of disclaimers (directed to laypersons no less) in tandem with typically unfounded promotional claims that otherwise would convert dietary supplements into unapproved new drugs. See Dietary Supplement Health and Education Act of 1994, Pub. L. No. 103-417, § 6, 108 Stat. 4325, 4329 (codified at 21 U.S.C. § 343(r)(6)(C) (2012)). From a public policy standpoint, that struck me as insane (talk about “snake oil”!); from a constitutional perspective, however, it better comports with the Supreme Court’s increasingly unforgiving application of the *Central Hudson* test.

Finally, let us not forget that the Court in *Western States* showed remarkable indifference to the considered choices that Congress had made about pharmacy compounding of genuinely unapproved drugs just five years earlier. See *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 360-65 (2002) (describing the practice of preparing customized drugs for patients with special needs and the problem of pharmacists manufacturing drugs under the guise of compounding, and explaining that, in 1997, Congress codified certain portions of an FDA policy granting a limited exception to new drug approval requirements for pharmacists who provide such compounding services); *id.* at 371-73 (holding that the prohibition on advertising the availability of particular compounded drugs failed the final prong of the *Central Hudson* test because, for instance, several other conditions included by Congress in the new provision might have sufficed to protect the government’s interests). Why on earth would the Court care about legislative judgments dating back more than half a century, especially insofar as Congress did not want physicians to hear certain things about drugs that had already undergone FDA approval (and why does she keep harping on the hazards of unapproved drugs when the issue before us concerns unapproved new uses for approved drugs)?

Professor Greene dismisses my hypothetical as atypical, but I never suggested that this represents the only application of the FDA’s rules that would violate the First Amendment—instead, it clearly demonstrates the overbroad operation of the Agency’s policies. Meanwhile, her continued preoccupation with false and misleading instances of off-label promotion clouds the issue. If off-label uses have such little merit, then the government should—as it has done in limited cases—just ban the practice altogether (except perhaps for certain specialties such as oncology). See, e.g., 21

U.S.C. § 333(e)(1) (2012) (prohibiting the distribution of human growth hormone for off-label use); *Planned Parenthood of Greater Tex. Surgical Health Servs. v. Abbott*, No. 13-51008, 2014 WL 1257965, at *14-17 (5th Cir. Mar. 27, 2014) (rejecting different constitutional objections to a Texas prohibition on off-label prescribing of the FDA-approved abortifacient mifepristone); see also Lars Noah, *Ambivalent Commitments to Federalism in Controlling the Practice of Medicine*, 53 U. KAN. L. REV. 149, 179, 188-93 (2004). Although it surely would offend the American Medical Association, which makes the idea politically unrealistic, such a conduct-focused solution to this supposedly intractable problem would not offend the Constitution, and then *Central Hudson's* first prong plainly would allow a ban on any affiliated advertising.

Another application of the FDA's rule against promoting off-label drug uses makes its constitutional infirmity even clearer, and this one represents a twist that not a single court or commentator has ever confronted—no doubt because, in practice, the situation would rarely arise. To extend my previous hypothetical, let us assume that Pharmacia finally gets its SNDA for Ridaclot, which allows the company to add Alzheimer's patients to the indications in the package insert and then relatively freely engage in advertising of this new use. At the same time, Prescott Pharmaceuticals (best known for sponsoring the recurring "Cheating Death" segment on *The Colbert Report*), secures an abbreviated new drug application (ANDA), see 21 U.S.C. § 355(j) (2012), for its generic version of Ridaclot. The labeling for the generic must mimic the brand-name in almost all respects. See 21 C.F.R. § 314.94(a)(8)(iv) (2013); *Mut. Pharm. Co. v. Bartlett*, 133 S. Ct. 2466, 2471, 2476 (2013); see also Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products, 78 Fed. Reg. 67,985, 67,988-89 (proposed Nov. 13, 2013) (proposing to loosen this requirement by allowing ANDA-holders to strengthen risk information unilaterally).

When the brand-name manufacturer gets agency approval for a new use, it generally secures three additional years of market exclusivity on just that use, which means that the FDA cannot approve an ANDA for that use until this period expires. Generic versions of the drug initially can only list the uses appearing in the originally approved labeling. See Lars Noah, *This Is Your Products Liability Restatement on Drugs*, 74 BROOK. L. REV. 839, 910 & n.310 (2009). As a result, Prescott's generic drug only indicates use as an anticoagulant, which means that the company also cannot advertise it as a safe and effective treatment for Alzheimer's disease even though the FDA has approved precisely such a statement for Ridaclot. After waiting for the three-year exclusivity period (and any method-of-use patents, in case they run longer) to expire, and without having to submit any further evidence to

the Agency, Prescott will get permission to add this indication to the labeling for its generic drug and then relatively freely engage in advertising for this not-so-new use.

What accounts for initially granting the brand-name company a monopoly over this new information that the FDA has anointed as truthful and nonmisleading? Whatever the explanation, does that justify making it a federal offense for a competitor to disseminate this very same information? In no sense does this prohibition help to guard against the making of false or misleading claims. If agency approval of an SNDA allowed a previously approved generic competitor to revise the labeling for its drug immediately, then brand-name manufacturers would, of course, have even less of an already weak incentive to seek FDA approval of new uses. The pursuit of such collateral purposes would not, however, stand much of a chance under the heightened scrutiny of *Western States*.

Instead of granting three years of partial exclusivity, Congress could amend the FDCA to grant the NDA-holder two more years of full exclusivity with the first added use (and perhaps another year with a second added use). This would have the dual benefit of improving the incentive for filing SNDAs—without having to bar off-label promotion—and ensuring that generic drug manufacturers do not encounter the prohibition on making off-label claims once the FDA approves their ANDAs. Congress crafted the six-month added exclusivity incentive for testing off-label uses in pediatric patients in roughly this manner. See 21 U.S.C. § 355a(b)–(c) (2012); see also *Mylan Labs., Inc. v. Thompson*, 389 F.3d 1272 (D.C. Cir. 2004); Jennifer S. Li et al., *Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program*, 297 JAMA 480 (2007). Delaying generic entry might seem like a steep price for patients and their insurers to pay, but the First Amendment casts serious doubt on the preferred current approach of casually trading away the speech rights of regulated entities and saving prosecutors the hassle of trying to separate the wheat from the chaff.

Why has this aspect of the problem gone entirely unnoticed? At present, generic drug manufacturers have little reason to advertise. As with expenditures for research and development, they free-ride on the marketing efforts of brand-name manufacturers, counting on dramatically lower prices coupled with generic substitution policies to gain market share. See Lars Noah, *Adding Insult to Injury: Paying for Harms Caused by a Competitor's Copycat Product*, 45 TORT TRIAL & INS. PRAC. L.J. 673, 678-79, 684 & n.53 (2010); cf. *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653 (2011) (barring a state effort to hamstring brand-name drug manufacturers in order to favor its message of encouraging the use of cheaper generic drugs). Nonetheless,

if that business model changed for some reason, then generic sellers would confront an absolute barrier to communicating any information about new FDA-approved uses during the brand-name manufacturer's period of market exclusivity. For present purposes, this scenario has powerful explanatory value in highlighting the constitutional flaws of the Agency's policies, and it suffers from none of Professor Greene's concerns about ease of verification.

In a related vein, the FDA's flat prohibition on off-label promotion enables still other parties to interfere with the commercial speech rights of drug manufacturers. Although courts have declined to recognize any private right of action for violations of the FDCA, infractions may provide the basis for seeking penalties under collateral statutes or common law. This means that, even if the Agency exercised its largely unreviewable enforcement discretion to look the other way so long as companies made sure to avoid false or misleading claims about uses that it had not approved, the opportunity for other public and private actors to make use of this bright line rule gives it a zero-tolerance quality. (The nonfinal and nonbinding guidance documents allowing limited forms of indirect promotion represent an unreliable expression of the FDA's enforcement policy and in no way amend the Agency's sweeping regulations.) In contrast, if those plaintiffs had to demonstrate that a drug advertisement violated the far more ambiguous FDA rules against making false or misleading claims, then they would find it tougher sledding absent a prior finding by the Agency of such a violation. See Lars Noah, *Reconceptualizing Federal Preemption of Tort Claims as the Government Standards Defense*, 37 WM. & MARY L. REV. 903, 954-56 & nn.212-13 (1996).

For instance, under the False Claims Act, whistleblowers have repeatedly pointed to off-label promotion as a basis for triggering prosecution even where the FDA later approved some of these uses. See Sandra H. Johnson, *Polluting Medical Judgment? False Assumptions in the Pursuit of False Claims Regarding Off-Label Prescribing*, 9 MINN. J. L. SCI. & TECH. 61, 104, 110 (2008); Natasha Singer, *Maker of Botox Settles Inquiry on Off-Label Use*, N.Y. TIMES, Sept. 2, 2010, at A1 (reporting several recent settlements totaling almost \$5 billion). Public and private parties also have pursued claims under state consumer protection statutes when pharmaceutical manufacturers cross the clear line created by the Agency's rules. See, e.g., *In re Epogen & Aranesp Off-Label Mktg. & Sales Practices Litig.*, 590 F. Supp. 2d 1282, 1289 (C.D. Cal. 2008); see also *Prohias v. Pfizer, Inc.*, 490 F. Supp. 2d 1228, 1234-35 (S.D. Fla. 2007) (declining to dismiss claims against the manufacturer of Lipitor® for advertisements that implied the cholesterol-lowering drug's usefulness in reducing the risk of heart disease before the FDA had approved such additional indications). Plaintiffs in these consumer fraud

cases sometimes also include (though generally without success so far) claims under the federal Racketeer Influenced and Corrupt Organizations (RICO) Act. *See, e.g.*, *Ironworkers Local Union 68 v. AstraZeneca Pharm., LP*, 634 F.3d 1352, 1356 & n.5, 1366-70 (11th Cir. 2011) (off-label marketing of antipsychotic Seroquel®); *see also* J. Gordon Cooney, Jr. et al., *Back to the Future: Civil RICO in Off-Label Promotion Litigation*, 77 DEF. COUNS. J. 168 (2010). Finally, in tort litigation, plaintiffs have secured sizeable recoveries, including multi-million dollar punitive damages awards, by pointing to violations of the Agency's prohibition on off-label claims. *See, e.g.*, *Proctor v. Davis*, 682 N.E.2d 1203, 1212-17 (Ill. App. Ct. 1997); *Wyeth v. Rowatt*, 244 P.3d 765, 772, 783-86 (Nev. 2010); *see also* Andrew E. Costa, *Negligence Per Se Theories in Pharmaceutical & Medical Device Litigation*, 57 ME. L. REV. 51, 75-76 & n.186 (2005).

Lastly, Professor Greene points out that the FDA's revised draft guidance document would have allowed Parmerica to distribute reprints of the peer-reviewed article describing Ridaclot's utility in Alzheimer's patients. I had conceded as much previously, but in practice manufacturers have not trusted this purported "safe harbor," both because of its many cumbersome conditions and because the Agency has disclaimed giving it binding effect. *See* Notice, Agency Information Collection Activities; Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices, 70 Fed. Reg. 56,708, 56,709 (Sept. 28, 2005) (estimating that the Agency would receive fewer than a dozen filings a year under a previous version of this exception). Also, no matter the caliber of the published research or the care in not overstating the results, the company definitely could not arrange for printed advertisements in prominent medical journals to announce this study.

Even if, after purchasing a pile of reprints, Parmerica affixed the disclaimers and additional information demanded by the Guidance (satisfying Professor Greene's understanding of the First Amendment as entitling the government to demand "the whole truth"), nothing would prevent the FDA from charging the company with a violation of its regulations banning off-label promotion, and, of course, any deviation from the Guidance would invite such a reaction. Moreover, the Agency could invoke its broadly construed authority over "labeling," and, in addition to pursuing sanctions against the manufacturer and its products, the FDA could initiate a "seizure" action (a form of pretrial detention) against the reprints themselves. If the government prevailed on the misbranding charges at trial, then the federal court would issue a "condemnation" order entitling the government to destroy the reprints. *See, e.g.*, *United States v. Articles of Drug*, 32

F.R.D. 32, 34-35 (S.D. Ill. 1963). All this for failing to pay the price—in time, effort, and money—needed to secure FDA permission to share potentially valuable new therapeutic information with physicians about a previously approved drug.

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