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John Wiley & Sons, Inc. v. Kirtsaeng: The Uncertain Future of the First-Sale Doctrine

Benjamin Hamborg

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Note

Rethinking Off-Label Regulation in the Wake of *Sorrell v. IMS Health*: Can State Involvement Compensate for Waning FDA Authority to Curb Commercial Free Speech?

Ashley A. Zborowsky*

Off-label promotion and the U.S. Food and Drug Administration's (FDA, the Agency) current restrictions on commercial "free speech" have garnered much attention in recent years due to a district court ruling in *United States v. Caronia*¹ and a subsequent Supreme Court decision in *Sorrell v. IMS Health*.² *United States v. Caronia* is currently pending review in the Second Circuit following *Sorrell*—a highly anticipated ruling. The outcome of the *Caronia* case could have a staggering effect on FDA regulatory authority with respect to promotional activity, and has been the topic of much scholarly debate. However, First Amendment rights and commercial free speech are not novel issues in the context of pharmaceutical and device law. While many entities have challenged the constitutionality of FDA's ban on off-label promotion, in and out of the courtroom, deference to Agency interpretations of relevant provisions of the Food, Drug and Cosmetic Act (FDCA) has enabled FDA to recover billions of dollars in penalties from manufacturers for off-label promotional activities.³

Off-label promotion is, essentially, the act of marketing or promoting regulated products for uses other than those ap-

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* Law Student at the University of Minnesota Law School. The author would like to thank Professor Ralph Hall, Brandon McDonough, and Terri Zborowsky for their thoughtful editing and feedback.

1. *United States v. Caronia*, 576 F. Supp. 2d 385 (E.D.N.Y. 2008).
2. *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653 (2011).
3. George S. Craft, Jr., *Promoting Off-Label in Pursuit of Profit: An Examination of a Fraudulent Business Model*, 8 HOUS. J. HEALTH L. & POL'Y 103, 108–120 (2007) (discussing the scope of both civil and criminal penalties in recent off-label and false claims enforcement).

proved by the FDA.⁴ Because the Court in *Sorrell* clearly establishes that pharmaceutical marketing is a form of protected speech,⁵ the FDA must consider other regulatory pathways to ensure the safety and efficacy of regulated products. The implications of the *Sorrell* decision will not be fully understood until it is applied by lower courts, and a thorough analysis of its holding is outside the scope of this Note. Still, legal scholars and industry actors have posited that, in the wake of *Sorrell*, FDA authority to regulate off-label promotion may be waning.⁶ However, the Agency's off-label ban is rooted in its longstanding mission to safeguard public health—for this reason, there remains a strong governmental interest in this issue that should be addressed.

This Note explores the regulatory landscape relative to off-label promotion and proposes alternatives to current FDA practices. Part I provides an overview of these practices and discusses physician autonomy to prescribe off-label. Part II discusses why other proposed alternatives to curtail off-label use—such as reimbursement—are insufficient to address the problem. Finally, Part III contemplates how state attempts at regulating the practice of medicine may provide a viable alternative to current regulatory uncertainties under the FDA. This Note concludes that state-level involvement, namely, by regulating off-label prescribing, may be the most effective way to ensure regulated products are used only for their approved indications.

4. See, e.g., Randall Stafford, *Regulating Off-Label Drug Use—Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1428 (2008). Manufacturing entities seeking regulatory approval must submit clinical data demonstrating the safety and effectiveness of a given product for a particular use. See *id.* at 1427. The product itself does not gain regulatory approval overall; rather, it receives approval for a specific indication or use—the treatment of hypertension for example. See *id.* Any use of the product outside of the approved indication(s) borne on the product label can be considered “off-label.” See *id.*

5. *Sorrell*, 131 S. Ct. at 2659 (“Speech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment.”).

6. See, e.g., *Analysis of US Supreme Court's Holding that a Ban on Sales of Prescription Drug Information Violates the First Amendment*, BAKER BOTTS (June 30, 2011), http://www.bakerbotts.com/file_upload/2011JunLifeSciencesSorrellVsIMSPage2.htm (addressing the issue of First Amendment rights in the context of *Caronia* and *Sorrell*).

I. OVERVIEW OF OFF-LABEL PROMOTION, REGULATION, AND PENALTIES

A. FDA REGULATION OF OFF-LABEL PROMOTION

The FDCA does not directly prohibit off-label promotion. Rather, two related statutory provisions indirectly provide authority for this ban. Section 355(a) of the FDCA prevents manufacturers from introducing a new product into interstate commerce that has not yet secured FDA approval.⁷ Marketing a drug or device for any use other than that for which it has been approved (including no use at all) violates this provision.⁸ Further, section 352(a) prohibits manufacturers from introducing into interstate commerce any “misbranded” drug or device.⁹ A product is considered misbranded if its label contains any false or misleading information or lacks sufficient information to support safe use.¹⁰ Advertising and promotional materials can be considered part of a product’s label if distributed by the manufacturer for purposes of explaining its use.¹¹ The promotional material need not physically accompany the sale of the product and may also take the form of verbal representations.¹²

However, once a product has gained FDA approval, it can be prescribed to treat any illness or disease state regardless of its approved indication(s).¹³ Approximately twenty-one percent

7. Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(a) (2006).

8. *See id.*; *see also* Krista Hessler Carver, *A Global View of the First Amendment Constraints on FDA*, 63 FOOD & DRUG L.J. 151, 167 (2008) (“According to the FDA, manufacturer promotion for an off-label use constitutes misbranding (because the product is not labeled for the promoted intended use).”).

9. 21 U.S.C. § 352 (2006). Introducing an adulterated or misbranded drug into interstate commerce is considered a “prohibited act” under the statute. *See* 21 U.S.C. § 331(a) (2006).

10. 21 U.S.C. § 352(a) & (f) (2006); *see also* Carver, *supra* note 8, at 156–57.

11. *See* Carver, *supra* note 8, at 163–165; *see also* Michelle M. Mello et al., *Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals*, 360 NEW ENG. J. MED. 1557, 1558 (2009) (“Printed and visual materials are considered part of a drug’s labeling if they are distributed by the manufacturer for the purpose of explaining the uses of the drug, even if they are not packaged with the drug.”).

12. Mello, *supra* note 11.

13. James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L.J.

of all prescriptions are prescribed for off-label uses.¹⁴ Off-label use, in many instances, generates the most sales for a given product.¹⁵ This is often the case in the field of pediatric medicine, where an estimated sixty-two percent of all outpatient prescriptions are used off-label for children.¹⁶ Therefore, the impetus for off-label promotion is derived from the discretion of physicians to act autonomously in caring for their patients.¹⁷ Off-label prescribing raises concerns from a regulatory perspective, where FDA has been administratively charged with safeguarding public health and welfare.¹⁸

The governmental interest in a uniform approval process for new drug and device indications is quite compelling. A new product must be demonstrated as “safe and effective” with the support of clinical evidence before it can be introduced into the U.S. market. The ban on off-label promotion is intended to curtail widespread use of products that have not yet met this burden for a particular indication, and may or may not pose a risk to public health. For this reason, the off-label ban seeks to incentivize clinical research to ensure optimal safety. However, the length and expense associated with FDA’s current process can effectively deter companies from seeking approval for additional efficacy indications.¹⁹ This is particularly true when off-label use of a product becomes common medical practice.²⁰ Where clinical trials to demonstrate safety and effectiveness

71, 76–77 (1998). Note that only manufacturers can promote for an off-label use, and are subject to federal regulation of marketing activities. Physicians, however, can prescribe for the same off-label use without consequence due to state regulation of the practice of medicine.

14. *Shopper Guide to Prescription Drugs: “Off-Label” Drug Use*, CONSUMERREPORTS.ORG, 4–5 (2007) [hereinafter CONSUMERREPORTS], available at <http://www.consumerreports.org/health/resources/pdf/best-buy-drugs/money-saving-guides/english/Off-Label-FINAL.pdf> (last visited Oct. 23, 2011).

15. *See id.*

16. Alicia T.F. Bazzano et al., *Off-Label Prescribing to Children in the United States Outpatient Setting*, 9 ACAD. PEDIATRICS 81, 84 (2009).

17. Beck, *supra* note 13, at 72.

18. *What We Do*, FOOD & DRUG ADMIN., <http://www.fda.gov/aboutfda/whatwedo/default.htm> (last visited Oct. 25, 2011).

19. *See* Stafford, *supra* note 4, at 1428 (arguing that off-label use may encourage manufacturers to “game the system”); *see also* Craft, *supra* note 3, at 103–31 (2007) (stating generally that off-label promotion is often the result of a calculated and fraudulent business plan).

20. *See* Stafford, *supra* note 4, at 1427.

would typically delay market entry, manufacturers of such products have little incentive to pursue regulatory approval once off-label use is pervasive and actively generating sales.²¹ As one scholar notes:

[T]he popularity of off-label uses has only increased in recent decades, perhaps due in part to the rigorous and expensive nature of the approval process. The new drug approval process may cost hundreds of millions of dollars. A discovery of a new use may occur after the drug has exceeded or is near the end of its normal patent protection; thus, the economic incentives for manufacturers to seek approval for new drug uses when a drug has gone off-patent is significantly reduced.²²

FDA has attempted to crack down on off-label activity in recent years for this reason, imposing billion dollar penalties on corporations that continue to engage in these practices.²³ Most notably, in 2009 Pfizer, Inc. paid an astounding \$2.3 billion—the largest criminal fine in U.S. history—for the off-label promotion of Bextra, a drug approved for the treatment of arthritis and severe menstrual pain.²⁴ The magnitude of this fine was only eclipsed by the \$16.8 billion in revenue generated by the sale of Bextra from 2001–2008.²⁵ Pfizer had previously been charged with misbranding in 2002 for its off-label promotion of the drug Neurontin.²⁶ Less than a decade later, the record-breaking penalties for Pfizer's recidivism signaled a trend towards heightened regulatory scrutiny of corporate marketing practices.²⁷

Despite increases in penalties and criminal sanctions, many manufacturers seem to view fines as a cost of doing business and continue to engage in off-label promotion simply because of the revenue it can generate.²⁸ Arguably, current FDA

21. CONSUMER REPORTS, *supra* note 14, at 1.

22. Briana R. Barron, *Silent Warning: The FDA's Ban on Off-label Speech: Is It Protecting Our Safety?* 94 MARQ. L. REV. 983, 989 (2011).

23. *See, e.g.*, Craft, *supra* note 3, at 105–06.

24. David Evans, *Pfizer Broke the Law by Promoting Drugs for Unapproved Uses*, BLOOMBERG (Nov. 9, 2009), <http://www.bloomberg.com/apps/news?pid=newsarchive&sid=a4yV1nYxCGoA>.

25. *Id.*

26. *Id.*

27. Mark P. Walters, *Medical Device Advertising to Receive Greater FDA Scrutiny*, FROMMER LAWRENCE & HAUG (Sept. 29, 2010), available at <http://www.fdalawyersblog.com/2010/09/medical-device-advertising-to.html> (“[E]xpanded CDRH staff will increase focus on advertising and promotion of medical devices, specifically targeting ‘off-label’ claims made by medical practitioners.”).

28. Melly Alazraki, *For Big Pharma, Is Breaking the Law the Price of Doing Business?*, DAILYFINANCE (Feb. 1, 2010), <http://www.dailyfinance.com/sto>

practices are insufficient to curb such lucrative activities.²⁹ Constitutional challenges to off-label regulation only frustrate the existing regulatory scheme. Thus, where *Sorrell* and subsequent cases can be interpreted to authorize such contentious practices on First Amendment grounds, it becomes imperative that additional regulatory alternatives be explored.³⁰

B. OFF-LABEL PROMOTION AS A FORM OF PROTECTED SPEECH

1. The Central Hudson Test

First Amendment challenges to FDA's ban on off-label speech prompted courts to apply the four-prong test set forth in *Central Hudson Gas & Electric Corp. v. Public Service Commission*.³¹ The test requires courts to consider whether (1) the speech concerns "lawful activity" that is not misleading, (2) "the asserted government interest to be served by the restriction on commercial speech is substantial," then—if both of these conditions have been met—whether (3) "the regulation directly advances the governmental interest asserted," and (4) the regulation "is not more extensive than necessary to serve that interest."³² Commercial speech must be "inherently" rather than "potentially" misleading.³³

Applying this test, courts have concluded that off-label speech *concerns* lawful activity as it relates to the underlying conduct of physicians, who can prescribe off-label at their professional discretion—constituting a lawful activity.³⁴ Though this element of the first prong is satisfied as it pertains to off-label promotion, FDA has consistently argued that off-label

ry/company-news/for-big-pharma-is-breaking-the-law-the-price-of-doing-business/19340271/.

29. See, e.g., Craft, *supra* note 3, at 122 (claiming that recent settlements for off-label conduct indicate these activities are likely to persist).

30. See, e.g., Rebecca Dresser & Joel Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37 J.L. MED. & ETHICS 476, 483 (2009) (arguing for further policy reform and congressional action as needed "to deter inappropriate off-label prescribing").

31. Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n, 447 U.S. 557, 566 (1980). The test espoused in *Central Hudson* has become the judicial touchstone for evaluating whether government restrictions on commercial speech violate the First Amendment generally—this includes off-label marketing activities. *Id.*

32. *Id.* at 557.

33. Barron, *supra* note 22, at 999–1000.

34. *Id.*

speech is inherently misleading due to the fact that the Agency has not yet evaluated nor approved the basis for such claims.³⁵ Lower courts, however, have rejected this argument, and truthful, non-misleading speech regarding off-label use has been held to satisfy the entire first prong of the *Central Hudson* test.³⁶

With respect to the second prong of the test, courts have had to determine whether the government interest to be served is substantial—arguably, this can be read as substantial *enough* to justify the restriction on free speech.³⁷ In the case of off-label promotion, there are two related interests at stake—the first is the integrity of the regulatory process itself, and the second, is safeguarding the public health.³⁸ The Supreme Court in *Thompson v. Western States Medical Center* held that “[p]reserving the new drug approval process is clearly an important governmental interest”³⁹ However, while *Western States* expressly acknowledged this interest as substantial, the Court questioned FDA’s assertion that the ban on commercial free speech is “not more extensive than is necessary to serve [those] interest[s].”⁴⁰

To satisfy the third prong of *Central Hudson*, the government must demonstrate that the regulation at issue directly advances its interest in a “material way.”⁴¹ In *Western States*, FDA argued that its “premarket approval process, under which manufacturers are required to put their proposed drugs through tests of safety and effectiveness in order to obtain . . . approval to market the drugs, is the best way to guarantee drug safety and effectiveness.”⁴² Applied in the context of off-label promotion, the ban could be construed to force compliance with the established regulatory process so as to achieve the Agency’s primary goal.⁴³ However, the Court ultimately held

35. *Id.* at 1000.

36. *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998); *see also* Barron, *supra* note 22, at 1000 (detailing the application of *Central Hudson* to off-label promotion and commercial speech regulation).

37. Carver, *supra* note 8, at 173.

38. Barron, *supra* note 22, at 1001; *see also* Carver *supra* note 8, at 173.

39. *Thompson v. Western States Med. Ctr.*, 535 U.S. 357, 358 (2002).

40. *Id.* at 358–59 (alteration in original) (quoting *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n*, 447 U.S. 557, 566 (1980)).

41. *Friedman*, 13 F. Supp. 2d at 71 (quoting *Edenfield v. Fane*, 507 U.S. 761, 770–71 (1993)).

42. *Western States*, 535 U.S. at 369.

43. *See* Beck, *supra* note 13, at 84–85 (discussing the patient perceptions

that—while the governmental interest in protecting the public health is in fact substantial—the statute at issue did not directly advance this goal.⁴⁴

With respect to the third and fourth prongs of the *Central Hudson* test, other courts, however, have found that restriction of manufacturers' promotional activities is "one of the few mechanisms available to FDA" to advance its regulatory goals.⁴⁵ Additionally, where the "drugs subject to FDA approval are *already* in interstate commerce . . . the obvious restriction on conduct is unavailable."⁴⁶ For these reasons, FDA has argued that there is no less restrictive means of curtailing off-label conduct than to ban the speech that facilitates or encourages such conduct.⁴⁷ Yet in *Washington Legal Foundation v. Friedman*, the U.S. District Court for the District of Columbia court held that FDA restrictions were "considerably more extensive than necessary to further the substantial government interest."⁴⁸ Similarly in *Western States*, the Court stated "[t]he fact that 'all of [these alternatives] could advance the Government's asserted interest in a manner less intrusive to . . . First Amendment rights' indicated that the law was 'more extensive than necessary.'"⁴⁹

Therefore, it is with the fourth prong of *Central Hudson* that FDA's ban on commercial speech has failed to pass constitutional muster.⁵⁰ For example, though a settlement agreement was ultimately reached, Allergan, Inc. recently argued in an FDA enforcement action that "FDA has not provided exceptions permitting communication of truthful medical evidence or oth-

of drugs being used off-label as either unapproved or disapproved).

44. *Western States*, 525 U.S. at 375. At issue in this case is § 127(a) of the Food and Drug Modernization Act of 1997 (FDAMA) restricting the advertising or promotion of compounded drugs, as compounds are exempted from FDA's standard drug approval process. *Id.* at 360.

45. *Friedman*, 13 F. Supp. 2d at 72.

46. *Id.*

47. *Western States*, 525 U.S. at 368–71.

48. *Friedman*, 13 F.Supp.2d at 73.

49. *Western States*, 525 U.S. at 371–72 (alteration in original) (quoting *Rubin v. Coors Brewing Co.*, 514 U.S. 476, 491 (1995)). The Court in *Western States* went on to find that the government interest "could be satisfied by the far less restrictive alternative of requiring each compounded drug to be labeled with a warning that the drug had not undergone FDA testing and that its risks were unknown." *Id.* at 376.

50. Barron, *supra* note 22, at 1003.

erwise accommodating First Amendment concerns.”⁵¹ Conceivably, the suppression of truthful, non-misleading speech regarding off-label use of a product is far-reaching in its attempt to regulate misuse of such products.⁵² Despite the fact that the Agency has managed to dodge the proverbial bullet when it comes to First Amendment challenges, existing case law is generally unfavorable. As such, FDA’s ban may not be sufficiently “narrowly tailored” to survive First Amendment challenges, particularly following the Supreme Court’s decision in *Sorrell*.⁵³

As noted by the Supreme Court in *Western States*, not all regulation of commercial speech is unconstitutional.⁵⁴ However, the Court had yet to officially recognize speech related to pharmaceutical marketing or promotion as entitled to First Amendment protection until just last year in *Sorrell*.⁵⁵

2. Recent Developments in First Amendment Jurisprudence: Potential Implications of *Sorrell v. IMS Health* and *United States v. Caronia*

On June 23, 2011, a six-three majority of the Supreme Court struck down a Vermont law that restricted the “sale, disclosure, and use of pharmacy records . . . reveal[ing] the prescribing practices of individual doctors.”⁵⁶ This process of pharmaceutical promotion is referred to as “detailing.”⁵⁷ The Vermont Prescription Confidentiality Law of 2007 (Act 80) prohibited such disclosure practices without provider consent, subject only to the exception that prescriber-identifying information could be disseminated and used for specified purposes.⁵⁸ By enacting this legislation, Vermont intended to impede man-

51. Memorandum of Law In Support of Motion for Preliminary Injunction at 12, *Allergan v. United States*, No. 09-1879 (D.C. Cir. filed Oct.1, 2009) (capitalization in original altered).

52. Barron, *supra* note 22, at 1002–03; *see also* Coleen Klasmeier & Martin H. Redish, *Off-Label Prescription Advertising, the FDA and the First Amendment: A Study in the Values of Commercial Speech Protection*, 37 AM. L.J. & MED. 315, 356 (2011) (“Whether it would be simpler . . . for the government to achieve its goal indirectly by suppressing protected speech is irrelevant to the constitutional inquiry. The suppression of fully protected, potentially valuable expression is far too high a price to pay for governmental convenience.”).

53. *See* ROPES & GRAY, *supra* note, at 1.

54. *Western States*, 535 U.S. at 367.

55. *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653 (2011).

56. *Id.* at 2659.

57. *Id.*

58. *Id.* at 2660.

ufacturers' ability to sway providers towards brand-name drugs in lieu of generic equivalents, thereby helping to reduce state health care costs.⁵⁹

Though the constitutional challenge to Act 80 was unsuccessful in district court, the Second Circuit overturned the ruling, holding that the statute "is a commercial speech restriction that does not directly advance the substantial state interests asserted by Vermont, and is not narrowly tailored to serve those interests, the statute cannot survive intermediate scrutiny under *Central Hudson*."⁶⁰ In his majority opinion, Justice Kennedy affirmed the decision of the Second Circuit, noting that the burden placed on protected expression *is not* justified by the State's asserted interest in physician confidentiality, protecting doctors from "harassing" sales tactics, *or* protecting the integrity of the physician-patient relationship.⁶¹ Further, the statute did not permissibly advance the State's goal of reducing health care costs.⁶² Lastly, the State offered no explanation as to why other available remedies—such as declining to meet with "detailers"—would be inadequate.⁶³ Justice Kennedy also specifically noted that Vermont does not, in fact, contend that the practice of detailing necessarily results in the dissemination of false or misleading information.⁶⁴

The Court in *Sorrell* expressly stated that "[s]peech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment."⁶⁵ The holding in this case may have a profound effect on FDA's ban of off-label promotion, despite the fact that the case concerns pharmaceutical marketing generally and does not specifically address FDA regulatory authority or off-label activity.⁶⁶ According to legal analysts, the *Sorrell* decision is "likely to affect future court decisions about FDA's ability to bar manufacturers from providing truthful information to physicians re-

59. *Id.* at 2661; *see also* ROPES & GRAY, *supra* note, at 1 (describing the purpose of Act 80).

60. *IMS Health Inc. v. Sorrell*, 630 F.3d 263, 267 (2nd Cir. 2010).

61. *Sorrell*, 131 S.Ct. at 2669–70.

62. *Id.* at 2670–71.

63. *Id.* at 2669.

64. *Id.* at 2672.

65. *Id.* at 2659.

66. ROPES & GRAY, *supra* note, at 2.

garding off-label uses of approved pharmaceutical products.”⁶⁷ Therefore, where the commercial speech at issue is both truthful and non-misleading, *Sorrell* may have the effect of halting a *Central Hudson* inquiry as to whether or not the restriction on speech is justified—deeming speech in aid of pharmaceutical marketing per se protected expression within the ambit of the First Amendment.⁶⁸

As indicated previously, the full effect of the Court’s holding in *Sorrell* will not be understood until it is applied by lower courts. Currently pending review in the Second Circuit, *U.S. v. Caronia* may be a pivotal ruling for this reason.⁶⁹ Unlike *Sorrell*, *Caronia* specifically deals with the issue of speech vis-à-vis off-label promotion. Alfred Caronia, a sales representative for Orphan Medical, Inc., pled guilty to felony misbranding related to off-label promotion of the drug Xyrem.⁷⁰ The district court for the Eastern District of New York refused to dismiss the criminal charges against Caronia—upholding FDA’s off-label ban under the four-part *Central Hudson* test—stating that it is “unable to identify non-speech restrictions that would likely constrain in any effective way manufacturers from circumventing [the] approval process.”⁷¹

Following this holding, it was thought that *Caronia* would make it *more* difficult for pharmaceutical and device manufacturers to prevail in off-label cases on First Amendment grounds alone.⁷² However, *Sorrell* quickly followed *Caronia*; whether or not the Second Circuit extends the analysis in *Sorrell* on review

67. BAKER BOTTS, *supra* note 6; *see also* ROPES & GRAY, *supra* note, at 3 (commenting that the *Sorrell* holding “plants a stake in the ground firmly on the side of First Amendment rights”).

68. *Sorrell*, 131 S. Ct. at 2659 (“Speech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment.”).

69. *See Caronia Update: What Went Down at the Oral Argument*, DRUG AND DEVICE LAW (Jan. 21, 2011, 2:15 PM), <http://druganddevicelaw.blogspot.com/2011/01/caronia-update-what-went-down-at-oral.html> [hereinafter *Caronia Update*] (“We’ve blogged about *United States v. Caronia* before. In fact, some might say we’re a bit obsessed by it, and with good reason; the First Amendment’s a big deal to us . . .”).

70. *United States v. Caronia*, 576 F. Supp. 2d 385, 388–89 (E.D.N.Y. 2008). Xyrem®, also known as sodium oxybate, is a federally-controlled substance approved for the treatment of narcolepsy. Misuse of the drug can have harmful side effects, especially at high doses. U.S. FOOD & DRUG ADMIN., MEDICATION GUIDE: XYREM 1–2 (Nov. 18, 2005), *available at* <http://www.fda.gov/downloads/drugs/drugsafety/ucm089830.pdf>.

71. *Caronia*, 576 F. Supp. 2d at 401.

72. SIDLEY AUSTIN, *supra* note 6, at 2.

to overturn Caronia's felony conviction may have broad implications for future challenges to FDA regulatory authority. Further challenges on First Amendment grounds in light of *Caronia* may erode FDA's ability to use off-label speech as a proxy for conduct. The relationship between misbranding, regulated speech, and the conduct FDA seeks to control presents a wide range of issues that cannot be adequately addressed under the existing regulatory framework.⁷³ This issue, however, is in many ways broader than *Caronia*, and the need to protect the public from potentially dangerous off-label use undoubtedly warrants further discussion.

C. THE SPEECH VERSUS CONDUCT DISTINCTION

The inherent problem with off-label promotion is that it encourages off-label conduct, which is the use of regulated products outside of their approved indications. Thus, FDA's regulatory authority to curb off-label speech does not necessarily strike at the heart of the issue it seeks to resolve:⁷⁴

A major defect in the FDA's current restrictive approach to the regulation of off-label promotion is that it reflects the FDA's decision to address conduct as to which it had repeatedly expressed concern by regulating speech endorsing that conduct—and doing so at a categorical level—rather than by regulating the underlying conduct itself.⁷⁵

This is due, in large part, to statutory constraints on FDA authority as well as federalism concerns with respect to individual states' regulation of medical practice with the state.⁷⁶ FDA's restriction on commercial speech is one of the few mechanisms available to the Agency to control harmful misuse of regulated products.⁷⁷

Off-label promotion is problematic—even that which is truthful and non-misleading because it arguably encourages off-label prescribing of products that have not yet demonstrated

73. See, e.g., Klasmeier, *supra* note 52, at 342–43 (arguing that, despite a strong public health interest, FDA's off-label ban is unjustifiable under existing commercial speech doctrine).

74. *Id.* at 354 (“[W]hile categorically prohibiting promotion of off-label use, the government has for the most part not restricted off-label use.”).

75. *Id.* at 335.

76. S. REP. NO. 74-361, at 3 (1935) (stating that the FDCA was “not intended as a medical practices act and [did] not interfere with the practice of the healing art”).

77. *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 72 (D.D.C. 1998).

safety and effectiveness *as required by* FDA.⁷⁸ Both FDA and courts have repeatedly acknowledged, however, that FDA does not have the statutory authority to regulate the practice of medicine.⁷⁹ Therefore, though FDA may seek to bar manufacturers from facilitating off-label conduct, the conduct itself is not unlawful nor within FDA's regulatory purview. Without the ability to regulate physician conduct, "the federal government has limited methods to ensure the quality and necessity of off-label drug use" in its attempts to secure and promote the public health.⁸⁰

Though FDA strongly enforces the ban on off-label promotion, it is both insufficient and impractical to sustain such a categorical standard in this domain. Further, in light of current uncertainties posed by *Sorrell* and *Caronia*, FDA's ability to use speech as a proxy to regulate undesirable conduct may soon be compromised.⁸¹ The speech/conduct distinction then becomes critical to addressing the regulatory dilemma facing FDA; that is, how to balance concerns of safety and efficacy with the competing interests of patient care and physician autonomy.⁸² This Note will argue that future efforts aimed at curtailing off-label use should be directed at physician conduct *rather than* that of manufacturers. Conduct-based control mechanisms can be expected to play a significant role in future off-label regulation, as speech-based restrictions are being met with heightened scrutiny under the First Amendment. Although this approach will necessarily require state-level involvement, FDA may not have many other options pending the outcome of *Caronia* and other potential constitutional challenges.

78. Klasmeier, *supra* note 52, at 332 ("Given the FDA's determination, often repeated in the context of off-label use, that new uses are by definition unsafe and ineffective because they lack FDA approval, the FDA's position in the unapproved new drugs context that not all such drugs are unsafe or ineffective is hard to comprehend.")

79. S. REP. NO. 74-361, at 3 (1935); *see also* Beck, *supra* note 13, at 76 ("FDA never has had authority to regulate the practice of medicine . . .").

80. Amy E. Todd, *No Need for More Regulation: Payors and Their Role in Balancing the Cost and Safety Considerations of Off-Label Prescriptions*, 37 AM. J.L. & MED. 422, 423 (2011).

81. *See Caronia Update*, *supra* note 69 ("*Caronia* represents an opportunity for a Court of Appeals to pass on the constitutionality of FDA's draconian and convoluted off-label promotion rules.")

82. *See Stafford*, *supra* note 4, at 1427 (citing both the pros and cons of off-label prescribing; namely, that access and treatment based on emerging evidence must be adequately weighted against safety considerations).

D. PHYSICIAN AUTONOMY WITH RESPECT TO OFF-LABEL PRESCRIBING

Within the bounds of acceptable medical practice, physicians enjoy broad discretion to prescribe any approved product for off-label use.⁸³ FDA has even recognized that off-label prescribing may, in fact, be the standard of care in some instances.⁸⁴ The advantages of physician autonomy with respect to off-label use are fairly straightforward; patients gain earlier access to treatments and therapies and physicians are allowed “to adopt new practices based on emerging evidence.”⁸⁵ Much literature exists regarding the efficacy of off-label uses in treating a variety of conditions and disease states—published by physicians and often disseminated by manufacturers in support of such use.⁸⁶ FDA’s ban on off-label speech has been touted as obstructing the dissemination of medical literature and emerging evidence to physicians, arguably inhibiting informed decision-making.⁸⁷

While physicians are of course subject to claims of medical malpractice, off-label prescribing is not itself evidence of malpractice *per se*.⁸⁸ Therefore, the tort system may not provide a reliable control mechanism with respect to off-label conduct and is by no means an effective substitute for regulatory oversight.⁸⁹ Yet because off-label use may constitute the accepted

83. See Mello, *supra* note 11, at 1557 (emphasizing the fact that physicians may freely prescribe drugs for off-label uses despite the fact that drug manufacturers may not promote for such uses).

84. U.S. FOOD & DRUG ADMIN., 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 3 (Jan. 2009), available at <http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0053-gdl.pdf> (“[O]ff-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care.”).

85. Stafford, *supra* note 4, at 1427–28 (“[A] key promotional strategy is providing physicians with journal articles about off-label uses.”).

86. Gregory Conko, *Hidden Truth: The Perils and Protections of Off-Label Drug and Medical Device Promotion*, 21 HEALTH MATRIX 149, 150 (2011) (“[Physicians not paid by a drug or device manufacturer] are free to tout to benefits of off-label uses in any way to any listener.”).

87. *Id.* at 151.

88. Todd, *supra* note 80, at 424 (citing the fact that an off-label drug use is never conclusive to establish malpractice liability, though off-label prescribing may be introduced as evidence to substantiate a claim for negligence).

89. *But see id.* at 439 (arguing that tort liability can effectively “fill the gaps” where payor or market legislation fails and that the threat of litigation

standard of care in some fields—oncology, for example—the reverse can also be true for physicians. The American Medical Association (AMA) has noted that, in some cases, physicians may be guilty of malpractice for *failure* to adhere to the off-label standard of care and has lobbied extensively to preserve physician autonomy in the interest of patient care.⁹⁰

In 2007, the AMA passed Resolution 918 reaffirming its position that the off-label use of FDA-approved drugs and devices, when supported by clinical evidence, expert consensus opinion, or accepted standards of care, is not only permissible but encouraged among physicians.⁹¹ The resolution lobbies support for “the autonomous clinical decision-making authority of a physician” and states that while ongoing research and clinical trials to verify outcomes “should be encouraged and supported,” the lack of such data should not impede off-label use of regulated products.⁹² Further, scientific trials should demonstrate the “clinical benefit” of an off-label use despite the fact that such trials *may not* lead to an approved indication.⁹³ Inside of the medical community, many seem to agree with this position, and argue that regulations should follow—not precede—science and that government should not impede a physician’s ability to practice medicine when an off-label use would be optimal for patient care.⁹⁴

Still, vast physician autonomy may compromise the integrity of a uniform approval process, as cited in the *New England Journal of Medicine*:

Physicians’ freedom to prescribe drugs off-label carries important advantages. . . . At the same time, off-label use has potentially negative consequences. It undercuts expectations that drug safety and efficacy have been fully evaluated. When newer, more expensive drugs are used off-label, it increases health care costs. It undermines the incentives for manufacturers to perform rigorous studies—and instead subtly encourages them to game the system by seeking approval for sec-

on “failure to warn” claims may be sufficient to keep manufacturers in check).

90. Margaret Z. Johns, *Informed Consent: Requiring Doctors to Disclose Off-Label Prescriptions and Conflicts of Interest*, 58 HASTINGS L.J. 967, 968–69 (2007).

91. AM. MED. ASS’N HOUSE OF DELEGATES, RESOLUTION 918: PROHIBITION ON THE USE OF FDA-APPROVED DRUGS AND MEDICAL DEVICES OFF-LABEL 1 (2007) (on file with author).

92. *Id.*

93. *Id.*

94. Beck, *supra* note 13, at 79 (arguing that clinical variation and the time delay in regulations results in the government impeding or otherwise hindering the practice of medicine).

ondary indications for which clinical trials are less complicated and less expensive. And off-label use may discourage evidence-based practice.⁹⁵

A 2006 study published in *Archives of Internal Medicine* evaluated 725 million prescriptions and found that twenty-one percent of them were off-label; of that twenty-one percent, seventy-three percent were for a use that lacked any “firm scientific evidence.”⁹⁶ Though slightly dated, this information bolsters FDA’s argument in favor of greater regulatory controls. Physicians may, in fact, have misconceptions about the FDA approval process and the level of evidence supporting a drug’s indications.⁹⁷

A survey conducted at the University of Chicago Medical Center found physicians were more likely to hold the erroneous belief that a drug has FDA approval for an indication *if* they themselves had prescribed it for that particular indication.⁹⁸ This and related studies demonstrate the potential dangers of off-label use and highlight the need for greater oversight of prescribing practices relative to such risks.⁹⁹ Because regulating the practice of medicine is traditionally a space wholly reserved for states, state involvement is required to scrutinize off-label prescribing practices.¹⁰⁰

II. ANALYSIS

A. THE CASE FOR STATE INVOLVEMENT: WHY REIMBURSEMENT ALONE IS INSUFFICIENT TO CURTAIL OFF-LABEL PRACTICES

It is widely argued that curbing reimbursement for unapproved uses will reduce off-label activity and, in fact, promote

95. Stafford, *supra* note 4, at 1427–28.

96. David Radley, Stan Finkelstein & Randall Stafford, *Off-label Prescribing Among Office-Based Physicians*, 66 ARCHIVES OF INTERNAL MED. 1021, 1023 (2006).

97. Rick Nauert, *Off-Label Use May be Off-Track*, PSYCH CENTRAL (Aug. 24, 2009), <http://psychcentral.com/news/2009/08/24/off-label-use-may-be-off-track/7926.html>.

98. *Id.*; *see also* Evans, *supra* note 24 (“Most physicians don’t keep track of FDA-approved uses of drugs . . .”).

99. Todd, *supra* note 80, at 426 (discussing the risks associated with off-label use) (“[W]hile off-label prescribing can be very beneficial to some patients, this common practice can also be unnecessary and, in some cases, very risky.”).

100. *Id.* at 429.

health care cost containment.¹⁰¹ Third-party payor reimbursement decisions for off-label prescriptions purport to act as a proxy for regulatory oversight, dissuading physicians (and their patients) from off-label use.¹⁰² In light of current regulatory uncertainties, this alternative seems much more capable of curtailing off-label use than enforcing a ban on promotion—even to the tune of \$2.3 billion.¹⁰³ Yet due to the benefits of off-label prescribing, many states have actually done the exact opposite—enacting legislation requiring insurers to cover off-label prescriptions for certain conditions such as cancer.¹⁰⁴

The Centers for Medicare and Medicaid Services (CMS) make up the largest payor of health care costs in the country.¹⁰⁵ CMS has made national coverage decisions have been made to reimburse those services deemed “reasonable and necessary” pursuant to requirements of the Social Security Act.¹⁰⁶ The “reasonable and necessary” standard is not, however, a corollary to FDA’s “safe and effective” benchmark requirement.¹⁰⁷ As a result, CMS routinely reimburses off-label use of regulated products.¹⁰⁸ Thus, because CMS coverage decisions heavily influence the coverage decisions of private third-party payors, mandates alone are unlikely to curtail off-label use.¹⁰⁹ This is true for several reasons, namely: 1) CMS coverage decisions are not binding across localities, though national coverage decisions preempt state mandates; 2) self-insured plans are exempt from state mandates under the Employee Retirement Income

101. *Id.* at 422–23.

102. *Id.*

103. *See generally* Evans, *supra* note 24 (discussing the recidivism of “Big Pharma” with respect to off-label activity despite the possibility of excessive fines and penalties being imposed by the government).

104. *2006 Prescription Drug Legislation*, NAT’L CONF. STATE LEGS. (March 2009), <http://www.ncsl.org/issues-research/health/archive-2006-prescription-drug-state-legislation.aspx>.

105. MEDPAC, REPORT TO THE CONGRESS: MEDICARE PAYMENT POLICY, app. B 8 (March 2003), *available at*: http://www.medpac.gov/documents/mar03_entire_report.pdf.

106. Social Security Act, 42 U.S.C. § 1395y(a)(1)(A) (2006) (“[N]o payment shall be made . . . for any items or services . . . which . . . are not are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.”).

107. *See id.*

108. *See, e.g.*, Todd, *supra* note 80, at 428, 434 (commenting that Medicare recently relaxed rules regarding payment for certain types of off-label cancer treatments).

109. *See id.* at 434 (“Most private insurers base their reimbursement models on Medicare’s rules.”).

Security Act (ERISA); and 3) the practice of medicine directly influences reimbursement; therefore, regulating the practice of medicine itself is sufficient to affect coverage determinations.¹¹⁰

1. Coverage Decisions Are Not Binding Across Localities

National Coverage Determinations (NCDs), administered by the Agency's national office, are usually reserved for items and services that affect a large number of beneficiaries.¹¹¹ NCDs cannot vary by region and all contractors are required to comply with such coverage decisions.¹¹² While NCDs are binding, the majority of coverage decisions are made at the local level through regional contractors.¹¹³ The country is divided into eleven regions, and each regional contractor issues its own Local Coverage Determinations (LCDs)—stipulating covered items and services for that jurisdiction.¹¹⁴ If a contractor serves multiple jurisdictions, uniform LCDs are encouraged.¹¹⁵ However, a regional LCD by one contractor does not necessarily affect nor influence the LCD of another.¹¹⁶ Contractors can develop their own LCDs for “reasonable and necessary” services not yet addressed by national determinations—making it especially difficult to regulate reimbursement for off-label uses.¹¹⁷

It is not uncommon that five or more LCDs apply to the same product or procedure.¹¹⁸ Moreover, national coverage decisions are federally regulated and preempt both regional decisions as well as state mandates either in favor of or against off-label use.¹¹⁹ Such evidence-based determinations typically influence the coverage decisions of other payors, despite the fact that “reasonable and necessary” does not apply to private parties.¹²⁰ It follows, then, that constraining off-label coverage at

110. *See id.* at 434–38 (“While physicians have the ability to prescribe off-label as they wish without governmental interference, the prospect of non-payment will guide how doctors practice medicine.”).

111. MEDPAC, *supra* note 105, at 246.

112. *Id.*

113. *Id.* at 245.

114. *Id.* at 247.

115. *Id.*

116. *Id.*

117. *Id.*

118. *Id.*

119. *Id.*

120. *See* Todd, *supra* note 80, at 434 (“Most private insurers base their reimbursement models on Medicare’s rules.”).

the state level would necessarily require multi-state cooperation *and* CMS involvement. This approach seems unlikely given the fact that even though both CMS and FDA belong to the Department of Health and Human Services (HHS) and could, logically, join forces to impose the off-label ban, neither agency has elected to pursue this option. For private payors, ERISA preemption renders self-insured plans immune to state coverage mandates and further complicates such tactics.¹²¹

2. ERISA Preemption for Self-Insured Plans Compromises Efficacy

With self-insured plans, large employers can administer their own benefits as they have enough employees to create a solvent risk pool.¹²² Typically, a self-insured employer will establish a special trust to pay any incurred claims.¹²³ The employer assumes liability for all payments, rather than purchasing health coverage at a premium from a third-party carrier.¹²⁴ According to a recent study, nearly forty-seven million American employees receive health benefits from some form of self-insured plan.¹²⁵ Because the Employee Retirement Income Security Act (ERISA) regulates such plans—placing them outside the realm of state control—the sheer number of insured may be sufficient to render coverage mandates both impractical and ineffective.¹²⁶

The Employee Retirement Income Security Act of 1974 ap-

121. *See id.* at 437–38.

122. *See* U.S. DEPT. OF LABOR, ANNUAL REPORT ON SELF-INSURED GROUP HEALTH PLANS (2011) at ii–1, available at <http://www.dol.gov/ebsa/pdf/ACAReportToCongress032811.pdf>; Patricia Butler, *ERISA Implications for State Health Care Access Initiatives: Impact of the Maryland “Fair Share Act” Court Decision*, STATE COVERAGE INITIATIVES (Nov. 2006), <http://www.statecoverage.org/node/170> (follow “ERISA Implications . . .” hyperlink) (describing the applicability of ERISA to state health care initiatives aimed at employer-based income subsidies).

123. Butler, *supra* note 122.

124. *Id.*

125. *See id.* This report contains general information regarding self-insured employee health benefit plans and financial information regarding the sponsoring employers as required by The Patient Protection and Affordable Care Act of 2010. *See also* Patient Protection and Affordable Care Act, Pub. L. No. 111–148, 124 Stat. 119 (2010).

126. Todd, *supra* note 80, at 429 (noting that states may act to control off-label use, though “[t]he Employee Retirement Income Security Act (ERISA), a federal statute, preempts any state legislation. Consequently, these insurance mandate statutes are vulnerable to an ERISA challenge.”) (citation omitted).

plies to pensions and other benefits programs, such as health insurance, sponsored by private employers.¹²⁷ Under ERISA, states cannot deem employee benefit plans as insurers and are prohibited from regulating such plans directly.¹²⁸ A state law will be preempted by ERISA if it: 1) “[r]efers to an ERISA plan, either explicitly or by requiring reference to an ERISA plan in order to comply with the state law” or 2) “[h]as a connection with an ERISA plan by substantially affecting its benefits, administration, or structure.”¹²⁹ Therefore, state mandates banning coverage for off-label usage would not extend to self-insured plans—a significant and growing number of the country’s total insured population—and, for this reason, cannot provide a viable alternative to the current regulatory scheme nor its proposed alternatives.¹³⁰ *The Practice of Medicine Directly Influences Reimbursement*

Though ERISA challenges may render a reimbursement model impracticable, state regulation of off-label prescribing could potentially have the analogous effect of influencing coverage decisions and is not constrained or preempted by any federal statutes. A payor reimbursement model may, in fact, induce physicians to comport with established standards; however, theoretically, the model should work both ways. Just as the prospect of nonpayment will guide physician decision-making, payors also have a strong incentive to decrease costs and eliminate unnecessary or investigational usage.¹³¹ In establishing formularies¹³² or compendia,¹³³ frequency of use and acceptable standards of care may impact a payor’s coverage determination.¹³⁴ For example, if physicians in Ohio are prohibit-

127. Employee Retirement Income Security Act (ERISA), Pub. L. No. 93-406, 88 Stat. 829 (codified as amended at 29 U.S.C. § 1001 *et seq.* (2006)).

128. Butler, *supra* note 122, at 3-4.

129. *Id.* at 5 (citations omitted).

130. See Todd, *supra* note 80, at 438 (stating that limitations to state mandates are inherent due to ERISA preemption).

131. See *id.* at 434-35.

132. A formulary is a list of drugs that is preferred by a health insurance plan. Michael Bihari, *Understanding Your Health Plan Drug Formulary*, ABOUT.COM (Feb. 25, 2010), http://healthinsurance.about.com/od/prescriptiondrugs/a/understanding_formulary.htm.

133. In the medical context, a compendium is a guide for drug administration for the treatment of disease. See *NCCN Drugs & Biologics Compendium*, NAT'L COMPREHENSIVE CANCER NETWORK, http://www.nccn.org/professionals/drug_compendium/content/contents.asp (last visited Mar. 11, 2012).

134. See Todd, *supra* note 80, at 435.

ed from prescribing mifepristone off-label, there is no reason for carriers serving the region to reimburse for such use.¹³⁵ Moreover—though the law was struck down on First Amendment grounds—prohibiting pharmaceutical detailing to curb state healthcare costs was fundamental to the Vermont statute in *Sorrell*; this bolsters the argument that the practice of medicine can directly influence reimbursement.¹³⁶

Though some coverage decisions are made on a case-by-case basis, widespread state law restrictions of physician off-label prescribing may act to effectively curtail off-label activity from a purely economic perspective.¹³⁷ Some combination of reimbursement and other state-based controls—regulating the practice of medicine being one such option—may work in tandem to curtail intra-state off-label activity and have the potential to be adopted by neighboring states if successful. A lack or decline in FDA regulatory power need not impart the issues of off-label control, safety, and cost containment decisions into the hands of private parties.¹³⁸

B. *CORDRAY V. PLANNED PARENTHOOD*: REGULATING OFF-LABEL CONDUCT THROUGH THE PRACTICE OF MEDICINE

A recent case out of Ohio has grappled with the issue of off-label use in regulating the practice of medicine. Outside of the context of abortion policy and reproductive rights, the case may be illustrative of the ways in which state-based controls can be leveraged to accomplish Agency goals.

1. Off-label Prohibition in the State of Ohio: Examining *Cordray*

In 2009, the Ohio Supreme Court upheld a statute prohib-

135. See discussion *infra* Part II.B.

136. See *Sorrell v. IMS Health, Inc.*, 131 S. Ct. 2653.

137. See Todd, *supra* note 80, at 434–35 (“[T]he prospect of nonpayment will guide how doctors practice medicine.”). Perhaps a case study of health care trends in states with similar laws (e.g., Ohio) is needed to examine the efficacy of such a model. However, it is without a doubt that state involvement in this realm is necessary. See *generally* Dresser, *supra* note (concluding that some regulation of the medical profession itself will be necessary to tackle the problem of off-label use).

138. Todd, *supra* note 80, at 429 (contemplating the best way to address the inherent risks in off-label use and arguing that the private market may also be capable of regulating off-label activity through other mechanisms, particularly where state and federal laws are susceptible to preemption or constitutional challenge).

iting the use of mifepristone¹³⁹ (“RU-486”) outside of its approved indication.¹⁴⁰ Local providers, including Planned Parenthood, challenged the constitutionality of R.C. 2919.123, which required in part that in order to prescribe RU-486 a physician must satisfy “all the criteria established by federal law . . . in accordance with all provisions of federal law that govern the use of RU-486 (mifepristone) for inducing abortions.”¹⁴¹ The statute defined *federal law* as “any law, rule, or regulation of the United States or any drug approval letter of the food and drug administration of the United States that governs or regulates the use of RU-486 (mifepristone) for the purpose of inducing abortion.”¹⁴²

Planned Parenthood asserted that “neither the FDA’s approval letter nor any other provision of federal law prohibit[ed] abortion providers from using” RU-486 off-label.¹⁴³ However, in determining how to construe the plain language of the statute, the state’s highest court held that the law effectively requires physicians to administer RU-486 in compliance with dosage indications and treatment protocols found in both the FDA approval letter *and* all labeling materials.¹⁴⁴ Though the dissenting opinion in this case argues that federal law does not specifically limit the use of RU-486 outside of the forty-nine-day gestational limit due to the fact that FDA cannot regulate the practice of medicine, the statute survived constitutional challenge as the plain language of R.C. 2919.123 was found to impose this limit—effectively regulating the practice of medicine in Ohio.¹⁴⁵

Therefore, while FDA-approved indications cannot be construed to limit medical judgment, states have the authority to regulate the practice of medicine and may enact legislation

139. Mifepristone, also known as RU-486, is indicated for use in the termination of pregnancy through 49 days of gestation—commonly referred to as a medical abortion—and has no other FDA-approved indication for use during pregnancy. *Cordray v. Planned Parenthood Cincinnati Region*, 911 N.E.2d 871, 874 (2009).

140. *Id.* at 873.

141. *Id.* at 875 (citing OHIO REV. CODE ANN. § 2919.123(F)(1) (LexisNexis 2010)).

142. OHIO REV. CODE ANN. § 2919.123(F)(1) (LexisNexis 2010).

143. *Cordray*, 911 N.E.2d at 876.

144. *Id.* at 877–78.

145. *See id.* at 879, 881.

forcing compliance with such indications.¹⁴⁶ Further, though Planned Parenthood challenged the constitutionality of the Ohio statute on grounds that it unduly burdens patients' rights to an abortion, legislation of this type need not be so restrictive.¹⁴⁷ Off-label restrictions can, in fact, accommodate orphan conditions and other disease states while simultaneously enabling states to curtail harmful misuse of regulated products. State-based controls on off-label use may serve as a more appropriate way to curb undesirable activity—removing manufacturers from the equation altogether.¹⁴⁸

2. The Practicality of Trading FDA Oversight for State-based Controls

Though this model is not without its flaws, the nature of the state legislative process is able to mitigate some of the issues it presents. Patient advocacy groups—as well as other special interest groups—may lobby for exceptions. State legislation can be “narrowly tailored” to address specific off-label activity that may be of particular concern, such as the controversial use of Avastin.¹⁴⁹ Additionally, as with the Ohio law, state legislation regulating off-label use via the practice of medicine may be less susceptible to constitutional challenges—particularly where statutory language is express.¹⁵⁰

Balancing concerns of patient care and physician autonomy with the broader goal of safeguarding public health may, how-

146. See Beck, *supra* note 13, at 76–77; *Buckman Co. v. Plaintiff's Legal Comm.*, 531 U.S. 341, 350 (stating that off-label use “is an accepted and necessary corollary of the FDA’s mission to regulate in this area without directly interfering with the practice of medicine”).

147. *Cordray*, 911 N.E.2d at 875–76.

148. See Todd, *supra* note 80, at 429 (commenting that a lack of federal regulatory power leaves ample room for state involvement, particularly where a strong state interest, such as public safety, is at stake).

149. Avastin, or bevacizumab, was developed by Genentech Pharmaceuticals, Inc. for the treatment of certain types of cancers. The drug is also currently used off-label to treat a form of macular degeneration. In late 2011 FDA Commissioner Margaret Hamburg announced that the Agency would withdraw approval of Avastin to treat metastatic breast cancer due to high risk of death from stroke, heart attack, or serious bleeding. The product remains on the market for the treatment of other cancers such as kidney, lung, and colon cancer. While the decision was incredibly controversial, the withdrawal of an indication does not prevent oncologists from using the drug to treat breast cancer patients. See Shari Roan, *Avastin Loses Approval as Breast Cancer Drug* (Nov. 18, 2011) L. A. TIMES, Nov. 18, 2011, at A9.

150. See generally *Cordray*, 911 N.E.2d at 877 (asserting that the legislative intent in enacting the statute at issue was clear and unambiguous).

ever, prove difficult with this model. Legislation of this type would require multi-state cooperation to ensure successful curtailing of off-label activity. Otherwise, residents could simply travel to states with fewer or more favorable off-label restrictions, defeating the intended efficacy of state-based controls. The most likely hurdles to adopting such state-based controls are consistency and contiguity. State legislatures will undoubtedly respond to *intra*-state pressures that may or may not coincide with the goals and interests of other—even neighboring—states. Michigan, for example, has no compelling reason to impose a similar ban on mifepristone as exists in Ohio, and so on.

Though widespread implementation of state-based controls will certainly prove difficult initially, state legislation of this type may be the only reliable way to curtail off-label activity in the wake of constitutional challenges to FDA's authority to do so. Waning federal regulatory power with respect to off-label promotion can only be compensated at the state level *unless* Congress elects to amend the existing regulatory scheme.¹⁵¹ Moreover, the commonly proposed alternative of reimbursement is, by itself, insufficient to effectively regulate off-label use.¹⁵²

CONCLUSION

With pending constitutional challenges to FDA regulatory authority, the existing ban on off-label promotion may soon lose its ability to accomplish Agency goals. Yet, as one scholar notes:

Invalidating the prohibition on off-label promotion would not affect the FDA's requirement that a drug be approved by the agency before it can be sold in interstate commerce. Once a drug was approved as safe and effective for one use, however, its manufacturer would be free to promote it for any other use. Regulators and prosecutors would be limited to policing manufacturer speech after-the-fact on a case-by-case basis. This is problematic because it would be ineffective Given medicine's high stakes, it is neither surprising nor unconstitutional that that the prophylactic rule that governs drug claims sup-

151. See Dresser *supra* note 30, at 476 (2009) (arguing that members of Congress should recognize a more affirmative role for government oversight in deterring inappropriate off-label prescribing).

152. Todd, *supra* note 80, at 442–43 (“The medical community must improve the quality and dissemination of information relied upon in order for payors to make informed evidence-based reimbursement decisions, and for the payor-centric enforcement model to be effective.”).

presses some truthful speech.¹⁵³

In the event that *Sorrell* is interpreted to diminish authority in this realm, it seems unlikely that Congress will amend the existing statutory scheme to widen the scope of FDA's regulatory power.¹⁵⁴ As such, state laws pertaining to off-label prescribing and reimbursement are alternate regulatory pathways that should be explored in the interest of public health.

While state-based controls may be impractical to implement on a sufficiently-large scale to impact off-label activity, few options remain to impose the sort of categorical ban that FDA ostensibly deems necessary to protect consumers. Still, in the wake of cases like *Sorrell* and *Caronia*, additional regulatory alternatives become imperative. Manufacturers are sure to pursue constitutional challenges to FDA's restriction of off-label promotion, driven largely by the potential profit margin—a regulatory approach that wholly eliminates manufacturers is desirable. Unless congressional action is taken, this is not possible at the federal level. For the time being, then, state-based controls may serve as an option to resolve current regulatory uncertainties.

153. Kate Greenwood, *The Ban on "Off-Label" Pharmaceutical Promotion: Constitutionally Permissible Prophylaxis Against False or Misleading Commercial Speech?*, 37 AM. J. L. & MED. 278, 297–98 (2011) (citations omitted).

154. See Conko, *supra* note 86, at 184–85 (“In an extreme alternative proposal, Congress could merely forbid doctors from using drugs and devices for off-label indications . . . [d]oing so would necessarily ‘inject[] Congress and the federal government directly into the practice of medicine,’ an area historically outside the reach of FDA’s authority.”) (alteration in original) (citations omitted).