

Misbranded/Misled: Chipping Away at the Food,
Drug, and Cosmetics Act & the Future of Off-Label
Promotion

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Prior to marketing any drug or device, Federal law requires manufacturers to prove to the Food and Drug Administration's (FDA) satisfaction that their product is safe and effective for its intended uses.¹ If the FDA discovers the manufacturer intends other, unapproved uses²—also referred to as “off-label” uses—sales of the drug or device are determined to be illegal and the manufacturer may be charged in violation of the Food, Drug, and Cosmetic Act (FDCA).³ The drug approval process serves as the FDA's primary means of protecting the public health by ensuring the safety, efficacy, and security of all pharmaceuticals and medical devices in the U.S. and prohibiting false advertising on the part of manufacturers.⁴ Yet that mandate has been steadily undercut over the past thirty years on multiple fronts, eroding the balance

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1. 21 C.F.R. § 860.7(g)(1).

2. See Randall S. Stafford, *Regulating Off-Label Drug Use — Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427 (2008) (describing how off-label use arises through many pathways, including use for unapproved clinical indications (e.g., the antipsychotic Seroquel prescribed for depression) or in unapproved populations (e.g., Paxil for depression in children)).

3. Under the FDCA, the FDA must license any “new drug” before it may be *marketed*, not used. The approval process begins with the submission of an Investigational New Drug Application (NDA). If the application is approved, the sponsor may proceed with animal testing, then clinical trials on human subjects. A drug may only be marketed and labeled for the uses for which it received approval from the FDA. If a manufacturer promotes without going through the NDA, then the Department of Justice may charge them in violation of the FDCA. Richard C. Ausness, “*There’s Danger Here, Cherie!*”: *Liability for the Promotion and Marketing of Drugs and Medical Devices for Off-Label Uses*, 73 BROOK. L. REV. 1256, 1257 (2008).

4. U.S. FOOD & DRUG ADMIN., *What We Do*, USFDA, <http://www.fda.gov/aboutfda/whatwedo/default.htm> (last updated Oct. 24, 2016).

between commercial speech and the FDA's important public health policy goals. Statutory, judicial, and administrative challenges to the FDCA present a serious threat to the FDA's authority, as well as its traditional approach to regulating the safety and efficacy of pharmaceuticals sold in the U.S. The result is a growing protection for manufacturers to defend themselves from liability for off-label promotional speech altogether—or at least where it is “wholly truthful and non-misleading.”⁵ This article traces the arc of the FDCA from the FDA Modernization Act of 1997 (FDAMA),⁶ to a number of Federal courts asserting a First Amendment right for drug manufacturers to promote their products off-label,⁷ and finally to the relaxation of administrative guidance from the FDA regarding “scientific exchange.”⁸

I. THE FDA'S TRADITIONAL APPROACH TO OFF-LABEL PROMOTION

Under the FDCA,⁹ the FDA is authorized to regulate and control the labeling of drugs.¹⁰ It is under this authority that the FDA acts as a gatekeeper to the pharmaceutical market as a whole, dictating which drugs are marketed

5. See *infra* Part I (discussing the traditional FDA approaches); see also Proposed Jury Instructions, *U.S. v. Vascular Solutions, Inc.*, Cr. No. 14-926 (W.D. Tex. 2016) (“It is also not a crime for a device company or its representatives to give doctors wholly truthful and non-misleading information about the unapproved use of a device.”).

6. Food and Drug Administration Modernization Act of 1997, 21 U.S.C. § 2201 et seq. (1997) [hereinafter FDAMA].

7. See, e.g., Thomas Sullivan, *The Impact of Caronia Case: What Happens Next?*, POL'Y & MED. (Jan. 17, 2013), <http://www.policymed.com/2013/01/the-impact-of-caronia-case-what-happens-next.html>; see also Jeffrey Chasnow & Geoffrey Levitt, *Preemption of Non-Federal Restraints on Off-Label Product Communications*, 71 FOOD & DRUG L.J. 249 (2016).

8. FDA's regulations regarding the promotion of investigational drugs states that they are not “intended to restrict the full exchange of scientific information concerning the drug” but rather “to restrict promotional claims of safety or effectiveness of the drug . . . and to preclude commercialization of the drug before it is approved.” 21 C.F.R. § 312.7.

9. Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301-399(f) (2012).

10. FDA-required labeling is generally approved by the FDA before distribution with the product; promotional labeling is not reviewed by the FDA before it is distributed, but is defined as any written, printed, or graphic matter that bears a “textual relationship” with a drug or device. Therefore, although a pamphlet sent to a physician's office may not carry a “physical attachment” to the specific drug, it is still considered to be promotional labeling due to a textual relationship with the drug. U.S. FOOD & DRUG ADMIN., *Drug advertising: a glossary of terms* (June 19, 2015), <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/ucm072025.htm> [hereinafter *Drug advertising: a glossary of terms*].

and sold in the US.¹¹ Only after the FDA has approved a pharmaceutical product's indications, through rigorous phases of testing and approval of marketing materials, is the manufacturer then free to label, promote and distribute its product.¹² The indication approval process is the product of significant administrative effort—for decades, the FDA has required that the labels of approved drugs follow the format contained in its “Uniform Labeling Requirements.”¹³ Among the subjects to be included in a drug's label are its “indications and usage” information which is derived directly from the seller's approved New Drug Application (NDA).¹⁴ This information cannot be unsubstantiated hearsay. As part of the NDA approval process, the manufacturer's products must be proven safe and effective for all indications, on the basis of “substantial evidence” from well-controlled clinical studies submitted to the FDA for independent review.¹⁵ Given the cost of well-controlled clinical studies and the fees associated with NDAs, manufacturers must often decide which possible indications, among many, to pursue.¹⁶ Therefore, the decisions a pharmaceutical company makes in the pre-market period regarding which indications are the focus of its clinical trials in large part determine the approved labeled indications and usage.¹⁷

The FDA's authority over pharmaceutical labeling and marketing is absolute. However, regulating the prescribing decisions of physicians is

11. DANIEL CARPENTER, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA 114, 613 (2010).

12. *Id.* at 591; *see also* 21 C.F.R. § 201.1 et seq. (2016).

13. CARPENTER, *supra* note 11, at 614-15.

14. 21 C.F.R. § 314.81(b)(2)-(3).

15. Promotion of Unapproved Drugs and Devices: Hearing Before the Senate Committee on Labor and Human Resources (1996) (testimony of William B. Schultz, Deputy Commissioner for Policy, Food and Drug Administration) <http://www.fda.gov/newsevents/testimony/ucm115098.htm> [hereafter Schultz Testimony].

16. Joseph A. DiMasi et al., *Innovation in the pharmaceutical industry: New estimates of R&D costs*, 47 J. OF HEALTH ECON., 20, 32 (2016) (finding that by the time a drug has made it through clinical testing and the FDA approval process, the cost to the pharmaceutical company is around \$2,870 million).

17. Aaron S. Kesselheim, *Off-Label Drug Use and Promotion: Balancing Public Health Goals and Commercial Speech*, 37 AM. J.L. & MED. 225 (2011).

beyond its mandate, due to statutory and constitutional limitations.¹⁸ As a consequence, the agency has taken a strong stand against off-label promotional activities on the part of manufacturers as a way of ensuring that doctors can be confident that a product is safe and effective for its indications.¹⁹ Patients, in turn, can have confidence in the quality of the products they are receiving and the public health is best served.²⁰ The FDA originally took the position that *any* claim from a manufacturer that a drug could be “safe and effective” for an off-label use was always “false or misleading,” although more recently it retreated from that strong position.²¹ Since then, the FDA has created a pathway through which additional indications can be approved, added to the drug’s label, and then promoted.²² Companies can file Supplemental New Drug Applications (sNDAs) following an earlier approval for the purpose of adding additional indications.²³ Between 2000 and 2006, there were 294 sNDAs filed for additional indications, although that number was only about two percent of

18. 21 U.S.C. § 396 (1997) (“Nothing in this Act shall be construed to limit or interfere with the authority of a healthcare practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate healthcare practitioner-patient relationship.”). In the FDA’s guidance to physicians prescribing off-label, the agency states they have the responsibility to be well informed about the product, on the basis of “firm scientific rationale and on sound medical evidence.” U.S. FOOD & DRUG ADMIN., OFF-LABEL AND INVESTIGATIONAL USE OF MARKETED DRUGS, BIOLOGICS, AND MEDICAL DEVICES - INFORMATION SHEET (2014) [hereinafter OFF-LABEL AND INVESTIGATIONAL USE]; *see also* *Marcus v. Specific Pharms. Inc.*, 77 N.Y.S.2d 508, 509-10 (N.Y. App. Term. 1948) (stating that a physician may still be liable for failing to warn patients of the potential hazards and defects associated with prescribed medications).

19. *See* OFF-LABEL AND INVESTIGATIONAL USE, *supra* note 18; *see also* Schultz Testimony, *supra* note 15.

20. *See* OFF-LABEL AND INVESTIGATIONAL USE, *supra* note 18; *see also* Schultz Testimony, *supra* note 15.

21. Jerry Avorn et al., *Forbidden and Permitted Statements about Medications—Loosening the Rules*, 373 NEW ENG. J. MED. 967, 968 (2015).

22. CARPENTER, *supra* note 11, at 613 (describing the primary reasons sNDAs have been filed since 1970, including chemistry revisions, manufacturing revisions, package changes, control supplements, labeling revisions (SLR), and other label changes).

23. Supplemental Indications for Approved Prescription Drugs: Hearing Before the H. Comm. on Gov’t Reform and Oversight, Subcomm. on H.R. and Intergovernmental Relations (1996) (testimony of Michael Friedman Deputy Commissioner for Operations, Food and Drug Administration) <http://www.hhs.gov/asl/testify/t960912a.html>.

the total 14,000 sNDAs filed during the same years.²⁴

However, from the manufacturer's perspective there are significant drawbacks to the sNDA system. Adding additional indications to the drug's label requires the submission of supplementary clinical data—collected on company time and expense—and FDA approval for an sNDA often takes as long as the original NDA.²⁵ The advantages are therefore typically outweighed by the costs and risks involved in applying for additional indications.²⁶ While the NDA and sNDA process protects the public health mission of the FDA through stringent regulation and a rigorous clinical testing process, it remains a burdensome obstacle for manufacturers who have to bear the additional fees, research costs, and scrutiny.²⁷

II. STATUTORY LOOPHOLES AND THE FDAMA

Given the burdens of the NDA and sNDA process, manufacturers face the question of how to market their drugs for off-label use without triggering liability under the FDCA.²⁸ A critical question involves whether they can legally provide information to physicians on non-indicated uses of their drugs.²⁹ Prior to the FDAMA,³⁰ the FDA's answer was largely no.³¹ However, FDA restrictions to provider-manufacturer communication came under attack from the American Medical Association (AMA) in the 1990s,

24. See Avorn, *supra*, note 21, at 968 (indicating other causes for sNDA filing).

25. See Veronica Henry, *Off-Label Prescribing Legal Implications*, 20 J. LEGAL MED. 365, 368 (1999).

26. *Id.*

27. DiMasi et al., *supra* note 16.

28. Elizabeth Richardson, *Health Policy Brief: Off-Label Drug Promotion*, HEALTH AFF. 3-4 (Jun. 30, 2016), http://healthaffairs.org/healthpolicybriefs/brief_pdfs/healthpolicybrief_159.pdf.

29. See, e.g., *United States v. Caronia*, 703 F.3d 149 (2d. Cir. 2012). As illustrated by the misbranding guilty plea of former Orphan consultant Dr. Gleason, physician consultants are often paid by pharmaceutical companies to speak about their drugs at various professional functions. These types of arrangements are commonplace in the healthcare industry; however, substantive conversations about off-label drug uses often cannot be had with pharmaceutical sales representatives for fear of triggering liability.

30. See 21 U.S.C. § 2201 et seq.

31. Avorn et al., *supra* note 21, at 967-68.

for limiting access to pharmaceutical research.³² Congress responded with FDAMA, which, under Section 114, authorized manufacturers to distribute unabridged peer reviewed publications or reference materials to healthcare practitioners, pharmacy benefit managers, health insurers, and federal and state governments.³³ Though the FDA described implementing the new law as “one of the most demanding challenges faced by the Agency in its 92 year history,”³⁴ it nonetheless moved forward with regulations requiring the distributed materials to disclose the manufacturer as the source and to indicate specifically that the FDA had not approved the information.³⁵ Yet the effect of these changes was to allow for the broader distribution of research relevant to off-label use.³⁶ Direct marketing of off-label indications remained prohibited, but the dissemination of accurate scientific information by manufacturers was acceptable—albeit with two corollaries: first, the materials had to be provided to the FDA in turn, and second, the manufacturer had to verify its plans to seek approval for the new indications.³⁷ Strict compliance guaranteed a “safe harbor” from prosecution for engaging in false or misleading advertising.³⁸

On its face, the new statutory pressure from FDAMA had not substantially altered the balance between commercial speech and the larger public health

32. James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use and Informed Consent: Debunking Myths and Misconceptions*, 53 FOOD & DRUG L.J. 71, 103 (1998) (explaining that AMA representatives called for the FDA to permit physicians increased access to information about off-label uses by allowing manufacturers to distribute scientific studies to physicians).

33. *Id.*

34. FDAMA: Hearing Before the Senate Committee on Commerce (1998) (testimony of Michael A. Friedman, Acting Commissioner of Food and Drugs, Food and Drug Administration) <http://www.fda.gov/NewsEvents/Testimony/ucm115096.htm>.

35. 21 U.S.C. §§ 360aa, 551.

36. Robert I. Field, *The FDA's New Guidance for Off-Label Promotion Is Only a Start*, 33 HEALTH CARE & L. 220, 249 (2008).

37. 21 U.S.C. §§ 360aa, 551.

38. In 1998, the federal district court for the District of Columbia prohibited the FDA from enforcing the FDAMA conditions as requirements, on the grounds that they infringed on free speech rights. *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998). In response to the court ruling, the FDA issued regulations adopting the FDAMA standards. 21 C.F.R. § 99.1 et seq.

mandate of the FDA. Direct marketing for off-label use remained prohibited and manufacturers seeking physicians to prescribe their products off-label had to essentially submit to the sNDA process or risk prosecution.³⁹ The FDAMA safe harbor had benefits too, promising greater patient access to new medical products and more effective management of the FDA's limited resources.⁴⁰ At the same time, FDAMA was also the first significant cession of the authority—previously absolute—granted by FDCA with regard to promotional labeling.⁴¹ The exception it created was narrow: the FDAMA only relaxed off-label marketing rules with regard to physicians and other qualified health care professionals, theoretically, so that manufacturers could in fact monitor the flow of information themselves.⁴² Still, the FDAMA safe harbor opened the door to attacks on the primacy of the FDA—it would take subsequent litigation to push it open further.⁴³

III. THE RISE OF FIRST AMENDMENT PHARMACEUTICAL PROMOTION LITIGATION

In its creation of the FDAMA safe harbor, the FDA carefully skirted issues of commercial free speech in order to avoid triggering constitutional

39. See Washington Legal Foundation, *supra* note 38.

40. FDAMA: Hearing Before the Senate Committee on Health, Education, Labor and Pensions (1999) (testimony of Jane E. Henney, Commissioner of Food and Drugs, Food and Drug Administration) <http://www.fda.gov/NewsEvents/Testimony/ucm115036.htm>.

41. Jennifer Washburn, *Undue Influence*, THE AMERICAN PROSPECT (Dec. 19, 2001), <http://prospect.org/article/undue-influence> (explaining how FDAMA enhanced the pharmaceutical industry's marketing powers by abolishing absolute prohibitions against manufacturers disseminating information about unapproved uses and easing restrictions on advertising).

42. Steven R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 FLA. L. REV. 181, 188 (1999).

43. It is worth noting that FDAMA's limitations on off-label promotion expired on September 30, 2006, and Congress has yet to reauthorize them. The FDA's draft guidance is an attempt to fill the void. The agency continues to require that materials be reprinted from bona fide independent peer-reviewed sources, but it omits mandates for prior agency approval and for manufacturers to verify their intent to conduct clinical trials of unapproved uses. See generally Robert I. Field, *The FDA's New Guidance for Off-Label Promotion Is Only a Start*, 33 PHARMACY & THERAPEUTICS 220 (2008).

challenges to the regulation.⁴⁴ Nevertheless, it was a dispute that would not be postponed for long. This tension between public health and truthful and non-misleading off-label promotion was elucidated by the United States Supreme Court's 2011 decision in *Sorrell v. IMS Health*, where a majority of the Court concluded that a state-imposed restriction on commercial speech was subject to a heightened standard of judicial review.⁴⁵ *Sorrell* involved a First Amendment challenge to Vermont's Act 80, which prohibited pharmaceutical companies from using "prescriber-identifying information" to market drugs to physicians.⁴⁶ Drug manufacturers purchase and use this data to more effectively promote drugs to physicians.⁴⁷ The Vermont legislature was concerned that prescriber-identifying information facilitated marketing tactics that caused physicians to prescribe more expensive brand name drugs over cheaper generic equivalents.⁴⁸ IMS Health, a physician prescribing data mining company, and the Pharmaceutical Research and Manufacturers of America challenged these restrictions as violating the Free Speech Clause and filed certiorari with the Supreme Court.⁴⁹ A six Justice majority led by Justice Kennedy struck down the law as unconstitutional due to what it characterized as unacceptable "viewpoint discrimination" aimed at suppressing the drug manufacturers' commercial message in favor of

44. *Washington Legal Foundation v. Henney*, 202 F.3d 331 (D.C. Cir. 2000) (re-framing the FDA's policies as ones in which manufacturer compliance with the FDA's safe harbors would not be used as evidence of misbranding—but that non-compliance could be used as such evidence—the government removed any constitutional issue; finding no constitutional controversy between the parties, the court vacated the district court's decisions and injunctions).

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

46. Prescriber-identifying information is data that pharmacies collect, pursuant to federal regulation, about customer prescriptions, including the identity of the prescribing physician. *Id.* at 2660.; see Andrew J. Wolf, *Detailing Commercial Speech: What Pharmaceutical Marketing Reveals About Bans on Commercial Speech*, 21 WM. & MARY BILL RTS. J. 1291 (2013)).

47. John N. Joseph et al., *Is Sorrell the Death Knell for FDA's Off-Label Marketing Restrictions?*, 5 J. HEALTH & LIFE SCI. L. 1, 5 (2012).

48. *Sorrell*, 131 S.Ct. at 2670.

49. *Id.* at 2662.

Vermont's message of cost effectiveness and balanced information.⁵⁰

Notwithstanding the Court's conclusion that Act 80 should be reviewed under strict scrutiny,⁵¹ the *Sorrell* majority decided that Act 80 would not survive even the lesser intermediate scrutiny test under *Central Hudson Gas & Electric Corp. v. Public Service Commission*, that is, whether the government's speech restriction directly advanced its asserted interest and was not more extensive than necessary.⁵² Addressing Vermont's argument that promotional speech based on prescriber-identifying information undermined the doctor-patient relationship by influencing medical treatment decisions, the majority reasoned that "the fear that speech might persuade provides no lawful basis for quieting it."⁵³ The majority concluded that Act 80's restrictions did not directly advance the state's purported goals and was unconstitutional.⁵⁴

As Justice Breyer warned in his *Sorrell* dissent, and as predicted by many commentators, it was not long before the pharmaceutical industry argued that the *Sorrell* rationale applied to FDA restrictions on truthful off-label promotional speech.⁵⁵ The Second Circuit's 2012 decision in the criminal case of *United States v. Caronia*⁵⁶ did just that, the first in a long line of cases spread of the "false and misleading" standard to the district court level. Alfred Caronia, a sales consultant for the pharmaceutical company Orphan

50. *Id.* at 2663-64.

51. The court found that Vermont's law "enact[ed] content- and speaker-based restrictions . . ." since prescribing information could be used for any speech except promotional speech and the only prohibited speakers were pharmaceutical manufacturers and their agents. *Id.* at 2663. Strict scrutiny was therefore demanded. *See also* *Reed v. Town of Gilbert*, 135 S. Ct. 2218, 2228 (2015) ("A law that is content based on its face is subject to strict scrutiny regardless of the government's benign motive, content-neutral justification, or lack of animus toward the ideas contained in the regulated speech.").

52. *Sorrell*, 131 S.Ct. at 2667-68 (citing *Central Hudson Gas & Elec. Corp. v. Public Serv. Comm'n of N.Y.*, 447 U.S. 557 (1980)).

53. *Id.* at 2670.

54. *Id.* at 2672.

55. *See Sorrell*, 131 S.Ct. at 2676-78; *see also* *Joseph et al.*, *supra* 47.

56. *U.S. v. Caronia*, 703 F.3d 149, 154 (2d. Cir. 2012).

Medical, was caught on video promoting Xyrem for unapproved uses.⁵⁷ He was charged in the Eastern District of New York with introducing a misbranded drug into interstate commerce and conspiracy to introduce a misbranded drug into interstate commerce, both are violations of the FDCA.⁵⁸ Caronia appealed his conviction to the Second Circuit, arguing that the misbranding provisions of the FDCA prohibit off-label promotion, and therefore, unconstitutionally restrict speech.⁵⁹

The majority, applying the reasoning from *Sorrell*, found that the FDA's position on misbranding imposed both content and speaker-based restrictions on off-label promotional speech—i.e., it allowed speech about government-approved uses while prohibiting speech about unapproved uses, targeting only one class of speakers (pharmaceutical manufacturers).⁶⁰ Additionally, the majority reasoned that the government's off-label speech restrictions did not advance a substantial interest because “even if pharmaceutical manufacturers are barred from off-label promotion, physicians can prescribe, and patients can use, drugs for off-label purposes.”⁶¹ The majority determined that restricting off-label speech by drug companies while allowing off-label uses by physicians “paternalistically interfered with the ability of physicians and patients to receive potentially relevant treatment information.”⁶² The Court also reasoned that the off-label restrictions were not narrowly tailored when there were multiple less restrictive means by

57. *Id.* at 156.

58. *Id.* at 159.

59. *Id.* at 160; Orphan pleaded guilty to a single count of introducing a misbranded drug into interstate commerce with the intent to defraud and mislead. It was ordered to pay \$12,262,078 in restitution and \$5 million in criminal fines. Dr. Peter Gleason, a physician paid by Orphan to promote Xyrem for off-label uses, pleaded guilty to a single count of misdemeanor misbranding and was sentenced to one year of probation. James E. Tysse et al., *Free Speech and the Future of Off-Label Pharmaceutical Marketing Regulation After United States v. Caronia*, LIFE SCI. L. & INDUSTRY REP., 7 LSLR 117 (2013).

60. Caronia, *supra* note 56, at 165.

61. *Id.* at 166.

62. *Id.*

which FDA could further its interests.⁶³ In short, the *Caronia* majority concluded that the misbranding provisions of the FDCA could not be interpreted as prohibiting truthful and non-misleading off-label promotion, because such an interpretation would run afoul of the First Amendment's free speech protections.⁶⁴

Notwithstanding the *Caronia* majority's sweeping denunciation of the FDA's ban on truthful off-label promotional speech, the government elected not to seek rehearing or otherwise appeal.⁶⁵ In early 2013, an FDA official explained that the agency did not believe that the *Caronia* decision would significantly affect the agency, since the court acknowledged that even the First Amendment did not preclude an enforcement action based on false or misleading speech.⁶⁶ The government seemed to decide that attempting to narrow and distinguish the Second Circuit's holding was a better strategy than risking a potentially unfavorable final ruling from the Supreme Court.⁶⁷ However, truthful non-misleading speech in aid of off-label promotion did not stay out of the courts, and *Caronia* and *Sorrell's* rationale proved influential.⁶⁸ While "false or misleading" speech is not an inviolable standard

63. *Id.* at 167-68 (suggesting that instead of restricting promotional speech on off-label uses, FDA could provide guidance to physicians and patients on how to distinguish between false or misleading information and truthful or non-misleading information).

64. The dissenting opinion took issue with the possible repercussions the majority's decision would have on FDA's drug-approval process, reading the majority's holding as allowing "any substance that may be legally sold for some purpose [to] be promoted by its manufacturer[s] for any purpose—so long as the manufacturer's statements are merely unsubstantiated, rather than demonstrably false or misleading." The dissent warned that such a reading would "invalidate the very definitions of 'drug' and 'device' that undergird the entire FDCA," and could render the FDCA unconstitutional. *Id.* at 168-69, 178.

65. Thomas M. Burton, *FDA Won't Appeal Free-Speech Marketing Decision*, WALL STREET J. (Jan. 23, 2013, 8:20 PM), <http://www.wsj.com/articles/SB10001424127887324539304578260323575925896>.

66. Jill Wechsler, *Tom Abrams: Caronia Won't Stop Off-Label Enforcement*, PHARMEXEC.COM (Jan. 29, 2013), www.pharmexec.com/tom-abrams-caronia-wont-stop-label-enforcement (quoting Tom Abrams, director of the Office of Prescription Drug Promotion in the Center for Drug Evaluation and Research).

67. *Id.*

68. *See, e.g.,* Caplinger v. Medtronic, Inc., 784 F.3d 1335, 1352 (10th Cir. 2015) (2016) (discussing the definition of misbranding in relation to FDCA); *see also* 1-800-411-Pain Referral Serv., LLC v. Otto, 744 F.3d 1045, 1054 (8th Cir. 2014) (discussing the application

across all jurisdictions, Federal courts in have increasingly adopted similar reasoning.⁶⁹ Pharmaceutical companies, citing *Caronia* and similar district court cases, petitioned the FDA to review its policies regarding communication of off-label or unapproved indications—resulting in a two-day conference in November of 2016 where the FDA heard public comments.⁷⁰

Yet despite a shifting legal standard, the FDA’s concerns about returning to the lawless “pre-1962 era”⁷¹ endure. Although *Thompson* and *Sorrell* do not protect false or misleading commercial speech,⁷² they invite a grim slippery slope argument: that judicial recognition of off-label promotion will inevitably lead courts to also strike down the FDA’s entire premarket approval structure, chipping away at the mandate of the FDCA.⁷³ While it is possible the courts will articulate an “arbitrary but workable” status quo,⁷⁴

of *Sorell*).

69. See *Allergan, Inc. v. United States*, No. 1:09-cv-01879 (D.D.C. 2010) (“although the Government has significant interests that could justify some restrictions of off-label promotional practices, there is no need for . . . the blanket suppression of off-label speech.”); see also *Vascular Solutions, supra* note 8; *Amarin Pharma, Inc. v. U.S. Food & Drug Admin.*, 119 F. Supp. 3d 196, 227-28 (S.D.N.Y. 2015) (holding that the FDA could not pursue misbranding sanctions against Amarin for statements that were truthful and nonmisleading).

70. Toni Clarke, *Under pressure, FDA to hold public meeting on off-label use*, REUTERS (May 6, 2015 9:35 PM) <http://www.reuters.com/article/us-fda-pharmaceuticals-constitution-idUSKBN0NS00F20150507>.

71. Memorandum of Law in Opposition to Plaintiffs’ Motion for Preliminary Injunction, at 1, *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 1196, 2015 WL 4387279 (S.D.N.Y. 2015) (referring to Drug Efficacy Amendment, Pub. Law. No. 87-781, 76 Stat. 1040, signed into law in 1962, strengthening and standardizing the FDA’s enforcement of drug trials and efficacy requirements).

72. See, e.g., *U.S. ex rel. Cestra v. Cephalon, Inc.*, 2015 WL 3498761 (E.D. Pa. 2015). Because the relator in a qui tam action for False Claims Act violations had alleged that the off-label statements were false and misleading, the court rejected the defendant’s motion to dismiss because *Caronia* did not control where the statements at issue may be false or misleading.

73. See Joseph et al., *supra* note 47, at 33 (noting the Government’s “compelling” argument that off-label detailing exacerbates the health risk by increasing the number of people using drugs for off-label purposes); Christopher T. Robertson, *When Truth Cannot Be Presumed: The Regulation of Drug Promotion Under an Expanding First Amendment*, 94 B.U.L.R. 545, 554 (2014).

74. See Toni M. Massaro, *Constitutional Law as Normal Science*, 21 CONST. COMMENT. 547, 548 (2004) (describing the Supreme Court’s preference for “seek[ing] to cabin the impact of any changes, and they [the Justices] emphasize the limited role that the Court realistically

the current judicial atmosphere seems to favor “wholly truthful and nonmisleading” commercial speech.⁷⁵ If the FDAMA safe harbor provision exposed vulnerabilities in the FDA’s public health mandate, then the rise of judicial protection for off-label promotion took advantage of those vulnerabilities. However, as significant as the legislative and judicial challenges to the FDCA have been, they are further bolstered by administrative regulation.

IV. THE REGULATION OF “SCIENTIFIC EXCHANGE”

Even if the rise of First Amendment litigation regarding off-label promotion creates binding precedent where all truthful and non-misleading statements in off-label promotion are constitutionally protected, the FDA still has the regulatory power to assert that a given promotional message is false or misleading.⁷⁶ What constitutes false or misleading speech is a subjective and fact-driven determination of the FDA Office of Prescription Drug Promotion (OPDP).⁷⁷ Because the OPDP generally does not determine what promotional materials are false or misleading until after launch of the product, a drug manufacturer that promotes off-label indications risks having these materials deemed outside the protections of the First Amendment.⁷⁸ Given the FDA’s opposition to off-label promotion, the agency may now be more apt to find promotional messages false or misleading.⁷⁹

However, given the existing statutory and legislative protections for

can, and constitutionally should, play in shaping public policy.”).

75. *Vascular Solutions*, *supra*, note 5.

76. *See* 21 U.S.C. § 352 (“A drug or device shall be deemed to be misbranded . . . If its labeling is false or misleading in any particular.”).

77. *Vascular Solutions*, *supra*, note 5.

78. Under 21 C.F.R. § 314.550, the manufacturer is required to submit all promotional materials for the first 120 days of the launch campaign to the FDA *during* the pre-approval review period. However, all promotional materials for after the 120 day launch period must be submitted to the FDA just 30 days before the intended time of initial dissemination.

79. Declaration of Janet Woodcock, M.D., *Amarin Pharma, Inc. v. U.S. Food & Drug Admin.*, No. 1:15-CV-03588-PAE (Jun. 23, 2015) (describing the public health reasons for the FDA’s opposition to limitless off-label promotion).

commercial speech, it seems unlikely the agency will enforce such a hard line.⁸⁰ The FDA is more likely to take another route, and continue to refine its distinction between “promotion” and “scientific exchange.”⁸¹ In response to both the FDAMA and the rise of First Amendment litigation, the FDA shifted its stance on commercial speech—part of which entails non-promotional information and research, conducted by individuals who are scientifically trained professionals and in a forum or context that is conducive and reflective of scientific discussion.⁸² In 2009 and 2014, the FDA released guidance with updated standards for reprint practices related to journal articles, scientific or medical reference texts, and clinical practice guidelines.⁸³ The draft guidance further updated FDA’s perspective on best practices for distributing scientific and medical publications on unapproved new uses.⁸⁴ In the case of the aforementioned guidance, it has echoed the FDAMA safe harbor provisions as well as the holdings of *Sorell* and *Caronia*. Additionally, it distinguished between the traditional “promotional”⁸⁵ speech and the dissemination of “wholly truthful and non-misleading” research for off-label uses.⁸⁶ In other words, while the former is still regulated in the traditional fashion, the latter has been deemed an

80. *Supra*, Part II, Part III.

81. *See* Communications and Activities Related to Off-Label Uses of Marketed Products and Use of Products Not Yet Legally Marketed; Request for Information and Comments, 76 F.R. 81508 (2011).

82. *See*, 21 C.F.R. § 312.7(a) (stating the administrative basis for scientific exchange safe harbor).

83. 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 (2009), <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm> (writing to address the sunset of FDAMA in 2007, effectively ending the sNDA-specific provisions of Section 401); FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: DISTRIBUTING SCIENTIFIC AND MEDICAL PUBLICATIONS ON UNAPPROVED NEW USES—RECOMMENDED PRACTICE 2 (2014), <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm387652.pdf> [hereinafter DISTRIBUTING SCIENTIFIC AND MEDICAL PUBLICATIONS].

84. DISTRIBUTING SCIENTIFIC AND MEDICAL PUBLICATIONS at 2.

85. Drug advertising: a glossary of terms, *supra* note 10.

86. DISTRIBUTING SCIENTIFIC AND MEDICAL PUBLICATIONS, *supra* note 83, at 6.

exception to FDCA under the administrative rulings of the FDA.⁸⁷

Although not enforceable regulation, the guidance provides the FDA's perspectives on off-label information dissemination and promotion in the course of litigation.⁸⁸ And where the administrative guidance of the past ten years has complimented the legislative and judicial developments, it has cemented them. Certainly, there are benefits to the current FDA pre-approval system—it allows doctors and manufacturers to exchange information about unproven uses, maintaining clarity and as much informed consent as possible, while still giving an incentive for manufacturers to study pharmaceuticals more systematically.⁸⁹ In a system where it is unlikely that any individual patient or doctor could conduct scientific studies to determine safety and efficacy of drugs, it is important to the public health that there be some means of disseminating information in a flexible yet discerning way.⁹⁰

However, achieving such an end through restricting the FDA's authority over off-label promotion risks undermining the FDA's regulatory regime as a whole.⁹¹ The head of the Cleveland Clinic called the legitimization of off-label promotion “a potential catastrophe for patients” due to the public health impact.⁹² In essence, courts and legislatures are putting a great deal of faith—first, in manufacturers *not* to conduct poor-quality studies for the purpose of showing products' utility for unapproved indications,⁹³ and second, in

87. *Id.*

88. *Id.*

89. Woodcock, *supra* note 79.

90. *Id.*

91. John E. Osborn, *Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information*, 10 YALE J. HEALTH POL'Y L. & ETHICS 299, 307 (2010).

92. Editorial, *The Limits of Free Speech*, NATURE (Dec. 19, 2012), <http://www.nature.com/news/the-limits-of-free-speech-1.12062>.

93. “There is no need for companies to design these studies to meet the FDA's standards for methodological rigor if the companies have no intention of submitting an application for approval of the new use, but rather intend to use the study findings only in marketing communications. Companies can design studies in ways that maximize the chances of obtaining a desired result and select which studies to emphasize in promotional communications, ignoring others that do not support their promotional message.” Aaron S.

physicians to independently evaluate claims about off-label uses.⁹⁴ Ultimately, undermining the FDCA in this way undermines the authority and project of the FDA, threatening the public health mandate which is the heart of its mission.

V. CONCLUSION

The FDA plays a critical role in ensuring that patients and physicians have confidence that prescribed medicines are safe and effective for their approved uses, protecting the public health through rigorous clinical standards and administrative safeguards. Yet, the practice of modern medicine has demands a more flexible framework of information sharing, pharmaceutical use, and discernment regarding prescription.⁹⁵ As a result of judicial and regulatory shifts, the FDA stands at a crossroads when it comes to off-label promotion and communication by pharmaceutical manufacturers. Whatever framework is ultimately adopted will certainly be informed by *Caronia*, FDAMA, and the FDA's own administrative governance—however, such a framework must also preserve the necessary authority of the FDA. At the November 2016 public meeting to review the FDA's policies on off-label promotion, FDA Commissioner Robert Califf remarked that going forward, there may be room for both flexibility of information-sharing as well as faithfulness to the FDA's public health mandate.⁹⁶ Yet neither can be truly accomplished without the FDA acting to the extent of its authority as arbiter

Kesselheim & Michelle M. Mello, *Prospects for Regulation of Off-Label Drug Promotion in an Era of Expanding Commercial Speech Protection*, 92 N.C. L. REV. 101, 144 (2014).

94. "Physicians must rely on their judgments of representatives' personal credibility. Some promotional claims may be inherently impossible for physicians to verify, such as a claim that other physicians are already widely prescribing the drug for a particular off-label use and have encountered no serious safety problems." *Id.* at 147.

95. James M. Spears et al., *Embracing 21st Century Information Sharing: Defining A New Paradigm for the Food and Drug Administration's Regulation of Biopharmaceutical Company Communications with Healthcare Professionals*, 70 FOOD & DRUG L.J. 143, 159-60 (2015).

96. Clarke, *supra* note 70.

of pharmaceutical safety and efficacy, and guardian of the U.S.'s long-standing regulatory framework. Any change—even a small change—has the power to influence what kind of information patients receive on drugs and devices, and the FDA alone has the ability and responsibility to ensure public health remains a priority.