Off-Label Promotion and the First Amendment

Recent First Amendment rulings usher in a fresh look at the rules governing off-label communications.

Warning: The reader is forewarned that [off-label promotion] is like a swamp laced with land mines; do not venture into this new claims-dissemination process without very great caution and attention to detail.
The data show that doctors widely prescribe medical products for off-label use and that they need more, not less, information. While it is recognized that manufacturers of medical products are most knowledgeable about their products and best situated to participate in a dialogue with physicians regarding off-label use, they do so in a murky regulatory world in which the penalty for missteps is state or federal criminal proceedings and potentially crippling fines. We are in a unique time when the regulatory framework is intersecting with resurgence in First Amendment jurisprudence, which very well may result in courts taking a fresh look at the regulatory scheme governing off-label communications.

Congress established the Food and Drug Administration (FDA) and set its mission to promote the public health and to ensure that drugs and devices are safe and effective. 21 U.S.C. §393. And as explained in the 1970s, “the major objective of the drug provisions of the Federal Food, Drug, and Cosmetic Act is to assure that drugs will be safe and effective for use under the conditions of use prescribed, recommended, or suggested in the labeling thereof.” Legal Status of Approved Labeling for Prescription Drugs, 37 Fed. Reg. 16,503 (Aug. 15, 1972).

Off-Label Use and New Use

“Off-label use” is when, in exercising professional judgment in the practice of medicine, a physician uses a product for an indication, dosage or duration not in the FDA approved labeling. “New use” and “new drug or device” are terms that the FDA uses when a manufacturer communicates concerning an “off-label use.” The FDA views disseminating information relating to a “new use” for a drug or device that it has not approved as “labeling,” and evidence of a new “intended use” that renders the drug or device adulterated or misbranded. 21 C.F.R. §99.405.

The medical profession recognizes off-label use as appropriate in the practice of medicine.
a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.” 21 U.S.C. §396.

The FDA has spoken on off-label use by physicians and has stated that if physicians use a product for an indication not in the approved labeling, “they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product’s use and effects.” See U.S. Food & Drug Admin., “Off-Label” and Investigational Use of Marketed Drugs, Biologics, and Medical Devices—Information Sheet, Guidance for Institutional Review Boards and Clinical Investigators, http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm.

The medical profession recognizes off-label use as appropriate in the practice of medicine: “Clinically appropriate medical practice at times requires the use of pharmaceuticals for ‘off-label’ indications.” Am. Med. Ass’n House of Delegates, Off Label Use of Pharmaceuticals, Resolution 820, (Sept. 21, 2005), available at http://tinyurl.com/ypfwmyo; see also Sigma Tau Pharmaceuticals, Inc. v. Schwartz, 288 F.3d 141 (4th Cir. 2002); Huntman v. Danek Medi-

Four in 10 doctors queried about 22 medications believed that at least one of the drugs was FDA-approved for a specific indication when it was not labeled as such and when scientific evidence did not back the prescribing decision.

### How Often Do Physicians Inappropriately Prescribe Off-Label?

A survey in the August 21, 2009, Pharmacoepidemiology and Drug Safety found that four in 10 doctors queried about 22 medications believed that at least one of the drugs was FDA-approved for a specific indication when it was not labeled as such and when scientific evidence did not back the prescribing decision. D.T. Chen, M.K. Wynia, R.M. Moloney, & G.C. Alexander, U.S. Physician Knowledge of the FDA-Approved Indications and Evidence Base for Commonly Prescribed Drugs: Results of a National Survey, 18 Pharmacoepidemiology and Drug Safety 1094–1100 (2009).


According to one source, “[i]n 2001, there were an estimated 150 million off-label prescriptions (21 percent of overall use) of the sampled medications.... Most off-label drug medicines (73 percent) had little or no scientific support.” David C. Radley et al., Off-Label Prescribing Among Office-Based Physicians, 166 Archives of Internal Med. 1021–66 (May 8, 2006).

### Why Do Doctors Write So Many Prescriptions for Off-Label Use Without Scientific Support?

According to Jerome L. Avorn, chief of the division of pharmacoepidemiology and pharmacoconomics at Brigham and Women’s Hospital in Massachusetts, the reason why doctors write so many prescriptions for off-label use without scientific support is that “[i]t is terribly, terribly hard for an individual practitioner to keep abreast of all the thousands of indications.... All this information about indications can overwhelm physicians.” Kevin B. O’Reilly, Physicians Know FDA-OK’d Uses for Drugs Half the Time, amednews.com, Sept. 7, 2009, http://www.ama-assn.org/amednews/2009/09/07/prsc0907.htm (last accessed Nov. 2, 2011).

According to the New England Journal of Medicine, “[i]t is unrealistic to expect each physician to have the time and expertise to subject [off-label] claims to the same kind of scrutiny that the FDA exercises when it reviews a drug application or a request for a new indication. The complexity of the assessment that is required, along with the high stakes of getting it wrong, provided the rationale for having a formal drug-approval process in the first place.

Aaron S. Kesselheim & Jerry Avorn, Pharmaceutical Promotion to Physicians and First Amendment Rights, 358 New England J. of Med. 1727, 1730–31 (Apr. 17, 2008). Some commentators attribute the gap in knowledge to the approval process itself: “Much critical information that the Food and Drug Administration (FDA) has at the time of approval may fail to make its way into the drug label and relevant journal articles.” Lisa M. Schwartz & Steven Woloshin, Lost in Transmission—FDA Drug Information that Never Reaches Clinicians, 361 New England J. of Med. 1717 (Oct. 29, 2009). Despite this knowledge gap, “[e]xerts agree that additional efforts—many of them currently undefined—will be needed to increase access to appropriate off-label drugs for patients with rare and other diseases while safeguarding against illegal marketing and potentially dangerous prescribing.” Tracy Hampton, Experts Weigh in on Promotion, Prescription of Off-Label Drugs, 297 JAMA 683–84 (Feb. 21, 2007).
What Does the Public Think of Off-Label Use?

According to a 2006 Wall Street Journal/Harris Interactive Poll, consumers have mixed views on whether doctors should have the leeway to prescribe drugs for uses for which the FDA hasn’t approved: “Forty-five percent of those surveyed [said] doctors ‘should be allowed to decide which prescription drug treatments to use with their patients regardless of what diseases they have or have not been approved for by the FDA,’” compared with 46 percent who said this shouldn’t be allowed.” Becky Bright, “Adults Are Divided on Off-Label Use of Prescription Drugs,” Wall. St. J. Online, Nov. 23, 2006, http://online.wsj.com/article/SB116422408807730936.html (last accessed Nov. 2, 2011). Further, 69 percent believed that pharmaceutical companies should not be allowed to “encourage” doctors to use a drug for a disease for which it had not been approved. Id. The Wall Street Journal interpreted the poll as indicating that “many Americans don’t want to hamper innovation, but would be supportive of greater limitations on off-label drug use.” Id. But a recent Internet-based, randomized, controlled trial assessed the U.S. public understanding of the “meaning” of FDA drug approval. The study concluded that “[a] substantial proportion of the public mistakenly believes that the FDA approves only extremely effective drugs and drugs lacking serious side effects.” Lisa M. Schwartz & Steven Woloshin, “Communicating Uncertainties About Prescription Drugs,” 171 Archives of Internal Med. 1463 (Sept. 12, 2011).

Why Does the FDA Regulate What Manufacturers Say About Off-Label Uses?

According to the FDA, it regulates what manufacturers say about off-label drug use because

[B]ased on its experience, FDA has found that the promotion of unapproved uses by manufacturers of the promoted products can subject patients to unnecessary and dangerous risks. . . . Promotion of unapproved uses can encourage physicians and patients to make decisions based on statements or claims that are, in many cases, supported by little or no data. Thus FDA’s position is that the promotion of unapproved uses, either by companies or other parties that benefit by the promotion, can place physicians and patients in positions where they cannot make an informed, unbiased decision.


The Safe Harbor

Congress recognized that the standard of care for a physician can constitute criminal conduct for a manufacturer and thus created a safe harbor—section 401 of the Food and Drug Administration Modernization Act (FDAMA)—which outlined certain conditions under which a manufacturer could disseminate information on unapproved or new medical product uses. If a manufacturer submitted a supplemental new drug application (SNDA) and complied with section 401 regulations, dissemination of certain materials concerning “new uses” would not be used as evidence of intent to promote the product off-label. Section 401 expired in 2006, and the FDA promulgated “final rules” implementing section 401 in 2009, “Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics and Devices.” 21 C.F.R. §99, available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=99. See also, 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.” http://www.fda.gov/op/GoodReprint.html.

The “safe harbor” applies to information about uses not included in FDA-approved labeling disseminated to a health-care practitioner, pharmacy benefits manager, health insurance issuer, group health plan, or government agency.

However, the “safe harbor” does not apply to information provided in response to a practitioner’s “unsolicited request.” The FDA has stated that a manufacturer’s response to an “unsolicited request” does not constitute “labeling” because it is a “personal communication between the requester and [manufacturer].” See Div. of Drug Advertising and Labeling Position on the Concept of Solicited and Unsolicited Requests (April 22, 1982). But this FDA “concept” is imprecise and so those communications could still be considered “promotional.”

A manufacturer may disseminate “new use” information that concerns an approved drug or device as long as it isn’t disseminated with promotional material, is not false or misleading, and does not present favorable information only, in which case the FDA may consider the information misleading, meaning “misbranded.” The information may take form as an “unabridged reprint[,] … a copy of a peer-reviewed and published clinical study,” 21 C.F.R. §99.101(a)(2)(i), or a “reference publication” including information about a clinical investigation, 21 C.F.R. §99.101(a)(2)(ii), as long as it is “considered… scientifically sound.” 21 C.F.R. §99.101(a)(2)(i), (a)(2)(ii). The FDA defines a reference publication as something that the disseminating manufacturer did not write, edit, or “influence,” that is generally available, and does not focus on products of the manufacturer distributing the publication. 21 C.F.R. §99.13(i). Further, the FDA will not permit a manufacturer to ground information in a letter to the editor, abstracts, or studies involving four or fewer subjects. 21 C.F.R. §99.101(b). Nor can the information derive from another manufacturer’s publication unless the distributing manufacturer has that manufacturer’s permission to disseminate it.

To obtain FDA approval to disseminate information regarding a “new use,” 60 days before disseminating it a manufacturer must submit the following to the FDA:

• A copy of the information;
• All information that the manufacturer has, including clinical trial information and the method used for selecting any bibliography;
• A supplemental application for a “new use” or the equivalent; and
• If the manufacturer has no additional information, a statement that it has no additional information relating to the “New Use.” 21 C.F.R. §99.201(a)(2).

If a manufacturer has not submitted a supplemental application

• If studies have been completed, a manufacturer must submit a copy of the protocols and a certification stating that studies have been completed and that

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The manufacturer must also include in the mandatory statement: (1) the approved labeling; (2) a bibliography listing materials that do not support the new use; and (3) additional information that the FDA deems “necessary to provide objectivity and balance.” 21 C.F.R. §99.103.

Industry Supported Activities

Twelve Factors to Determine Independence
Noting that “[d]emarcating the line between activities that are performed by or on behalf of the company, and thus, subject to regulation, and activities that are essentially independent of their influence has become more difficult due to the increasing role industry has played in supporting postgraduate and continuing education for health care professionals,” the FDA identified factors to evaluate industry-supported scientific and educational activities to determine whether a company supporting an activity “is in a position to influence the presentation of information related to its products” or to “transform an ostensibly independent program into a promotional vehicle.” Industry Guidance on Industry Supported Scientific and Educational Activities, 62 Fed. Reg. 64,095, 64,099 (Dec. 3, 1997). The factors only apply to “company-supported activities that relate to the supporting company’s products or to competing products” and are intended to clarify the difference between promotional and non-promotional activities for activity designers. 62 Fed. Reg. 64,096. The factors are

1. Did the program provider rather than the supporting company control content and select presenters and moderators?
2. Did the program meaningfully disclose relationships?
3. What was the program’s focus; for instance, did it focus on a product?
4. Did the relationship between the provider and the company permit the company to exert control over the provider?
5. Did the provider have a history of failing to meet independence standards?
6. Is the provider involved in the company’s sales or marketing?
7. Did the agenda include multiple presentations of the same program?
8. Did audience selection reflect marketing goals, or did the company’s marketing department influence its selection?
9. Did the program offer opportunity for discussion?
10. Did the program provider or the supporting company disseminate additional product information after the program?
11. Did the program include ancillary marketing efforts?
12. Did anyone complain that the supporting company attempted “to influence content.”


The FDA also takes into account a category of catch-all “additional considerations,” such as whether the written agreement between a supporting company and the program provider reflected that the later would design and direct the program. Id. at 64,099.

Promotion of FDA-Regulated Medical Products Using the Internet and Social Media Tools
In November 2009, the FDA held two days of meetings on promoting FDA-regulated products with social media attended by a variety of stakeholders many of whom presented written materials and addressed the issue. The industry has long awaited guidance from the FDA on this topic. An archived webcast of the meeting is available at http://www.capitolconnection.net/capcon/fda/111209/FDAarchive.htm (last accessed Nov. 2, 2011).

Government Accountability Office Study
In July 2008, the U.S. Government Accountability Office (GAO) reviewed the FDA’s

July 15, 2011, Citizen’s Petition Regarding Safe Harbor

On July 15, 2011, seven major manufacturers of marketed drugs and devices filed a citizen’s petition seeking a clearly defined free speech safe harbor for information that enables a scientific exchange of extra-label, truthful and non-misleading information. This petition presents as clear an explanation of the Byzantine rules governing off-label communications as may be possible and represents a significant attempt to bring clarity to this murky regulatory environment.

Commercial Speech and the First Amendment

First Amendment concerns have hounded the FDA as it reeled in who could speak, what they could say, and when and where they could say it. In the past, with a notable exception or two, discussed below, the FDA prevailed on First Amendment challenges, perhaps because what is at stake is the entire regulatory scheme itself. Irrespective of the stakes, a new day is dawning on the First Amendment, and the FDA’s old arguments may not endure the scrutiny. As explained by the Seventh Circuit, Defendants’ lead argument is that the Food, Drug, and Cosmetic Act violates the First Amendment by restricting promotional materials to those that the FDA has approved. The argument starts from the premise that federal law allows customers of any approved medical device or drug to put it to any use that the customer sees fit. These “off-label uses” being lawful, the argument goes, it must be lawful to tell customers about them. Until the last 30 years, such an argument would have been laughed out of court. U.S. v. Caputo, 517 F.3d 935, 937 (7th Cir. 2008).

Well, the laughter has stopped, and courts are taking a fresh look at this First Amendment issue. The FDA originally took two positions respecting the relationship between the First Amendment and off-label or new use:

- The FDA off-label restrictions regulated conduct not speech.
- And if the Court does find the dissemination of information did constitute speech, it constituted commercial speech; as such, in regulating it the FDA restrictions satisfied the Central Hudson test.

See Summary on Final Guidance on Industry Supported Scientific and Educational Activities, 62, Fed. Reg. 64,074, 64,082; 62 C.F.R, 64,074, 64,082.

The Notable Exception

In Washington Legal Foundation v. Friedman, Judge Lamberth of the District of Columbia held that through the FDA’s purview of intermediate First Amendment scrutiny. 13 F. Supp. 2d 51, 59 (D.D.C. 1998). Judge Lamberth entered a permanent injunction prohibiting the FDA from enforcing “any regulation, guidance, policy, order or other official action” to “prohibit, restrict, sanction, or otherwise seek to limit any pharmaceutical or medical device manufacturer or any other person from” particular speech. Id. at 74. The speech is

- Disseminating reprints of materials from “bona fide peer-reviewed professional journals,”
- Disseminating textbooks or portions of textbooks, and
- Suggesting content or speakers to an independent program provider.

Id.

Judge Lamberth found that the FDA regulation overstepped the boundary necessary to serve the government’s interests in regulating off-label communications and less restrictive alternatives existed. Washington Legal Foundation v. Friedman, 13 F. Supp. 2d 51, 74 (D.D.C. 1998).

On appeal, the Fourth Circuit noted that “as a result of the government’s clarification at oral argument, the dispute between the parties has disappeared before our eyes.” 202 F.3d 331, 334 (D.C Cir. 2000). The Fourth Circuit dismissed the appeal and vacated the trial court injunction. When the parties later asked Judge Lamberth to enforce whatever remained of the injunction, the court stated:

This year, the Court of Appeals was poised to finally galvanize a rule of law in this area. Yet, for whatever reason, the opportunity was spent debating not the U.S. Constitution’s First Amendment, but its Article III case or controversy requirement. In fact, after the Court of Appeals’ opinion, we have even less First Amendment law than before; this is because the Court vacated all of this Court’s previous constitutional rulings on the matter.

As for this Court’s part in the controversy, the Court is confident that it has done its best…. It has decided the underlying [constitutional] issue at least twice, and senses it will be called on to do so again before the controversy is concluded. For now, however, the issue must be given a temporary rest.


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

Sorrell is not an off-label promotion case but it offers a major pronouncement of the Supreme Court reasoning on the First Amendment in the context of FDA-approved products. 131 S. Ct. 2653 (2011).

Pharmacies collect prescribing information (PI), including a prescriber’s name and address; the name, dosage, and quantity of the drug; the date and location where the prescription was filled; and the patient’s age and gender. Manufacturers purchase PI to focus their marketing messages to individual prescribers and rely on sales representatives, referred to as “detailers,” to visit individual physicians to provide information to the physicians on their products. In 2007, Vermont enacted a “Prescription Confidentiality Law” that prohibited pharmacies from selling PI for marketing purposes and barred manufacturers from using PI for marketing purposes.

The district court found in favor of Vermont, but the Second Circuit reversed, finding that the statute violated the First Amendment to the U.S. Constitution by burdening the speech of pharmaceutical marketers and data miners without adequate justification. A nearly identical statute was considered by the First Circuit and, because the First Circuit viewed the prescribing information as a commodity,
“mere beef jerky,” *IMS Health Inc. v Ayotte*, 550 F.3d 42, 53 (CA1 2008), and the Second Circuit viewed it as speech akin to a “cookbook, laboratory result or train schedule,” the Supreme Court granted certiorari.

The Supreme Court analysis began by stating that “[s]peech in aid of pharmaceutical marketing, however, is a form of expression protected by the Free Speech Clause of the First Amendment.” 131 S. Ct. at 2659. The Court found that the law warranted the First Amendment. “Id. at 2665. The Court wrote that “[t]he First Amendment requires heightened scrutiny whenever the government creates a ‘regulation of speech because of disagreement with the message it conveys.’” *Id.* at 2664. The Court wrote that “[t]he First Amendment requires heightened scrutiny whenever the government creates a ‘regulation of speech because of disagreement with the message it conveys.’” *Id.* at 2664.

The court went on to state: “The Constitutional issues raised in Sorrell’s motion are very much unsettled, not only in the circuit but nationwide.” The court ruled that “[i]t is clear to the Court that the promotion of off-label uses of an FDA-approved prescription drug is speech not conduct.”

"Sorrell... plainly paves the way for courts to review the First Amendment implications of the patchwork regulatory scheme governing off-label communications."
ing that “[t]he statute is therefore clearly aimed at influencing the supply of information, a core First Amendment concern…. [T]he First Amendment teaches that courts should assume that truthful commercial information ‘is not in itself harmful.’” 630 F.3d 263, 272 (2d Cir. 2010) (internal citation omitted). The Second Circuit concluded that the state could achieve its goals with less restrictive means:

In other words the statute seeks to alter the marketplace of ideas by taking out some truthful information that the state thinks could be used too effectively. The state’s approach to regulating the interaction between detailers and doctors is premised on limiting the information available to physicians as a means of impacting their conduct. This approach is antithetical to a long line of Supreme Court cases stressing that courts must be very skeptical of government efforts to prevent the dissemination of information in order to affect conduct. Id. at 277–78.

**From “Notable Exception” to Developing Trend?**

On October 14, 2011, Par Pharmaceuticals filed a declaratory judgment action in the U.S. District Court of the District of Columbia seeking a preliminary injunction preventing the federal government from criminalizing truthful speech that is not misleading to health care providers concerning its FDA-regulated products. At issue in Par is the drug Magace, a drug to treat weight loss or wasting in AIDS patients, which doctors use off-label more frequently with other populations such as geriatric and cancer patients. Par may pick up where Washington Legal Foundation v. Friedman left off, as a party has again asked that court to issue an injunction barring the FDA from prohibiting truthful speech that doesn’t mislead concerning regulated products. Perhaps this iteration of First Amendment challenges in that court will not “disappear before our eyes” as it did in *Washington Legal Foundation v. Friedman*.

**Conclusion**

The boundary between permissible and impermissible speech regarding off-label or new uses is vague, and the civil and criminal penalties for a real or imagined misstep are severe. Yet the data show that physicians and the consuming public require more, not less, truthful scientific information regarding the uses to which they put medical products. The current compliance and enforcement regime may not only fail to satisfy the mounting First Amendment challenges, but it may also fail the underlying interest of the improving public health, which it is designed to serve.