



OFF-LABEL, NOT OFF-LIMITS: The FDA needs to create a safe harbor for off-label drug use

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On December 3, 2012, the U.S. Court of Appeals for the Second Circuit issued a landmark ruling in *United States v. Caronia*,¹ which, if confirmed on a near-certain appeal to the Supreme Court, will have a profound impact on pharmaceutical promotion in the United States. In its decision, the Second Circuit overturned the federal prosecution of a pharmaceutical sales representative who had communicated truthful information about a drug used in a manner not formally reviewed by the Food and Drug Administration (FDA)—i.e., “off label.” The court ruled that “criminalizing the truthful off-label promotion of FDA-approved prescription drugs” was an unconstitutional limitation on free speech in violation of the First Amendment.²

The *Caronia* case highlights two major emerging trends in medicine and law: the widespread prescription of FDA-approved medications for off-label uses; and the increasing application of federal criminal law to regulate pharmaceutical promotion. However the Supreme Court ultimately decides the First Amendment question in *Caronia*, the FDA needs to rethink its off-label speech regulations, which have become overly broad and unnecessarily opaque. This paper looks briefly at the incidence of off-label drug prescription and at federal application of criminal law to enforce rules on pharmaceutical promotion and

proposes that the FDA should adopt a “safe harbor” to allow drug companies to communicate truthful information about off-label drug use to physicians. Our preferred approach is not about helping drug companies but rather to improve medical research and public health by increasing learning about what happens after drugs are licensed and making the best use of pharmaceuticals on the market.

OFF-LABEL DRUG PRESCRIPTIONS: AN OVERVIEW

Pharmaceuticals that are available for use and marketing under FDA regulations are also commonly prescribed for uses and indications beyond those listed on the drug’s FDA-approved label. Some of these off-label uses include treatments for diseases or symptoms not formally reviewed by the FDA, some involve dosages or delivery mechanisms not reviewed by the agency, and some involve patient populations (e.g., pediatric or geriatric) not tested in clinical trials submitted for agency approval. Such uses, while supported by publications in peer-reviewed medical journals, typically do not offer sufficient economic payback to warrant full review under the FDA’s 50-year-old system for testing and approving new medicines—a system that requires large, cumbersome, and expensive randomized clinical trials, typically controlled with a placebo or standard of care. Nevertheless, prescribing physicians often find such uses invaluable in treating their patient populations.

How common is off-label drug prescription? A 2006 study in the *Archives of Internal Medicine* estimates that 21 percent of commonly used drugs are prescribed for off-label uses.³ Doctors find off-label drugs particularly valuable in life-threatening emergencies: 36 percent of all drugs used in intensive-care units are for off-label indications, according to a 2011 study in the *Journal of Critical Care*.⁴

In narrow population groups, the share of drugs used off-label rises. Notwithstanding Congress’s effort to create incentives for pharmaceutical testing of drugs

used on children in the FDA Modernization Act of 1997,⁵ a 2007 study in the *Archives of Pediatrics & Adolescent Medicine* found that almost 79 percent of children in pediatric hospitals received one or more off-label drugs while admitted.⁶ Because patients with psychiatric disorders are often excluded from clinical trials and often display significant crossover in symptoms, off-label drug use is also particularly common in psychiatric practice. Off-label prescriptions of antipsychotic drugs alone cost an estimated \$6 billion in 2008.⁷

Off-label drug uses are often widely accepted, and private insurance companies as well as Medicare and Medicaid will reimburse for these off-label uses because the medical community or medical compendiums on effective treatment consider them “standard of care.” In cancer treatment, for instance, many patients are routinely treated with one or more drugs for an off-label indication. Tricyclic antidepressants have largely been supplanted by more focused drugs to treat depression, but their off-label use to treat neuropathic pains associated with strokes, spinal-cord injuries, or cerebral palsy is a common and preferred medical treatment.⁸ Selective serotonin reuptake inhibitors (SSRIs) such as citalopram (Celexa) are commonly prescribed for alcoholism and other addictive disorders, obsessive-compulsive disorder, fibromyalgia, and stuttering.⁹ Morphine is commonly used off-label to treat pain in children,¹⁰ magnesium sulfate to treat premature labor,¹¹ and azathioprine to treat atopic dermatitis and psoriasis.¹² Even the use of aspirin as a preventive measure for patients at high risk of coronary disease—a commonly accepted guideline—is an off-label use.¹³

THE FDA’S SPEECH REGIME ON OFF-LABEL DRUG PROMOTION

The big problem, from a public health perspective, is that doctors often lack adequate information about off-label drug use because those best-positioned to inform them about the benefits and risks associated with such uses—the drug manufacturers themselves—are

effectively precluded from doing so by the FDA. Under the 1938 Food, Drug, and Cosmetic Act,¹⁴ the FDA has authority to regulate promotional materials for pharmaceutical products. The FDA not only requires approval for product labeling but also prohibits drug “misbranding,” including for off-label uses.¹⁵

In principle, the FDA is all for a robust exchange of scientific information between a drug or device company and the research and patient community, and the agency recognizes that companies often have the most up-to-date information on a drug’s risks and benefits. But the FDA’s official line is that companies can share only “scientific” information, not “promotional” information. That line is awfully blurry and ignores the fact that much information about a product’s potential uses (both from a safety and an efficacy perspective) evolves when patients and physicians experiment with FDA-approved medicines outside of the constructs of clinical trials and science journals.

For instance, companies must tell patients and doctors about safety issues related to off-label uses when it learns about them. But the FDA won’t let companies talk about the efficacy of off-label drug use because that would be “promotional.” In one case, the FDA wouldn’t let Allergan warn doctors that a commonly used dose of its cosmetic drug Botox, used off-label for juvenile cerebral palsy, was likely too high for that patient class, because it would have implied that the lower dose was safe and effective—a judgment that the FDA didn’t want to endorse.¹⁶ Instead, the FDA would allow only a much more generalized—and potentially less effective—warning regarding all juvenile uses.

Under the 1997 FDA Modernization Act, as interpreted by the FDA’s labyrinthine rules, companies can, in theory, communicate scientific information on their medicines by distributing independent articles from medical journals.¹⁷ But since companies sponsor the lion’s share of all drug research, much of the relevant literature will be disqualified by the FDA’s rules. Even those articles that make the cut may be

months or years behind the latest research and may touch only a small fraction of what a company may know about the off-label uses of its products.

Assume that you’re at a scientific conference and that you have a deadly disease. You ask a company’s researcher about a particular product in a room full of researchers and patients who are all interested in the same subject. The company researcher can’t answer—even when the answer would interest everyone in the room. The researcher will tell you to wait for a sidebar and then convey the information to you one-on-one. Why? If the researcher communicates to the broader audience, the government might deem that “promotional.”

Ironically, patients, doctors, insurers, and government researchers are free to say whatever they want about off-label uses—even to the point of saying that generic X is a better off-label treatment than branded drug Y—but the company isn’t allowed to enter into that debate or dialogue. In practice, companies face a minefield without a map. Companies such as Par Pharmaceuticals are even worried about talking to doctors about on-label indications, such as AIDS-associated wasting for one of their drugs, because so many doctors use the drug off-label for cancer. Just explaining the drug’s ability to stimulate appetite to a doctor who also treated cancer patients might, in itself, be evidence of the company’s “intent” to misbrand the drug and set the company up for government civil or criminal action.

THE FEDERAL CRIMINAL LAW ENFORCEMENT OF OFF-LABEL DRUG PROMOTION

Companies’ fear of federal criminal action to enforce off-label drug promotion is not merely hypothetical. Claims of illicit off-label drug promotion have been among the most commonly asserted Medicaid-fraud allegations in federal enforcement actions.¹⁸ Manufacturers cannot afford to fight a criminal investigation because

Selected Recent Drug-Misbranding Non-Prosecution Agreements in the Pharmaceutical Industry

Company	Jurisdiction	Fine/Settlement	Corporate Monitor	Term of NPA
Merck & Co., Inc.	U.S. Attorney, District of Massachusetts	\$950,000,000	No	60 months
GlaxoSmith Kline plc	U.S. Attorney, District of Massachusetts; DOJ Civil Division	\$3,000,000,000	Yes	60 months
Forest Laboratories, Inc.	U.S. Attorney, District of Massachusetts	\$313,158,058	No	60 months
Elan Corporation Plc	U.S. Attorney, District of Massachusetts	\$203,540,783	No	60 months
Ortho-McNeil-Janssen Pharmaceuticals, Inc.	U.S. Attorney, District of Massachusetts	\$81,513,407	No	60 months

the potential repercussions for a company convicted of a crime include “debarment” from federal contracting—precluding the company from being reimbursed by Medicare or Medicaid,¹⁹ effectively a corporate death sentence for a pharmaceutical manufacturer.

Rather than bet the company on a criminal trial over off-label drug promotion, pharmaceutical companies are increasingly entering into “non-prosecution agreements” (NPAs) with the Department of Justice and U.S. Attorneys’ Offices and “corporate integrity agreements” (CIAs) with the Department of Health and Human Services to avoid prosecution. Such agreements involve significant fines (sometimes in the billions of dollars), significantly modified business practices (sometimes overseen by “corporate monitors” who report to a federal prosecutor), and even the removal of top executives.²⁰

In 2012, GlaxoSmithKline paid a record \$3 billion fine after entering into an NPA and a CIA to resolve allegations of off-label promotion of a pair of antidepressants: paroxetine (Paxil) for use by children; and bupropion (Wellbutrin) as a weight-loss aid.²¹ (A partial list of this and other recent federal NPAs involving alleged “drug misbranding” is shown above.) Also in 2012, Abbott Laboratories paid a \$1.6 billion fine and pleaded guilty to a criminal misdemeanor for the off-label promotion of the anticonvulsant epilepsy drug valproic acid (Depakote) for schizophrenia, bipolar disorder, and migraines²²—notwithstanding that such uses are well-established standards of care in the medical community,

approved for reimbursement by the federal government and private insurers. In 2009, Eli Lilly and Pfizer paid \$1.4 billion and \$2.3 billion, respectively, for alleged promotion of drugs for off-label uses.²³

The cost of the burgeoning application of criminal law to enforce the FDA’s off-label speech code goes far beyond the criminal fines imposed. As coauthor James Copland discussed in more detail in a 2012 *Legal Policy Report* on the subject, the process whereby federal prosecutors and regulators enter into NPAs and CIAs lacks transparency and judicial oversight, and the broad sweep of these arrangements imposes a little-appreciated regulatory burden with real economic impact.²⁴

OUR PROPOSAL: A SAFE HARBOR FOR TRUTHFUL SPEECH

By far the most serious consequence of the FDA’s onerous limitations on off-label drug promotion, amplified by the heavy hand of federal criminal law, is the regime’s adverse impact on public health. Simply put, limiting companies’ ability to communicate with doctors about new advances in medicine serves patients poorly. The American Medical Association (AMA) has called for streamlining the process for adding new indications to a drug’s FDA-approved label,²⁵ which would ameliorate the economic calculus that leads companies to forgo the multiyear, exceptionally expensive “supplemental new drug application” pro-

cess for gaining a new label indication under current FDA guidelines.

But given that the FDA is unlikely to streamline its procedures anytime soon, it should at least work to facilitate the communication of the best science available to doctors and other learned intermediaries. Scientific knowledge could be captured and disseminated much better by a “safe harbor” on off-label drug use and promotion that recognizes that patients and physicians are collaborators in developing information on when a drug works (or doesn’t work), and for whom.

Under such a safe harbor, the FDA would give companies the ability to communicate truthful science-based off-label information about their products to the physician community. However, companies should also be required to share comprehensive data on safety and efficacy for off-label uses with researchers, regulators, and insurers, who can then mine the information to rapidly validate emerging uses for established therapies. Indeed, we should view these uses less as “off-label uses” and more as “emerging uses.”

The physician community is highly trained and sophisticated, and a supplemental warning accompanying such information—emphasizing that the use in

question is not FDA-approved and that safety and efficacy information is still emerging from additional research—should enable physicians to evaluate the information with due skepticism.

Ideally, the FDA would couple the safe harbor with a streamlined FDA system for adding (or removing) new label indications, including information for specific subpopulations of patients. This would provide a valuable tool for researchers and patients looking for objective information on new treatments as well as repurpose older medicines for new uses.

At a minimum, the FDA needs to allow those with the greatest knowledge of—and greatest incentive to disseminate information about—medical advances to communicate with prescribing physicians. Americans should be concerned that they may not get the medicines they need because their physicians are unaware of new medical applications that may help them, due to the heavy hand of federal criminal law discouraging truthful speech. We shouldn’t be telling companies to shut up when what they have to say can save lives—a message that Congress and the FDA should embrace and one that the Supreme Court should heed when it takes up the *Caronia* case for review.

ENDNOTES

¹ United States v. Caronia, No. 09–5006–CR, 2012 WL 5992141 (2d Cir. Dec. 23, 2012).

² The Court’s holding, in full, reads: “[W]e decline to adopt the government’s construction of the [Food, Drug, and Cosmetic Act’s (FDCA’s)] misbranding provisions to prohibit manufacturer promotion alone as it would unconstitutionally restrict free speech. We construe the misbranding provisions of the FDCA as not prohibiting and criminalizing the truthful off-label promotion of FDA-approved prescription drugs.” *Ibid.*, 15.

³ David C. Radley, Stan N. Finkelstein, and Randall S. Stafford, “Off-Label Prescribing among Office-Based Physicians,” *Archives of Internal Medicine* 166, no. 9 (May 2006): 1021–26.

⁴ Ishaq Lat et al., “Off-Label Medication Use in Adult Critical Care Patients,” *Journal of Critical Care* 26, no. 1 (2011): 89–94.

⁵ Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997).

⁶ S. S. Shah et al., “Off-Label Drug Use in Hospitalized Children” (published correction appears in *Archives of Pediatrics & Adolescent Medicine* 161, no. 7 [2007]: 655), *Archives of Pediatrics & Adolescent Medicine* 161, no. 3 (2007): 282–90.

- ⁷ G. C. Alexander et al., “Increasing Off-Label Use of Antipsychotic Medications in the United States, 1995–2008,” *Pharmacoepidemiol Drug Safety* 20, no. 2 (2011): 177–84.
- ⁸ R. H. Dworkin et al., “Recommendations for the Pharmacological Management of Neuropathic Pain: An Overview and Literature Update,” *Mayo Clinic Proceedings* 85, no. 3, suppl. (2010): S3–S14.
- ⁹ Drug Facts and Comparisons 4.0; <http://www.factsandcomparisons.com/>.
- ¹⁰ Shah et al., “Off-Label Drug Use in Hospitalized Children,” 284.
- ¹¹ Drug Facts and Comparisons 4.0; <http://www.factsandcomparisons.com/>.
- ¹² M. E. Schram et al., “Off-Label Use of Azathioprine in Dermatology: A Systematic Review,” *Archives of Dermatology* 147, no. 4 (2011): 474–88.
- ¹³ R. S. Stafford, “Regulating Off-Label Drug Use: Rethinking the Role of the FDA,” *New England Journal of Medicine* 358, no. 14 (2008): 1427–29.
- ¹⁴ Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040 (1938).
- ¹⁵ M. M. Mello, D. M. Studdert, and T. A. Brennan, “Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals,” *New England Journal of Medicine* 360, no. 15 (2009): 1557–66.
- ¹⁶ See Gregory Conko, “Hidden Truth: The Perils and Protection of Off-Label Drug and Medical Device Promotion,” *Health Matrix* 21, no 149 (2011): 149–87; <http://law.case.edu/journals/HealthMatrix/Documents/Conko.FINAL.clr%20REVISED%205.15.pdf>.
- ¹⁷ J. H. Tanne, “FDA Allows Drug Firms to Distribute Journal Articles about Unapproved Uses,” *BMJ* (2009): 338:b187.
- ¹⁸ Z. P. Qureshi et al., “Enforcement Actions Involving Medicaid Fraud and Abuse, 1996–2009,” *Archives of Internal Medicine* 171, no. 8 (2011): 785–87.
- ¹⁹ Cf. Deferred Prosecution Agreement, U.S. Dep’t of Justice, Re: Johnson & Johnson (Crim. Div., Fraud Sec., April 8, 2011); <http://gibsondunn.com/publications/Documents/JohnsonAndJohnson.pdf> (hereinafter, “J&J DPA”), 3 (“Were the Department to initiate a prosecution of J&J or one of its operating companies and obtain a conviction, instead of entering into this Agreement to defer prosecution, J&J could be subject to exclusion from participation in federal health care programs pursuant to 42 U.S.C. § 1320a-7(a)”).
- ²⁰ See, generally, James R. Copland, *The Shadow Regulatory State: The Rise of Deferred Prosecution Agreements*, Civil Justice Report No. 14 (New York, The Manhattan Institute for Policy Research, 2012).
- ²¹ Katie Thomas and Michael S. Schmidt, “Glaxo Agrees to Pay \$3 Billion in Fraud Settlement,” *New York Times* (July 2, 2012), <http://www.nytimes.com/2012/07/03/business/glaxosmithkline-agrees-to-pay-3-billion-in-fraud-settlement.html?pagewanted=all>.
- ²² See <http://www.pharmawatchdog.com/abbott-settles-depakote-illegal-marketing-case>.
- ²³ Z. Kmietowicz, “Eli Lilly Pays Record \$1.4bn for Promoting Off-Label Use of Olanzapine,” *BMJ* (2009): 338:b217; and M. Ratner, “Pfizer Settles Largest Ever Fraud Suit for Off-Label Promotion,” *Nature Biotechnology* 27, no. 11 (2009): 961–62.
- ²⁴ Copland, *The Shadow Regulatory State*.
- ²⁵ Joseph W. Cranston et al., *Report of the Council on Scientific Affairs: Unlabeled Indications of Food and Drug Administration-Approved Drugs*, Drug Information Journal Vol. 32 (Illinois, American Medical Association, 1998).