

# Health Policy Brief

JUNE 30, 2016

## **Off-Label Drug Promotion.** Drug companies are largely prohibited from promoting a drug for uses that have not been approved by the Food and Drug Administration.

### WHAT'S THE ISSUE?

In the United States, the sale and marketing of pharmaceutical products is primarily regulated by the Food and Drug Administration (FDA), and drug companies are largely prohibited from promoting a drug for uses that have not been approved by the agency. However, the FDA generally does not restrict physician prescribing practices, and many drugs are prescribed “off label”—that is, for indications that have not been approved by the agency. In recent years there has been renewed debate over whether and how the FDA should regulate the pharmaceutical industry’s communication to physicians around off-label uses, spurred in part by high-profile court cases as well as broader shifts in the health care landscape.

### WHAT'S THE BACKGROUND?

A drug is used off label any time it is administered in a way that has not been approved by the FDA. This includes prescribing a drug for a different disease or symptom, in a population that has not been included in the label, or with a different dosage level or formulation. The practice is both legal and common. An [estimated](#) one in five prescriptions written are for an off-label use, and in some cases, such use is the accepted standard of care and recommended in clinical practice guidelines. Mifepristone, for example, was recently approved for use at

a lower dose to induce medical abortions (200 mg instead of the previously approved dosage of 600 mg), but this lower dosage was considered standard practice for many years.

Providers might choose to prescribe off label for many reasons. The medication might not have been studied in certain populations prior to approval, but the drug might still be helpful for those groups. In some cases, two conditions might share key clinical features (for example, psychiatric diseases such as anxiety and post-traumatic stress disorder [PTSD]), but one of the conditions (as in the case of PTSD) might have fewer therapeutic options formally approved for its treatment. In other cases, two drugs might be similar in terms of their chemical structure or mechanism of action (and thus in the same “class”), and the prescriber might choose to substitute one for the other even if they are not approved for the same indications. A physician might also be motivated to prescribe off label if a patient is seriously ill and other treatment options are limited or exhausted.

Although common, off-label use is often not supported by good clinical evidence of effectiveness. One [study](#) found that 73 percent of medications prescribed for off-label purposes had poor or no scientific support, while [another](#) found that 48 percent of off-label prescriptions for critical care patients lacked adequate evidence. The problem is particularly acute in

# 73%

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populations that are difficult to study, such as children and pregnant women, and the consequences can be serious. Off-label use that is not supported by adequate evidence is associated with [significantly higher rates](#) of adverse drug reactions. Given the well-known gaps in the postmarket safety surveillance system, the true extent of these adverse events is likely underappreciated.

### *FDA regulation of off-label promotion*

Under FDA rules, any promotional materials distributed by a company should be truthful, balanced, nonmisleading, and supported by substantial evidence. In addition, it has been illegal for drug manufacturers to directly promote or advertise a drug for any indication that the FDA has not approved. However, companies are not categorically prohibited from disseminating information about off-label uses, and the FDA’s approach to regulating and enforcing the distinction between *communication* and *promotion* has evolved over the past several decades in response to both legislative changes and legal challenges.

Manufacturers can communicate about off-label uses of their drugs in a number of ways. Companies are permitted to respond to unsolicited requests from health care professionals about unapproved uses and might also support independent continuing medical education activities at which off-label uses are discussed. Since the passage of the Food and Drug Administration Modernization Act (FDAMA) of 1997, companies are also permitted to distribute peer-reviewed journals and reference books that discuss off-label uses, although this practice is subject to certain limitations. In 2014 the FDA expanded this authority to include non-peer-reviewed [clinical practice guidelines](#).

Under Section 114 of the FDAMA, companies were also given the power to share health care economic information about approved uses of their drugs with formulary committees, managed care organizations, and other entities that make reimbursement and coverage decisions. However, it is unclear how often drug companies have used this pathway, which [some](#) attribute to a lack of clarity on how the FDA interprets that section of the law, as well as to the availability of alternative channels for health economic communication (principally, the Academy of Managed Care Pharmacy’s *Format for Formulary Submissions*, which provides comprehensive drug information to managed care organizations).

The FDA has released multiple guidance documents detailing its current thinking about manufacturer communication and promotion, including updates—in 2011 and 2014, respectively—to its guidance on responding to unsolicited requests and disseminating journal articles, reference texts, and clinical practice guidelines. Nevertheless, it is not always clear what behavior falls into one of these safe harbors, and manufacturers have substantial incentives to push the boundaries of the law. The FDA also has limited capacity to review and monitor all forms and avenues of communication. Violations are common, and many of these violations have led to serious and costly patient harm.

In 2012, for example, GlaxoSmithKline (GSK) was fined \$3 billion by the federal government, in part for off-label promotion of several of its drugs. One of those drugs, the antidepressant paroxetine (Paxil), was promoted for use in adolescents on the basis of a flawed 2001 study, despite clear evidence linking the drug to suicidal thoughts in that population and despite the FDA’s never approving the drug for pediatric use. In 2002 alone, roughly two million off-label prescriptions were written for paroxetine in children. A black-box warning was finally added in 2004 to the drug’s label indicating its serious safety issues, ultimately contributing to a reduction in its off-label use.

All told, the federal government has collected more than \$15 billion in civil and criminal fines from pharmaceutical companies for similar cases over the past decade. It is unclear how effective such settlements are in deterring these practices, as the revenues generated from off-label prescribing are substantial and can far outweigh the penalties.

### *The role of the courts*

The courts have also played (and are continuing to play) a prominent role in shaping the FDA’s approach to regulating off-label promotion. Three recent cases in particular—*Sorrell v. IMS Health*, *United States v. Caronia*, and *Amarin Pharma v. FDA*—have reignited debates over the limits of the FDA’s authority to regulate commercial speech and will likely have substantial implications for agency policy making.

In the 2011 case of *Sorrell v. IMS Health*, the US Supreme Court ruled that a Vermont statute prohibiting the sale, disclosure, or use of physician prescribing records for the purpose

# 48%

A 2011 study found that 48 percent of off-label prescriptions for critical care patients lacked adequate evidence.

of marketing violated the First Amendment. In its majority opinion, the court rejected the state's argument that these restrictions advanced a substantial government interest and concluded that the statute placed an undue burden on commercial speech.

This decision was subsequently cited in the 2012 decision in the *United States v. Caronia*, which vacated the conviction against a former Orphan Medical sales representative. Caronia had been prosecuted for promoting sodium oxybate (Xyrem)—which was approved for the very rare disease of narcolepsy with cataplexy—for a range of off-label uses, including insomnia, fibromyalgia, and Parkinson's disease, despite the lack of evidence that the drug was useful in these cases (and despite substantial evidence of its risks). In its ruling, the court determined that the First Amendment's protection of commercial speech supported Caronia's ability to engage in truthful off-label promotion of FDA-approved drugs. (The actual truthfulness of Caronia's speech was not an issue raised at trial, as the federal government believed it to be sufficient to prove that Caronia had engaged in off-label promotion.) Although the FDA declined to appeal and stated that the ruling would not affect its enforcement, many view this decision as a landmark case that opened the door to further legal challenges to the agency's authority.

Three years later, Amarin Pharma sued the FDA over its right to promote an unapproved indication for its prescription omega-3 fish oil product (Vascepa). Amarin sought to claim that "supportive but not conclusive research shows that EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease" for people with persistently high levels of triglycerides in their blood. The FDA rejected the company's application for this claim, as recent research had raised questions about the link between a reduction in triglyceride levels and reduced overall cardiovascular risk. Amarin argued that the wording of its claim was nonetheless truthful and nonmisleading and that it should therefore be permitted to communicate this information to providers without fear of federal prosecution. In August 2015 the district court judge sided with the company, granting Amarin a preliminary injunction. In March 2016 the FDA and Amarin reached a settlement that permits the company to promote the off-label use of Vascepa.

Taken together, these cases present a serious challenge to the FDA's historical approach to regulating off-label communication and

might foreclose manufacturers or their representatives from being prosecuted for off-label promotional speech that is truthful and nonmisleading.

### *The influence of broader health system trends*

The renewed focus on off-label promotion is also being driven by broader trends in the health care system. Rising prescription drug costs have led to an increased emphasis on the comparative value of treatments on the market, as evidenced by the emergence of groups such as the Institute for Clinical and Economic Review and the development of tools such as Memorial Sloan Kettering's [DrugAbacus](#), which allows individuals to assess the price of a given drug relative to its value.

At the same time, the enormous amount of electronic data generated by the health care system has created new opportunities to conduct research and develop evidence on the safety, effectiveness, and value of drugs once they are on the market; and it has significantly increased the amount, type, and potential usefulness of information available to support medical decision making.

The confluence of these larger trends, combined with the recent court rulings favoring commercial speech, has increased the pressure on the FDA to review and update its policies, guidance, and regulations so as to reflect these changes and to clarify the distinction between permissible and impermissible off-label communication.

### WHAT'S THE DEBATE?

At the center of the debate over off-label communication is the question of how the FDA can best safeguard public health while also supporting fully informed decision making by providers and patients. Many have [raised concerns](#) over the impact of legal cases such as *Caronia* and *Amarin*, arguing that any relaxation of the FDA's restrictions on promotion would only intensify the prevalence—and therefore the problems—associated with off-label prescribing: namely, the lack of high-quality evidence supporting those prescribing decisions and the greater associated risks to patients.

Currently, a manufacturer can expand a drug's approved indications through a supplemental New Drug Application, but performing the required clinical trials is a costly and time-consuming process, and manufacturers have

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little incentive to do this for drugs that are already used widely off label. The incentives are also low in cases in which the drug is about to lose patent protection or is already subject to generic competition. Reducing restrictions on manufacturer communication might, in turn, reduce the incentive to conduct the kind of prospective, well-controlled trials that the FDA usually requires before it approves a drug for a new indication.

Furthermore, while the proliferation of health care data and information sources has great potential to advance medical knowledge and practice, the quality of the research being conducted on these data varies substantially. Providers typically do not have the time—or the capacity—to keep up with and evaluate the majority of research conducted on drugs in the post-market setting. Even if well designed, a given trial can produce misleading or incomplete results, and poorly designed or conducted studies can seriously misrepresent the benefits or risks of a treatment. The publication of clinical research is also subject to several biases. Positive results are more likely to be reported in the literature, and published analyses do not always provide adequate information on their design or methodology. This lack of transparency can seriously hamper a provider’s ability to fully assess the evidence base, even assuming they have the time to do so.

However, [others counter](#) that the truthful, nonmisleading promotion by pharmaceutical companies of drugs for off-label uses not only is protected by the First Amendment, but—with the appropriate safeguards and caveats in place—can be an invaluable source of information for both provider and patients, as manufacturers have the most up-to-date and comprehensive information about their products. Critics also note that the supplemental New Drug Approval process is too slow to keep pace with all medical advances and that preventing a manufacturer from communicating about an off-label use or the comparative value of its products might unnecessarily impede innovation in medical practice, negatively affect patient care, and increase health costs.

Critics of the current regulatory regime also argue that existing FDA regulations, guidance, and policies are inconsistent and do not provide enough clarity for manufacturers attempting to comply with the law. The recent court decisions have introduced further uncertainty to an already complicated policy arena and have led to calls for an updated reg-

ulatory framework that can better address the needs of all stakeholders.

## WHAT’S NEXT?

In response to these calls, the FDA has pledged to review and update its regulations and guidance documents where necessary to establish standards for truthful nonmisleading communication of scientific information. The agency recently [announced](#) that it would be releasing four guidance documents in 2016 related to communication practices, although the exact timelines for publication are unclear.

The calls for regulatory clarity have also been reflected in recent legislative proposals. The 21st Century Cures legislation, which passed the House in July 2015, would establish deadlines for agency guidance on off-label communication and would allow companies to proactively disseminate health economic information about off-label uses to health care payers under section 114 of the FDAMA. The future of the Cures Act is unclear, although the US Senate Committee on Health, Education, Labor, and Pensions recently approved the last of nineteen pieces of legislation that could eventually become the companion bill to the Cures Act.

The issue of off-label communication has also been raised for inclusion in the next iteration of the Prescription Drug User Fee Act of 1992, a key source of funding for the agency that is reauthorized every five years. The next version of the legislation will be voted on in 2017, but negotiations over its provisions have already begun.

In the meantime, these issues will continue to play out in the courts, and there are signs that the government is already beginning to adapt its enforcement approach to reflect the precedent established by cases such as *Sorrell* and *Caronia*. In a recent case involving a medical device company charged with illegal off-label promotion (*United States v. Vascular Solutions*), the Department of Justice [submitted](#) jury instructions stating that it was “not a crime for a device company or its representative to give doctors wholly truthful and nonmisleading information about the unapproved use of a device.”

More broadly, improving off-label prescribing and ensuring the availability and dissemination of complete and accurate information will require better systems for collecting, sharing, and analyzing data on drugs once

**About Health Policy Briefs**

Written by

**Elizabeth Richardson**Research Associate  
Duke-Robert J. Margolis, MD,  
Center for Health Policy

Editorial review by

**Aaron S. Kesselheim**Associate Professor of Medicine  
at Harvard Medical School  
Director, Program on Regulation,  
Therapeutics, and Law (PORTAL)  
Division of Pharmacoepidemiology  
and Pharmacoeconomics  
Brigham and Women's Hospital**Ian Spatz**Senior Adviser  
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*Health Affairs***Tracy Gnadinger**Associate Editor  
*Health Affairs*Health Policy Briefs are produced under  
a partnership of *Health Affairs* and the  
Robert Wood Johnson Foundation.Cite as: "Health Policy Brief: Off-Label  
Drug Promotion," *Health Affairs*,  
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they are on the market. Efforts are under way to improve the postmarket collection and analysis of data, and there have also been encouraging steps taken to improve transparency and data sharing in the clinical research field. However, these efforts will take time, and while they are an important supplement to the FDA's regulatory oversight, they are not

a replacement. The agency will still occupy a central and critical role in ensuring that manufacturers communicate about their products in a truthful, nonmisleading way. It remains to be seen how its regulatory approach will evolve over time and what the implications will be for patients. ■

**RESOURCES**

Jerry Avorn, Ameet Sarpatwari, and Aaron S. Kesselheim, "[Forbidden and Permitted Statements about Medications—Loosening the Rules](#)," *New England Journal of Medicine* 373, no. 10 (2015):967–73.

Gregory W. Daniel, Morgan H. Romine, Jeff Allen, Nicholas Bagley, Amy Comstock Rick, Coleen Kalsmeier, Mark B. McClellan, Sarina E. Coates, Joy Liu, Peter Pitts, Marc Scheineson, and Richard L. Schilsky, [Policy Options for Off-Label Communication: Supporting Better Information, Better Evidence, and Better Care](#) (Durham, NC: Duke-Margolis Center for Health Policy, February 2016).

Food and Drug Administration, [Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practice](#) (Washington, DC: FDA, February 2014).

Food and Drug Administration, [Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information about Prescription Drugs and Medical Devices](#) (Washington, DC: FDA, December 2011).

Coleen Kalsmeier and Martin H. Redish, "[Off-Label Prescription Advertising, the FDA, and the First Amendment: A Study in the Values of Commercial Speech Protection](#)," *American Journal of Law and Medicine* 37, no. 2–3 (2011):315–57.

Aaron S. Kesselheim and Michelle M. Mello, "[Prospects for Regulation of Off-Label Drug Promotion in an Era of Expanding Commercial Speech Protection](#)," *North Carolina Law Review* 92 (2014):101–62.

Eleanor M. Peretto, Laurie Burke, Elisabeth M. Oehrlein, and Mena Gaballah, "[FDAMA Section 114: Why the Renewed Interest?](#)" *Journal of Managed Care and Specialty Pharmacy* 21, no. 5 (2015):368–74.

Joshua M. Sharfstein and Alta Charo, "[The Promotion of Medical Products in the 21st Century: Off-Label Marketing and First Amendment Concerns](#)," *Journal of the American Medical Association* 314, no. 17 (2015):1795–6.

Christopher M. Wittich, Christopher M. Burkle, and William L. Lanier, "[Ten Common Questions \(and Their Answers\) about Off-Label Drug Use](#)," *Mayo Clinic Proceedings* 87, no. 10 (2012):982–90.