

## VIEWPOINT

## HEALTH CARE POLICY AND LAW

# Promotion of Drugs for Off-label Uses

## The US Food and Drug Administration at a Crossroads

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Since 1962, the US Food and Drug Administration (FDA) has required companies to establish, with adequate and well-controlled clinical trials, a drug's safety and efficacy for each intended use and has prohibited the "off-label" promotion of drugs. For companies to market an approved medicine for new indications, they must first conduct trials and submit data to establish safety and efficacy, as was the case for the initial approval.

The FDA's approach to off-label promotion is in jeopardy, however. In response to recent US Supreme Court decisions strengthening First Amendment protection for companies, the pharmaceutical industry has framed off-label marketing as a free speech right. Drug companies have won several important court cases that have weakened the FDA's authority to regulate off-label marketing. Although the legal issue—whether the FDA's restrictions on off-label marketing are unconstitutional—remains unresolved, the agency has initiated a comprehensive review of its approach to off-label marketing. On November 9 and 10, 2016, the FDA will convene a public hearing to address "its regulations and policies governing firms' communications about unapproved uses of approved/cleared medical products."<sup>1</sup>

The Food, Drug, and Cosmetic Act grants the FDA the authority to approve drugs for specific indications and to prohibit the sale of "misbranded" drugs. When used for a new condition or population, a drug's risk-benefit ratio may change, or new safety considerations may emerge. By requiring studies before permitting marketing of new uses, the FDA gives companies incentives to produce the needed evidence for sound medical decisions.

Off-label uses can be clinically appropriate, and physicians are free to prescribe medicines off-label. To help facilitate well-informed decisions, the FDA has created safe harbors that allow companies to communicate about potential new uses with physicians. Under current FDA guidance, drug companies may respond to unsolicited questions from physicians and proactively circulate peer-reviewed journal articles about off-label uses if the articles are based on adequate and well-controlled studies.<sup>2,3</sup>

Recently, companies have begun to challenge this framework for communicating with clinicians about off-label uses of drugs. Some have argued that more extensive marketing is not merely good policy, but a constitutionally protected right. In a watershed 2012 case, *United States v Caronia*, the US Court of Appeals for the Second Circuit in New York sided with the industry. In

that case, a pharmaceutical detailer had promoted sodium oxybate (Xyrem), approved to treat narcolepsy, for off-label uses, including chronic pain, and a jury convicted him of misbranding the drug. In a 2 to 1 decision, the appellate court vacated the conviction on First Amendment grounds.<sup>4</sup> The court ruled that the government could not prosecute the detailer simply for making off-label promotional statements, but was also careful not to entirely strike down the FDA's authority to regulate off-label promotion. It suggested that the FDA might have prevailed if it had treated promotional speech merely as evidence of criminal conduct (namely, the selling of a misbranded drug) and not as criminal itself. This draws on a well-established rule that the use of speech as evidence to prove criminal conduct does not violate, or even implicate, the First Amendment. This rule in fact sustains the FDA's authority to forbid the marketing of entirely *unapproved* drugs. A company that markets an unapproved drug cannot defend its actions by arguing that its treatment claims are constitutionally protected speech.<sup>5</sup>

In 2015, a US district court in Manhattan went beyond *Caronia*, in a case involving Amarin Pharmaceuticals.<sup>6</sup> The trial judge concluded that drug companies have a First Amendment right to market any off-label use to physicians as long their statements are not false or misleading.<sup>7</sup> The judge barred the FDA from using such promotional statements as evidence of misbranding, effectively rejecting the legal argument that was left open by the *Caronia* case.

On this logic, once a drug is approved for any indication, it can be promoted to physicians for any use as long as a judge, not the FDA, views the marketing to be truthful and nonmisleading. But judges are not experts in trial design, pharmaceutical regulation, or the evaluation of medical evidence, and the effects of drugs cannot be known unless they are carefully studied. The *Amarin* decision invites a world where companies no longer pursue broad clinical indications for new drugs but instead seek the narrowest possible indication for approval and then market the drug for any new use for which there is *some* evidence, no matter how weak. Companies would no longer have to conduct rigorous trials and submit, to the FDA, data demonstrating the safety and efficacy of new uses. Such an approach would compromise the future evidence base for medicines, expose patients to a greater risk of adverse events, and increase pharmaceutical spending without evidence that the expenditures would help improve patients' health.<sup>8</sup>

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The *Amarin* decision, however, is not a definitive ruling. The FDA did not appeal, so it remains a lower court decision that does not bind other courts. Appellate courts (most importantly, the Supreme Court—soon to receive a new Justice) could affirm the constitutionality of the FDA's longstanding practice, if future cases are brought before them. Indeed, in May 2016, in another case a panel of judges from the same federal appeals court that decided the *Caronia* case expressed approval of the “marketing as evidence of misbranding” theory left undecided in *Caronia*. The court did not rule on this issue, however. Instead it found on the facts that the company had not engaged in off-label promotion.<sup>9</sup>

The FDA also has additional legal arguments on its side and should vigorously defend its existing regulatory regime by bringing cases against off-label promotion and fully litigating them. For example, commercial speech is not an absolute right and can be regulated to ensure that the public has access to accurate and reliable information.<sup>6</sup> The FDA's restrictions on off-label marketing serve this end.

If the FDA does not staunchly defend its authority to regulate off-label promotion, it may lose it incrementally. In September 2015, shortly after the *Amarin* decision, Pacira Pharmaceuticals brought a First Amendment challenge when the FDA sought to prevent the company from marketing a postsurgical analgesic (bupivacaine liposome injectable suspension, or Exparel) for uses in surgical sites that had not been studied in the trials supporting the drug's approval. The agency settled the case, in this instance by expanding the label to encompass broader surgical uses.<sup>10</sup> If the FDA resolves these cases by broadening labels without new evidence (as seems to be the case here), the results are even more wide-reaching than they were in the *Amarin* case. In that case, the judge authorized off-

label marketing only to physicians, in part because the judge viewed them as sufficiently expert to evaluate the marketing claims. But when the FDA broadens a label, this permits marketing not only to physicians but also to the public.

The FDA is also under pressure from some members of Congress to ease its stance on off-label marketing. In May 2016, Fred Upton (R-Michigan) and Joseph Pitts (R-Pennsylvania), 2 ranking members of the House Energy and Commerce Committee, sent a letter to Sylvia Burwell, the Secretary of Health and Human Services. Pointing to the *Amarin* and *Caronia* decisions, they urged the FDA to revise its rules and guidance to permit drug companies to promote off-label uses and raised the possibility of legislative amendments if the agency did not make changes on its own.

At the November 2016 hearing, the FDA is explicitly inviting input about the implications of allowing drug companies to promote off-label uses of medical products. The agency is also accepting written comments until January 9, 2017.<sup>1</sup> The range of questions the agency has posed shows that it is aware that the move could have far-reaching effects, including weakening firms' incentives to conduct trials, diminishing patients' incentives to enroll in trials, and unleashing a flood of unsubstantiated marketing to physicians and the public. Although companies have many venues to interact with the FDA on these issues, the hearing and the submission of written comments will provide an important opportunity for physicians, insurers, and patient groups to also make their views known. The existing regulatory regime has protected the public and helped provide physicians with rigorous evidence over many decades. Drug companies' disputed First Amendment rights should not catalyze a major shift in the agency's enforcement authority; any changes should be approached with an abundance of caution.

#### ARTICLE INFORMATION

**Published Online:** November 7, 2016.  
doi:10.1001/jamainternmed.2016.7151

**Conflict of Interest Disclosures:** None reported.

**Funding/Support:** The work was funded in part by the Laura and John Arnold Foundation, through a research grant to Yale University to support the Collaboration for Research Integrity and Transparency (CRIT).

**Role of the Funder/Sponsor:** The sponsor had no role in the design or drafting of the article and did not review the article prior to submission.

**Disclaimer:** The views expressed herein are those of the authors.

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