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Recommended Citation

Christopher Robertson & Aaron S. Kesselheim, *Regulating Off-Label Promotion — A Critical Test*, 375 The New England Journal of Medicine 2313 (2016).
Available at: https://scholarship.law.bu.edu/faculty_scholarship/965

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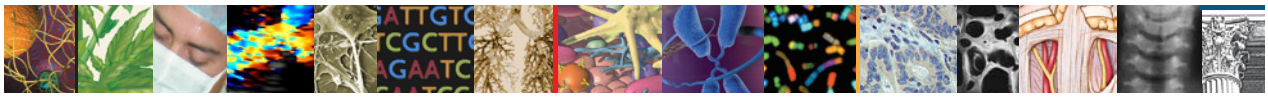

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

DECEMBER 15, 2016

Regulating Off-Label Promotion — A Critical Test

Christopher Robertson, J.D., Ph.D., and Aaron S. Kesselheim, M.D., J.D., M.P.H.

In 2012, the U.S. Court of Appeals for the Second Circuit handed down a landmark decision in the case of pharmaceutical sales representative Alfred Caronia. The Food and Drug Administration (FDA) had approved sodium oxybate (Xyrem) for treating narcolepsy, but Caronia promoted it for a wide range of nonapproved (off-label) indications, including insomnia, Parkinson's disease, and fibromyalgia. Off-label use is common, especially in specialties such as oncology, in which it may even be considered the standard of care. However, surveys have revealed that supporting evidence is lacking for a majority of off-label uses of medical products.[1] The uses Caronia proposed were not based on high-quality data and were likely to cause patients substantial harm (sodium oxybate, or gamma-hydroxybutyrate, is also known as the "date-rape drug" in nonclinical use).

Nonetheless, because prosecutors relied on Caronia's own words to show that he intended the drug to be used for nonapproved purposes, in violation of the Food, Drug, and Cosmetic Act (FDCA), the appeals court reversed the conviction, holding that Caronia's sales pitches were protected commercial speech under the First Amendment.

In recent years, the U.S. Supreme Court has expanded the conception of what counts as "speech" in the eyes of the law and has generally increased its legal protections. For example, in a 2011 case, the Court held that protected speech included sales data used by pharmaceutical manufacturers to more efficiently target marketing to physicians.

Still, the *Caronia* decision subverted decades of presumptions about how the government could oversee the behavior of the pharmaceutical and medical device industries. For over 50 years, the FDCA has required that drugs (and later, high-risk devices) be labeled for all uses intended by their manufacturers and that their safety and efficacy for those uses be first demonstrated in clinical trials. The FDA created "safe harbors" allowing companies to distribute peer-reviewed literature or answer physician questions. However, until the Second Circuit's *Caronia* decision, if a company promoted intended uses that had not been FDA-approved, that promotion would be clear evidence that the product was misbranded and that its sale for those uses was illegal. The fact that the work of pharmaceutical sales representatives involved speech did not matter before *Caronia*.

Many observers worried that if other federal courts, or even the Supreme Court, adopted *Caronia*'s holding, it could adversely affect the U.S. health care system, by substituting marketing for science.

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Manufacturers could secure FDA approval of products for very narrow indications on the basis of highly limited data and then widely promote case series, poorly designed trials, and inadequately controlled observational "real-world" evidence to support additional uses, to the potential detriment of patients and payers.

Since that decision, the government has continued to obtain large settlements in investigations of off-label promotion, which suggests that the pre-*Caronia* approach still carries some weight. Yet two subsequent Second Circuit cases have followed *Caronia*'s precedent. In a 2015 case involving a prescription fish oil approved for treating patients with very high triglyceride levels, Amarin Pharmaceuticals sought to promote the product for patients with moderately high levels, an indication that the FDA did not consider scientifically valid absent additional supporting data.[2] Instead of developing and providing those data, Amarin went to court. After the FDA received an unfavorable preliminary decision, it settled the case, letting the manufacturer make its contested claims and even providing a special preclearance pathway for future claims Amarin might want to make. In another 2015 case involving the off-label use of a postsurgical pain-relief drug, the FDA hastily approved the broader contested indication, averting any court decision that would add further weight to *Caronia* and *Amarin*.

Legal battles have also erupted in at least two other federal circuits. These cases involve whistleblowers who reported off-label marketing by manufacturers of high-risk medical devices. A Texas jury found executives not guilty, but a Massachusetts jury convicted two executives. In the latter case (*Facteau*), the prosecutors alleged that although the company sought FDA approval for a narrow use of its device for opening up sinuses, it had always intended to market it for broader uses for delivering drugs. The jury convicted the two executives of 10 misdemeanor counts.

When the *Facteau* case is ultimately reviewed by the First Circuit, it will be the first real test of *Caronia*'s reasoning outside the Second Circuit. The prosecutor's strategy has been to emphasize that the *Facteau* jury, unlike the *Caronia* jury, was instructed to rely not merely on speech in determining whether the product was misbranded, but on actions as well. We do not see how that point helps, since the prosecution still relied on the defendants' speech — including e-mail messages, phone calls, training videos, and marketing brochures — as evidence of their illegal intent to sell a misbranded product. If the Constitution forbids doing A — as *Caronia* held — it would also forbid doing A+B.

Instead, we believe that the First Circuit and other courts need to reject *Caronia* on its merits. The FDCA's intent requirement is like innumerable other laws that require juries to determine whether a party had a certain intent when undertaking certain acts. It may be perfectly legal to buy a gun or drive across state lines, but if a defendant's own speech reveals he or she did so as part of a conspiracy to sell cocaine or a murder-for-hire plot, that speech is routinely used to prove the illegal intent. Before *Caronia*, such uses of speech as evidence were not considered violations of the First Amendment.

Defendants in these cases are also trying to lure the courts into evaluating whether their off-label promotional claims are true or false. Though the First Amendment does not protect false and fraudulent speech, the principle is irrelevant to a misbranding case.[3] (Similarly, in a cocaine case, the defendant's speech may be used as evidence of an illegal intent, regardless of whether it is true.)

The more important question is: Should the FDA or the courts evaluate product claims? Congress established the FDA's premarketing approval process to channel claims about safety and efficacy into an expert agency, where the claims can be evaluated rigorously and independently on the basis of submitted evidence. The process thus creates an incentive for companies to undertake the scientific research that is required for FDA approval, an incentive that applies to both original intended uses and new uses. In fact, about half of the FDA's approvals

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each year are for new uses of previously approved drugs, which turn off-label uses into on-label ones.[4] This gateway function remains a key way of ensuring that health care is based on robust science, so that patients are protected and wasteful spending is minimized.

Still, sensing that the time may be ripe for a major policy shift, the drug and biologics industry recently released proposed guidelines for a new approach to off-label promotion.[5] They seek a rollback of FDA regulation, so that they can instead "responsibly" promote new uses to physicians, even beyond the safe harbors the FDA already allows. The FDA, for its part, is undertaking a comprehensive review of its rules about off-label promotion.

An audio interview with Dr. Robertson is available at NEJM.org

We fear that these developments could be the beginning of an FDA retreat from the FDCA's fundamental precepts, which require that basic standards for proof of safety and efficacy be met for every intended use of a drug or high-risk medical device. Rather than acceding to the views of two judges in one federal circuit, we hope that the FDA continues to stand on principle. The U.S. Constitution should not be misconstrued in such a way as to undermine the primary functions of federal regulation in this area: to protect patients and to create a high-quality market for drugs and devices that is driven by science rather than hype.

Disclosure forms provided by the authors are available at NEJM.org.

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This article was published on November 2, 2016, at NEJM.org.

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DOI: 10.1056/NEJMp1611755
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NIH Policy on Single-IRB Review — A New Era in Multicenter Studies

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Review of the ethics of multicenter clinical studies is typically conducted by the institutional review board (IRB) of each participating center. Extensive evidence suggests that the current practice is costly, is unnecessarily duplicative, and delays commencement of research.[1] The U.S. government has permitted single-IRB review and other streamlined review models since 1991, but few investigators have taken advantage of those options.[2]

In June 2016, the National Institutes of Health (NIH) issued new guidance on single-IRB review of multicenter studies.[3] The policy was introduced as a means to increase the efficiency of multicenter studies, reduce the time to study initiation, promote consistency of ethics review, alleviate the burden on investigators and administrators, and eventually reduce research costs. Under the new policy, U.S. centers participating in NIH-funded multicenter studies must use a single IRB for initial and ongoing ethics review. As of May 25, 2017, this policy will apply to investigators submitting applications for nonexempt multicenter studies involving human participants and using a common study protocol. The policy does not apply if it is prohibited by "federal, tribal, or state law, regulation or policy."[3] The NIH will consider other exceptions with appropriate justification.

The single-IRB policy ushers in new and important responsibilities for investigators. A proposal for use of a single IRB must be included with the initial application, and at that time all involved U.S. institutions must agree to use the selected IRB. If funding is awarded, federal guidance requires a signed IRB-authorization agree-

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