The Promotion of Medical Products in the 21st Century
Off-label Marketing and First Amendment Concerns

On August 7, 2015, Federal District Court Judge Paul Engelmayer blocked the US Food and Drug Administration (FDA) from enforcing restrictions on the marketing and promotion of off-label use of the drug icosapent ethyl (Vascepa), manufactured by Amarin Pharma Inc.1 If the case heralds the future of jurisprudence, responsibility for the oversight of the truthfulness of pharmaceutical promotions may shift from the nation’s leading science-based regulatory agency, the FDA, to the courts. If it does, the market for medications in the 21st century may revert to a time of more claims and less evidence to guide clinical care.

The case centers on Amarin’s request to promote its drug, an FDA-approved icosapentacenoic acid type of omega-3 fatty acid made from fish oil, for reducing triglyceride levels. After consulting with its advisory committee, the FDA rejected this request on the grounds that there is insufficient evidence that triglyceride reduction prevents cardiovascular disease.2 Without a “clinical rationale” for the claim, the FDA determined its use would be misleading. Amarin objected and sued on the basis that its representatives have a constitutional right under the First Amendment to promote the reduction in triglycerides, even without compelling evidence of clinical value.

In doing so, Amarin challenged the US approach to drug regulation that has been in place for more than 50 years. Beginning with the Pure Food and Drugs Act of 1906, federal agencies have been protecting the public from adulterated and misbranded drugs. After use of an untested formulation of an antimicrobial drug called sulfaflanilimide resulted in the deaths of more than a hundred children and adults in the 1930s, Congress required manufacturers to prove their drugs were safe before marketing. Then in 1962, when broad marketing for secondary uses of thalidomide caused thousands of severe birth defects worldwide, Congress required the FDA to find that drugs worked for specific indications and that their risks were reasonable in light of their probable benefits, before approving them for use.

The 1962 law established that safety and effectiveness are inextricably linked concepts and that claims of effectiveness must be supported by data from “adequate and well-controlled” clinical trials. A product can be “safe and effective” for one intended use, for which the benefits are demonstrated to exceed the risks, but not “safe and effective” for another. Panels of experts subsequently concluded that thousands of marketed drug uses were unsupported by evidence, and many unproven drugs were removed from the market.3

Requiring companies to demonstrate to the FDA that specific uses of drugs are safe and effective before promoting them has led to the development of many breakthrough medical products. Companies invest in the necessary research and then earn substantial profits through subsequent sales. Food and Drug Administration approval allows companies to market broadly, delays the approval of generic versions, and keeps poorly supported claims for ineffective medications from confusing physicians and patients. That the FDA’s adoption of a stringent regulatory review occurred at the dawn of the golden age of the pharmaceutical industry is no coincidence.

Yet despite this history, recently courts have undermined the FDA’s authority to require that a drug demonstrate safety and efficacy for each use in advance of marketing.

Yet despite this history, recently courts have undermined the FDA’s authority to require that a drug demonstrate safety and efficacy for each use in advance of marketing.4 Yet despite this history, recently courts have undermined the FDA’s authority to require that a drug demonstrate safety and efficacy for each use in advance of marketing.5

If the case heralds the future of jurisprudence, responsibility for the oversight of the truthfulness of pharmaceutical promotions may shift from the nation’s leading science-based regulatory agency, the FDA, to the courts. The courts suggested that less speech-restrictive options are available, such as educating physicians to distinguish between misleading statements and those backed by evidence. As a matter of legal precedent, these 2 decisions were narrower than might appear, but they left ample room for expansion as well.

Indeed, the Amarin decision continues this trend. The FDA told the court that a ruling in favor of the company “would reflect a frontal assault...on the framework for new drug approval that Congress created in 1962.” Judge Engelmayer responded by writing “the short answer is that the...drug-approval framework precludes modern First Amendment law respecting commercial speech.”

Copyright 2015 American Medical Association. All rights reserved.
Unwittingly, the Amarin decision shows what a less regulated system might look like. Judge Engelmayer devoted the last section of the decision to his own close editing of statements to accompany communications to physicians. For example, he rejected the FDA’s language: “The available evidence does not establish that reducing triglycerides with a drug reduces the risk of cardiovascular events among patients already treated with statins,” because—in the court’s view—it erroneously implies that “triglyceride level reductions...have been affirmatively shown not to reduce the risk of cardiovascular events.” Of course, the FDA’s language implies no such thing. Indeed, it is allowing Amarin to market its drug for triglyceride reduction that most certainly implies that there is some benefit, which is precisely what FDA found misleading.

The Amarin case and related court decisions fail to respect the FDA’s evolving approach to First Amendment concerns. Physicians are generally free to prescribe medications as they judge best, and payers make their own evidence-based judgments about reimbursement. The FDA’s rules already permit scientific journals and conferences to present information about off-label uses for drugs. Sponsors can respond to questions from physicians, even if related to off-label uses, and provide reprints of peer-reviewed journal articles. The agency’s goal is not to restrict speech or to keep patients and physicians uninformed. It is to facilitate physician decision making by supporting independently verified information, rather than information of unknown quality from a self-interested source. Contrary to the assertion in the court decisions, the marketplace of ideas and physician discretion does not work well without accurate information from well-designed studies.

If the Amarin case represents the direction of jurisprudence on commercial speech, the FDA will face a daunting legal burden before taking regulatory action to protect the public. For example, if the data on a particular scientific question are mixed, companies can market the off-label use of the drug, leaving the FDA with the time-consuming burden of proving to a court that the company’s statements were false or misleading. Given the known harm of broad off-label promotion of such medications as antipsychotic drugs, the public health consequences of opening the doors to such marketing may be substantial.

Over time, liberalizing off-label marketing may well lead companies to increasingly forgo key research that truly establishes the safety and efficacy of their products. Courts would then be drawn further into negotiating promotional language. The FDA’s review of safety and effectiveness data is without peer in the world; sidelining the agency will undermine clinical care and scientific progress.

If these court decisions are not reversed, the FDA will have to choose among unattractive alternative approaches. The agency might focus its energy on identifying off-label statements that are demonstrably false and the cause of significant public health harm. Alternatively, the FDA might offer pathways for off-label marketing to companies based on clinical experience and other evidence that are far short of usual standards. Even if successful, these approaches still leave an enormous gray zone of equivocal evidence that could be used in marketing, to the detriment of physician decision making and patient therapy.

Judges should refrain, unburden core regulatory functions. History amply demonstrates that there is compelling public interest in unbiased evaluation of evidence; in clear, accurate communication; and in maintaining incentives for research. It should not be necessary to wait for another tragedy before the FDA can once again do its job to protect the public.

ARTICLE INFORMATION
Published Online: September 14, 2015. doi:10.1001/jama.2015.12045.

Conflict of Interest Disclosures. All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Sharfstein reported that he served as the principal deputy commissioner of the FDA from 2009-2011. No other conflicts were disclosed.

Correction: This was corrected September 17, 2015, to change the year of federal court decision.

REFERENCES