FDA capitulates to pharmaceutical company on drug claims

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Last week the US Food and Drug Administration (FDA) agreed to drop restrictions it had imposed on Pacira Pharmaceuticals' marketing of its pain drug Exparel in order to settle a lawsuit filed by the drug maker in September. It marks the latest episode of the drug industry's attempts to roll-back restrictions on "off-label" marketing practices based on "free speech" claims.

The FDA approved Exparel to relieve post-surgery pain in 2011 based on clinical trials that administered the drug to the site of surgery for bunion and hemorrhoid removal. After launching the drug in 2012, Pacira promoted Exparel to treat pain for a wide variety of surgeries.

In September, the FDA issued the Parsippany, New Jersey-based company a Warning Letter stating that the firm could only promote it for treatments tested in the clinical trials. Pacira sued the FDA, arguing that it had a First Amendment right to promote the drug for unapproved, or "off-label," uses as long as the information was truthful. Rather than pursuing the case the court, the FDA rescinded the Warning Letter—a move rarely made by the FDA.

The drug is central to Pacira's business strategy as its sales represented 95 percent of its $197.6 million in revenues in 2014. Shares in the company surged 15 percent on news of the settlement.

The drug industry as a whole closely followed the Pacira proceedings, with eleven drug companies—including Johnson & Johnson, Pfizer, GlaxoSmithKline, Novartis, and Sanofi—writing *amicus curiae* briefs for the case.

"The support by a consortium of major drug companies shows they're clearly interested in obtaining the ability to do off-label marketing themselves, even if they haven't been front and center of the fight," James Beck, an attorney at Reed Smith, told the *Financial Times.*

Although the FDA emphasized that "this resolution is specific to the parties involved in this matter," Pacira's lawsuit constitutes the latest effort by the drug industry to chip away at restrictions on the off-label marketing of drugs.

The 1938 federal Food, Drug and Cosmetics Act (FDCA) gave the FDA the authority to regulate drug advertising, which is now overseen by the agency's Office of Prescription Drug Promotion (OPDP), and, to a certain extent, the Federal Trade Commission.

Drugs approved by the FDA can be prescribed by doctors as they see fit, including for "off-label" uses. However, pharmaceutical companies are prohibited from promoting the drug for uses, or information about its safety and efficacy, not indicated by the FDA approved "label" for the drug. (This prohibition is accomplished indirectly through laws barring the interstate commerce of drugs without an FDA-approved label or misbranded drugs).

The drug industry has received substantial fines in recent years for illegally promoting medications for off-label uses, including the $3 billion paid by GlaxoSmithKline in 2012 for, among other things, the off-label promotion of its anti-depressant drugs Paxil and Wellbutrin.

The pharmaceutical industry, unsurprisingly, has sought to weaken these off-label restrictions. Not only would this allow drug companies to avoid costly fines, it would also preclude the need to conduct costly clinical trials proving the drug's safety and efficacy for different conditions. Instead, they could rely on the looser standards of anecdotal evidence from patients and doctors.

Moreover, since the United States is the only country in the world other than New Zealand to allow direct-to-consumer advertising of pharmaceuticals, the slackening of off-label restrictions could prove to be a marketing boon for drug companies.

To this end, the drug industry has been assisted by recent federal legislation, the loosening of regulatory agency standards, and friendly court decisions.

For example, the FDA Modernization Act of 1997 (FDAMA) included a provision (Section 401) that allowed drug and device manufacturers, in certain instances, to distribute scientific and medical journal articles on off-label uses.

The criteria for First Amendment challenges to government restrictions was established by the 1980 Supreme Court decision *Central Hudson Gas & Electric Corp. v. Public Service Commission of New York.* This test was applied by the Supreme Court in the 2002 case *Thompson v. Western States Medical Center*, which invalidated FDA prohibitions on advertising pharmacy compounding services.

Further precedents for off-label promotions were established by lawsuits initiated by the Washington Legal Foundation, a non-profit legal organization established in 1977 to promote pro-business and free-market positions, which regularly partners with right-wing think tanks such as the American Enterprise Institute, the Cato Institute and the Heritage Foundation.

The US District Court for the District of Columbia ruled in 1998 (*Washington Legal Foundation v. Friedman*) that FDA restrictions on the distribution of certain types of off-label information by pharmaceutical companies to healthcare professionals were unconstitutional violations of free speech. A year later, the same court ruled (*Washington Legal Foundation v. Henney*) that its previous decision also applied to Section 401 of the FDAMA.

These two cases, concludes a 2000 article in the *Indiana Law Review*, "have increased the ability of pharmaceutical manufacturers to disseminate off-label information about their products."

"To some," the article continues, "this means that healthcare professionals will receive the latest, most innovative information available about the products they prescribe and be better equipped to treat suffering patients. To others this spells disaster and puts patients and the companies themselves at risk."

The FDAMA expired in 2006 and in 2009 the FDA issued new guidance rules. Although the "safe harbor" provision of the FDAMA was not included, the new guidelines were "more permissive than the FDAMA, because companies are no longer required to submit advanced copies to the FDA and are not restricted to the dissemination of journal articles on

off-label uses for which they have filed or will file an sNDA [supplemental New Drug Application]," according to a 2009 article reviewing the topic in the journal *Pharmacy and Therapeutics.*

Seeing an opening for off-label marketing, the pharmaceutical industry has in recent years initiated a number of lawsuits challenging FDA restrictions on First Amendment grounds.

In 2009, US drug maker Allergan unsuccessfully sought to market Botox for off-label uses on the basis of free speech claims. A year later, however, the company resolved these allegations with the Justice Department by pleading guilty to a criminal misdemeanor for misbranding the drug and agreeing to pay $600 million in fines.

A significant milestone came with the Supreme Court's 2011 decision, *Sorrell v. IMS Health Inc.*, which struck down a 2007 Vermont law that restricted the sale of records of doctor's prescribing practices for use in marketing without the consent of doctors. The Court—led by the right wing, Anthony Kennedy, John Roberts, Antonin Scalia, Clarence Thomas, and Samuel Alito, but joined by Justice Sonia Sotomayor—ruled that the law violated the First Amendment rights of pharmaceutical manufacturers and data mining companies.

Citing the *Sorrell* ruling, Allergan once again attempted to justify off-label promotions using free speech arguments in response to a 2010 whistleblower lawsuit initiated by ophthalmologists who claimed the company attempted to induce physicians to prescribe Allergan's eye treatment, Restasis, by offering doctors business advisory services to improve their practices. However, the Department of Justice, in a 2014 filing on the case, disagreed with Allergan's argument that the federal Anti-Kickback Statutes excluded regulating speech.

In 2012, the US Second Circuit Court (New York) ruled in *U.S. v. Caronia* that a sales representative for Orphan Medical, Alfred Caronia, could not be prosecuted for promoting off-label uses of the company's drug, Xyrem, as long as the information he provided was truthful.

Citing the *Central Hudson*, *Thompson*, and *Sorrell* cases, US Circuit Judge Denny Chin wrote in the 2-1 decision that "the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug."

In her lone 30-page dissent, US Circuit Judge Debra Ann Livingston observed: "If drug manufacturers were allowed to promote FDA-approved drugs for non-approved uses, they would have little incentive to seek FDA approval for those uses."

"Our system of drug regulation developed to protect consumers from misleading and unsubstantiated claims about drugs' safety and efficacy, and the prohibition on off-label promotion by drug manufacturers is essential to maintaining the effectiveness of that system." Thus, she concludes that the decision "calls into question a fundamental regime of federal regulation that has existed for more than a century."

In August of 2014, the drug industry's trade organization, the Pharmaceutical Research & Manufacturers of America (PhRMA), submitted an *amicus curiae* brief to the lawsuit over the off-label marketing of the blood-clot fighting drug Integrilin by the drug's manufacturer Millennium Pharmaceuticals, its partner Schering-Plough, and Merck, which acquired Schering-Plough in 2009. PhRMA argued that the court should throw out the case because the off-label information was truthful.

The PhRMA brief was filed just as the FDA was winding down its public comment period on its draft guidance for the pharmaceutical industry to distribute scientific medical publications about the risks of approved medications.

Since the FDA had only posted one comment to its web site, the watchdog group Public Citizen filed a Freedom of Information (FOIA) request in October for the full text of the comments. The organization discovered that 99 percent of the 1,782 comments received by the agency were negative—the only positive ones came from the pharmaceutical industry and a single academic.

Sidney M. Wolfe, M.D., the senior advisor for Public Citizen's Health Research Group, argued in the *Journal of the American Medical Association* that the FDA's proposed actions "would allow pharmaceutical companies who believe that the FDA-approved drug-labeling information overstates the risks of their drugs to tell physicians that the risks are, in fact, lower."

"Laws and regulations requiring FDA approval of the drug label would have little meaning if a company, without the agency either reviewing the data or approving it, can disseminate this information in this manner (i.e., through "detailing")," Wolfe wrote.

In August of 2015, the Second Circuit Court issued the drug industry another favorable ruling. US District Judge Paul Engelmayer ruled in favor of the Irish drug company Amarin, which argued that it should be allowed to promote off-label claims for its cardiovascular drug Vascepa on the basis of the company's right to free speech.

The fish oil-derived drug lowers high triglyceride levels, which have been linked to heart disease. The FDA, however, did not allow the company to claim that the drug reduced the risk of heart disease when taken in conjunction with statins without conducting a larger heart safety study.

Amarin sued the regulatory agency this past May to allow the company to tell doctors that it lowered blood lipids, which could be good for patients with heart disease. The broader label would help it compete with GlaxoSMithKline's generic Lovaza.

Amarin, whose US operations are centered in New Jersey, filed the lawsuit in New York because of the previously friendly rulings by the Second Circuit.

"This is the first decision, I think, that clearly and unequivocally rebuffs the government's view that off-label promotion can be prosecuted, even if truthful and nonmisleading," Joel Kutzberg, a lawyer with Cahill Gordon & Reindel, the firm that represented the Amarin in the case, told *The New York Times.*

The favorable ruling gave Pacira the confidence to sue the FDA the following month, citing the Amarin ruling.

By settling the Pacira case, the FDA precluded a Supreme Court ruling on the matter—a ruling that, if past cases are any indication, would be favorable to the drug industry.

The FDA is currently developing its own guidelines for off-label marketing, while the FDA's approval process itself will be given a general overhaul under the 21st Century Cures Act. The recent nomination by President Barack Obama of Robert Califf, who has close ties to the drug industry, as the next FDA commissioner, suggests that any changes at the FDA will promote the interests of the pharmaceutical industry.