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CLIENT ALERT

FDA Loses Battle to Limit Truthful, Non-Misleading Off-Label Promotion of Approved Drugs

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Pharmaceutical manufacturer Amarin Pharma Inc.'s momentous win in New York federal court affirms a drug manufacturer's First Amendment right to truthfully promote non-FDA—approved uses of its product. On August 7, 2015, Judge Paul Engelmayer of the Southern District of New York issued the first known affirmative protection of off-label promotion of a specific prescription drug. *Amarin Pharma, Inc. et al. v. U.S. Food & Drug Admin., et al.*, Opinion & Order, No. 1:15-cv-03588 (S.D.N.Y.). The court granted preliminary relief that permits Amarin to engage in truthful and non-misleading speech promoting the off-label use of its triglyceride-lowering drug Vascepa to treat patients who have lower levels of triglycerides than the patients for whom the FDA approved its use. Critically, the court went even further and held that truthful and non-misleading speech may not form the basis of a prosecution by the Food and Drug Administration (FDA) for misbranding. The court's decision rested heavily on the Second Circuit's 2012 decision in *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012), and indicated for the first time how district courts might entertain offensive uses of *Caronia* by drug manufacturers.

Statutory and Legal Landscape

In recent years, the FDA has actively pursued criminal misbranding charges against pharmaceutical companies for marketing and promoting non-FDA—approved (off-label) uses of their drugs. FDA's stated goals are to encourage use of its drug review and approval process, and to deter manufacturers from evading the FDA's review process for other uses of approved drugs.

The 1962 Drug Amendments revised the Food, Drug and Cosmetic Act (FDCA) to require manufacturers to show that their drugs are safe and effective for their intended uses before their drugs are approved for distribution. Notably, the FDCA does not expressly prohibit the promotion or marketing of drugs for off-label use, and the FDA does not prohibit doctors from lawfully prescribing FDA-approved drugs for off-label uses.

Nonetheless, the FDA has taken the position that manufacturers who market or promote an approved drug for an unapproved or off-label use may be held criminally liable for "misbranding" under 21 U.S.C. § 331(a). Section 331(a) prohibits "[t]he introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded." A drug is considered "misbranded" if its labeling does not include "adequate directions for use." 21 U.S.C. § 352(f). The FDA has defined "adequate directions for use" to mean "directions under which the lay[person] can use a drug safely and for the purposes for which it is intended." 21 C.F.R. § 201.5. In turn, "intended use" is "the objective intent of the persons legally responsible for the labeling of drugs." 21 C.F.R. § 201.128. Under the FDA's regulations, promotional statements by a manufacturer or its representatives may serve, and have been used, as proof of a manufacturer's intended use. 21 C.F.R. § 201.5.

In 2012 in *Caronia*, the Court of Appeals for the Second Circuit vacated the conviction of a pharmaceutical sales representative for conspiring to introduce a misbranded drug into interstate commerce in violation of 21 U.S.C. §§ 331(a) and 333(a)(1). The drug manufacturer's sales representative had been caught on tape promoting the drug Xyrem to doctors for unapproved uses.

The Second Circuit recognized that the representative's conduct to promote the off-label use had consisted of only truthful and non-misleading speech. It also held that a manufacturer's speech promoting off-label use is constitutionally protected commercial speech. In order to avoid infringing the First Amendment, the Court held, the misbranding provisions of the FDCA must be construed as not prohibiting or criminalizing the truthful off-label promotion of FDA approved prescription drugs.

Amarin's Lawsuit

On July 26, 2012, the FDA approved Amarin's drug Vascepa, an ethyl ester of an omega-3 fatty acid obtained from fish oil, for treating adult patients with triglyceride levels above 500 mg/dL of blood ("severe hypertriglyceridemia" or "very high triglycerides"). Amarin later sought approval to market Vascepa for patients with triglyceride levels between 200 and 499 mg/dL of blood and who are already on statin therapy (persistently high triglycerides). According to the court, it is undisputed that Vascepa is effective at reducing such triglyceride levels, that Vascepa is safe, and that the FDA has allowed a chemically similar dietary supplement to be sold to the public with claims that omega-3 fatty acids may reduce the risk of coronary heart disease. But recent scientific studies have left unclear whether reducing the triglyceride levels of persons with persistently high triglycerides reduces cardiovascular risk.

In light of this uncertainty, on April 27, 2015, the FDA issued Amarin a Complete Response Letter (CRL). The CRL denied Amarin approval to market Vascepa for treating adults with persistently high triglycerides. The CRL also warned that FDA may consider Vascepa to be misbranded under the FDCA if it is marketed for patients with persistently high triglycerides before FDA approval.

On May 7, 2015, shortly after receiving the CRL, Amarin filed a complaint alleging that it wishes to make truthful statements to health care professionals regarding Vascepa, including that a study it completed demonstrates that Vascepa significantly reduces triglyceride levels in patients with persistently high triglyceride levels. Amarin complained that this constitutionally protected speech is chilled by the FDA's threat in the CRL to bring a misbranding action based on off-label promotion. Pointing to *Caronia*, the company urged the court to recognize that FDA's prohibitions on off-label promotion, as applied to truthful and non-misleading speech, are unconstitutional under the First Amendment, and that Amarin may engage in this speech free from the risk of criminal prosecution.

The court agreed, granting Amarin the preliminary relief sought. The court discounted the FDA's argument that *Caronia* was a fact-bound decision. It held that "under *Caronia*, the FDA may *not* bring [a misbranding action] based on truthful promotional speech alone, consistent with the First Amendment." Holding that truthful and non-misleading speech cannot be the act upon which an action for misbranding is based, the court acknowledged that *Caronia* does not limit the FDA's ability to use promotional speech to establish intent in a misbranding action with a proper *actus reus*. While the court protected truthful and non-misleading speech, it recognized that manufacturers must be cognizant that unscripted, unapproved off-label promotion could prove risky. The court observed that consultation with the FDA before promoting off-label use "may prove a helpful prophylactic."

Impact of Amarin

Amarin marks the first affirmative and court-sanctioned use of *Caronia* to shield a drug manufacturer's truthful promotional activities from FDA's criminal prosecution. It remains to be seen, however, whether FDA will seek review of the decision,

whether other courts will permit similar offensive use of *Caronia*, and whether other circuits will adopt the same reasoning as *Caronia*. While these issues play out, it is also worth watching the potential impact of *Amarin* on the preemption doctrine.

Amarin also lends support to the growing body of cases shielding manufacturers from civil liability for their truthful off-label promotion of medical devices. District courts have relied on *Caronia* to hold that federal law preempts civil claims by consumers based on off-label promotion of medical devices because federal law does not bar off-label promotion. *See, e.g.*, *Schuler v. Medtronic, Inc.*, No. CV 14-00241-R, 2014 WL 988516, at *1 (C.D. Cal. Mar. 12, 2014) (defendant's alleged off-label promotion could not evade preemption because federal law does not bar off-label promotion); *accord Otis-Wisher v. Medtronic, Inc.*, No. 14-3491, 2015 WL 3557011, at *2 (2d Cir. June 9, 2015) (affirming dismissal of plaintiff's fraud claims premised on allegedly misleading off-label promotion for failure to plead with the particularity required under Federal Rule of Civil Procedure 9(b) but noting that "[t]he weight of authority both in this Circuit and elsewhere casts doubts on the viability of such claims" because the FDCA does not prohibit off-label promotion).

In contrast, in the context of generic drugs, *Amarin* might provide plaintiffs with additional arguments against preemption of failure to warn claims. Courts often dismiss failure to warn claims against generic drug manufacturers as preempted by the Hatch-Waxman Amendments, which require the composition and labeling of generic drugs to match what is approved by the FDA in connection with the branded version of the drug. But if drug companies have the First Amendment right to speak in a truthful and non-misleading manner about off-label use of a drug, plaintiffs may argue that generic drug manufacturers also have the First Amendment right to speak truthfully about the product risks, even if the labeling for the branded version does not contain the same warnings.

Other Articles in This Month's Edition:

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