

Client Alert

FDA & Life Sciences Practice Group

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Amarin and FDA Reach Settlement Agreement in Off-Label Speech/First Amendment Case

On March 8, 2016, Amarin Pharmaceuticals, Inc. (“Amarin”) and the Food and Drug Administration (“FDA” or the “Agency”) reached a settlement agreement in a closely followed case involving Amarin’s First Amendment rights to engage in truthful and non-misleading speech promoting an off-label use of Vascepa®. Amarin and FDA had been engaged in settlement talks since last August, when Judge Engelmayer, in the Southern District of New York, granted a motion for preliminary injunction (PI) in favor of Amarin.

In the August decision, Judge Engelmayer held that FDA may not bring a misbranding action under the Food, Drug & Cosmetic Act (FD&C Act) “based on truthful promotional speech alone, consistent with the First Amendment.” *Amarin Pharma, Inc. v. United States Food and Drug Administration*, 119 F. Supp. 3d 196, 224 (S.D.N.Y. 2015).

This decision was in accord with the precedent set by the Second Circuit’s 2012 decision in a criminal misbranding case, *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012). Judge Engelmayer preliminarily enjoined FDA from taking action against Amarin for making certain truthful and non-misleading statements to health care professionals to promote Vascepa® for the off-label use of treating patients with persistently high triglycerides.

The settlement agreement resolves all causes of action raised by Amarin in its complaint, which sought a declaratory judgment and injunctive relief. Not surprisingly, given Amarin’s preliminary injunction win, the agreement provides a number of benefits for Amarin. As described in more detail in Section II below, the agreement binds FDA to certain conclusions in Judge Engelmayer’s August 2015 decision. The agreement also provides for specific procedures whereby Amarin has the option to submit to FDA up to two proposed off-label communications per year about Vascepa® to determine whether FDA has concerns with the proposed

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communications. The procedures set forth in the agreement require FDA to respond with any concerns within 60 days.

This client alert summarizes Judge Engelmayer's decision on the Amarin PI motion and analyzes the settlement agreement and its implications. The alert also discusses the implications of the resolution of this case, on top of other recent industry victories in off-label cases.

I. *Amarin v. FDA* – The August 2015 Decision

Vascepa® consists of pure eicosapentaenoic acid (“EPA”), which is an omega-3 fatty acid, and it is FDA-approved as an adjunct to diet to reduce triglyceride levels in adults with severe (≥ 500 mg/dL) hypertriglyceridemia. In pursuit of an additional indication, Amarin also conducted a clinical trial, known as the ANCHOR trial, to evaluate the drug in statin-treated patients with “persistently high” triglyceride levels (≥ 200 and ≤ 500 mg/DL), pursuant to a Special Protocol Agreement (SPA) with FDA. Generally, the successful completion of a study conducted under a SPA will lead to FDA approval of drug or a supplemental indication for a drug, so long as the SPA protocol is followed and the objectives of the study are met. At the conclusion of the ANCHOR trial, Amarin believed that it had achieved the objectives outlined in the SPA, and it submitted a supplemental new drug application (sNDA) to FDA to market Vascepa for the reduction of triglyceride levels in patients with persistently high triglyceride levels.

In spite of the apparent success under the SPA, during FDA's review of the sNDA, concerns were raised about the clinical validity of the triglyceride lowering endpoint in the ANCHOR study, even though FDA had agreed to that study endpoint in the SPA. These concerns were based on data from other studies that called into question whether the reduction of triglyceride levels would lead to a reduction in cardiovascular events more generally. As a result of these concerns, FDA ultimately issued Amarin a complete response letter indicating that the Agency needed additional data showing the correlation between reduced triglycerides and reduced cardiovascular events before it could approve the sNDA. According to the [Amarin complaint](#), the letter concluded with a warning that any effort by Amarin to market Vascepa® for the proposed supplemental use could constitute misbranding under the FD&C Act.

In May 2015, Amarin filed a [declaratory judgment action](#) claiming that FDA's threat of prosecution for marketing Vascepa® had a chilling effect on the company's speech in violation of the First Amendment. Amarin sought declaratory and injunctive relief that would prevent FDA from bringing an enforcement action against the company for disseminating certain information related to the ANCHOR trial results to health care professionals, including specific statements about, and summaries of, the ANCHOR trial, including the effect of Vascepa® on patients with persistently high triglycerides. In its complaint, Amarin proposed making relevant disclosures with these communications to ensure that the communications were not false or misleading.

In response to this complaint, Dr. Janet Woodcock, the Director of FDA's Center for Drug Evaluation and Research, issued a letter (the “[Woodcock Letter](#)”), in June 2015, which narrowed the issues in the case. Dr. Woodcock criticized Amarin for not first asking FDA for permission to make certain statements before suing the Agency, signaling the agency's strong preference for cooperative dialogue rather than legal challenges. Nonetheless, she explicitly sanctioned the dissemination of a specific summary of the ANCHOR trial that

FDA had reviewed, noting that it did not omit material information or otherwise introduce bias by emphasizing or deemphasizing certain information. She also stated that Amarin could disseminate other truthful and non-misleading summaries of the ANCHOR trial, if they do not raise those types of concerns.

The court heard oral argument on Amarin's preliminary injunction motion in July 2015, and in the August ruling, the court found that consistent with the First Amendment, "FDA may not bring [a misbranding action] based on truthful promotional speech alone." *Amarin*, 119 F. Supp. 3d at 224. The court went on to review the statements and accompanying disclosures that Amarin and FDA had agreed upon over the course of the lawsuit, and it found that, "based on current information," the statements were truthful and non-misleading. *Id.* at 231. The court also resolved issues regarding the wording of the contested statements and disclosures. *See id.* at 233-35. In doing so, the Court specifically sanctioned Amarin's dissemination of the following truthful and non-misleading statements to health care professionals:

- Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease. Vascepa should not be taken in place of a healthy diet and lifestyle or statin therapy.
- Vascepa is not FDA-approved for the treatment of statin-treated patients with mixed dyslipidemia and high (≥ 200 mg/dL and < 500 mg/dL) triglyceride levels due to current uncertainty regarding the benefit, if any, of drug-induced changes in lipid/lipoprotein parameters beyond statin-lowered low-density lipoprotein cholesterol on cardiovascular risk among statin-treated patients with residually high triglycerides. No prospective study has been conducted to test and support what, if any, benefit exists.
- Recent cardiovascular outcomes trials (ACCORD-Lipid, AIM-HIGH, and HPS2-THRIVE), while not designed to test the effect of lowering triglyceride levels in patients with high triglyceride levels after statin therapy, each failed to demonstrate incremental cardiovascular benefit of adding a second lipid-altering drug (fenofibrate or formulations of niacin), despite raising high-density lipoprotein cholesterol and reducing triglyceride levels, among statin-treated patients with well-controlled low-density lipoprotein cholesterol.
- The ANCHOR trial demonstrates that Vascepa lowers triglyceride levels in patients with high (≥ 200 mg/dL and < 500 mg/dL) triglyceride levels not controlled by diet and statin therapy.
- In the ANCHOR trial, Vascepa 4g/day significantly reduced TG [triglycerides], non-HDL-C [non-high-density lipoprotein cholesterol or non-"good cholesterol,"] Apo B [Apolipoprotein B], VLDL-C [very-low-density lipoprotein cholesterol], TC [total cholesterol] and HDL-C [high-density lipoprotein cholesterol or "good cholesterol"] levels from baseline relative to placebo in patients with high (≥ 200 mg/dL and < 500 mg/dL) triglyceride levels not controlled by diet and statin therapy. The reduction in TG [triglycerides] observed with Vascepa was not associated with elevations in LDL-C [low-density lipoprotein cholesterol or "bad cholesterol] relative to placebo.

To ensure that these statements are not misleading, the court also sanctioned the following disclosures:

- FDA has not approved Vascepa to reduce the risk of coronary heart disease;
- The effect of Vascepa on the risk of cardiovascular mortality and morbidity has not been determined;
- A cardiovascular outcomes study of Vascepa designed to evaluate the efficacy of Vascepa in reducing cardiovascular mortality and morbidity in a high-risk patient population on statin therapy is currently underway;
- Vascepa may not be eligible for reimbursement under government healthcare programs, such as Medicare or Medicaid, for treatment of statin-treated patients with mixed dyslipidemia and high (≥ 200 mg/dL and < 500 mg/dL) triglyceride levels or to reduce the risk of coronary heart disease. We encourage you to check that for yourself; and
- Any potential financial or affiliation biases between the firm and those who conducted the ANCHOR study.

II. The Amarin/FDA Settlement Agreement and Its Implications

As mentioned, the March 7 settlement agreement resolves all causes of action raised in Amarin's complaint in a manner that is very favorable to Amarin. Not surprisingly, Amarin was successful in getting FDA to agree to be bound by the New York district court's decision on the PI motion regarding Amarin's ability to disseminate the specific promotional statements and disclosures at issue in that decision to health care professionals. *See* [Settlement Agreement](#).

In addition to this successful resolution as to the particular statements at issue in the PI decision, Amarin successfully got FDA to agree to the principle driving the PI decision, not limited to those particular statements, namely, that Amarin may engage in "truthful and non-misleading speech promoting the off-label use of Vascepa®, i.e., to treat patients with persistently high triglycerides, and under *Caronia*, such speech may not form the basis of a prosecution for misbranding." *Id.* Interestingly, this principle is not expressly limited to certain speakers at Amarin (e.g., those serving in scientific roles, as opposed to sales representatives); it is not expressly limited to a certain setting (e.g., a scientific setting as opposed to a promotional setting); and it is not expressly limited by the education or expertise of the recipient (e.g., to physicians and other health care professionals).

The agreement also provides for optional procedures, moving forward, whereby Amarin may submit to FDA up to two proposed communications per calendar year about the off-label use of Vascepa®, prior to disseminating the communications, to determine whether FDA has concerns with the proposed communications. The procedures set forth in the agreement require FDA to respond with any concerns within 60 calendar days. Of course, anyone can ask for this type of advisory opinion under 21 C.F.R. § 202.1(j), but one innovation here is that the agreement imposes a specific time-frame for FDA to respond.

Another innovation, and potential benefit for Amarin, is that if there is a dispute at the conclusion of that informal dispute-resolution procedure, Judge Engelmayer can resolve it. It is quite unusual for the government to agree to this type of ongoing judicial supervision.

Nonetheless, FDA has taken steps to try to limit the impact. First, of course, the settlement applies only to Amarin. In addition, the inclusion of the phrase “under *Caronia*” may signal that the government intends to argue in other courts that *Caronia* was wrongly decided or at least incorrectly interpreted by Judge Engelmayer’s PI decision. For example, the government has sought to interpret *Caronia* as limited to cases where the government is directly prosecuting the off-label promotion itself—and thus as leaving the government free to rely on truthful, non-misleading off-label promotion to prove that the drug or device is misbranded, so long as the government prosecutes the sale of the misbranded product and does not prosecute the off-label promotion itself. The government has not yet found a court willing to draw this very fine distinction, nor is it likely to do so, because using truthful speech about a lawful use of a lawful product to transform the sale of that product into a crime violates the First Amendment just as much as directly prosecuting the truthful speech would.

Finally, the provision does not address whether the government can rely on evidence other than promotional speech to prove an off-label intended use. FDA traditionally has relied on external statements made to the marketplace to determine a product’s intended use. Recently, however, the government has sought to evade the First Amendment bar on bringing a misbranding prosecution based on truthful promotional speech by claiming that it can rely instead on circumstantial evidence (e.g., the design of the product or the types of doctors targeted by sales representatives) or evidence regarding the subjective intent of the manufacturer (e.g., internal company documents) to prove that an off-label use is “intended.”

III. Implications of the Amarin Settlement

The settlement agreement between Amarin and FDA closely follows two other industry victories in off-label promotion cases. On February 29, 2016, King & Spalding secured an acquittal on all charges for Vascular Solutions, Inc. (VSI) in a criminal prosecution based on alleged off-label promotion of a medical device. VSI’s CEO, Howard Root, also won an acquittal on all charges. The case against VSI and Root is the only known off-label promotion case against a publicly traded company to ever go to trial, and the case included the first jury instructions stating that truthful speech is a defense to FD&C Act violations.

In addition, the Amarin and FDA settlement follows another well-publicized settlement agreement between FDA and Pacira Pharmaceuticals, Inc. in December 2015. Pacira also had filed a declaratory judgment action, seeking to be allowed to market its drug product, Exparel, for use as an anesthetic in specific surgeries, such as cholecystectomy and colectomy procedures. FDA had issued a warning letter citing Pacira for making these specific claims, on the rationale that Pacira’s approved indication for use as a local post-surgical anesthetic did not permit Pacira to promote its use in connection with specific types of surgery. However, after Pacira filed its declaratory judgment action, FDA rescinded the warning letter, and pursuant to a settlement agreement, the Agency is now allowing Pacira to make those claims.

The favorable outcomes for Amarin, Pacira, and VSI, as well as Mr. Caronia and Mr. Root, demonstrate that litigation, both offensive and defensive, can be a powerful tool to shape off-label policy and to protect the rights of manufacturers. Such litigation has been particularly effective during a period in which FDA has been seemingly immobilized on the issue. In 2014, in a citizen petition response, FDA promised to issue comprehensive draft guidance on off-label manufacturer communications in that calendar year, but that guidance still has not issued. It is well-known, at this point, that the Agency’s inaction is due to a lack of

consensus among senior leadership at FDA and in the Department of Health and Human Services (HHS). The Amarin settlement, in addition to other industry wins, puts additional pressure on FDA to take action—and highlights the need for Congress to take action if FDA fails to do so.

The success of the Amarin and Pacira declaratory judgment actions has the potential to embolden other manufacturers to file declaratory judgment actions against FDA when they want to make what they believe to be truthful and non-misleading off-label statements in reasonable contexts, when those statements are outside the four corners of FDA's current policy. One advantage of filing a declaratory judgment action is that a company can choose the product, the use, and the promotional statements that are the subject of the action. A company will bring such a lawsuit only when it believes that a court is likely to find the off-label communication at issue to be reasonable, even if that communication falls outside of the narrow exceptions recognized by FDA (let alone DOJ) to the general prohibition against off-label promotion. Even with the recent successes, it is not likely that companies could obtain such favorable results with every type of off-label communication; the cases to date have focused on certain types of communications that were well supported.

Filing a declaratory judgment, however, may not be necessary. The Woodcock Letter in the Amarin litigation reminds us that a company has another choice, namely, it can ask FDA for a formal or informal advisory opinion. Asking FDA for an advisory opinion arguably puts both FDA and the company into a win-win position. It allows FDA to make policy decisions in the off-label space on a one-off basis, such that the Agency can act without needing to resolve larger policy issues that are tying up the Agency in internal disagreement. FDA can single out specific facts that distinguish a particular arrangement to protect a single proposed practice without necessarily setting a broader precedent or changing official FDA policy. For example, although the Woodcock Letter arguably opened the door to disseminating truthful and non-misleading summaries about studies regarding off-label uses, companies that want to disseminate similar summaries may consider seeking FDA advisory opinions to determine whether FDA agrees that the summaries are truthful and non-misleading before they are disseminated. At the same time, an advisory opinion can allow companies to proceed with certain desired communications with impunity and without risk of challenge. This advisory opinion approach may also allow industry to tee up discrete issues, such as whether it is appropriate to disseminate a reprint of a study that is not deemed adequate and well-controlled as would be necessary to rely on it for FDA approval, so long as the study is based on sound science and the limits of the study are adequately disclosed. And of course, if a manufacturer seeks an FDA advisory opinion and FDA does not oblige, the manufacturer can then proceed with filing a declaratory judgment action. That, in fact, is what appears to have happened with Pacira.

To the extent that seeking these types of advisory opinions becomes more common, it may also be difficult for FDA to articulate why other manufacturers should not receive the same prompt responses to which Amarin is entitled under the settlement agreement.

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In addition, our team calls upon the expertise of lawyers in several related areas within the firm, including the civil and criminal litigation group, the appellate group, and the government advocacy and public policy group, which have effectively represented clients who are the targets of government initiated lawsuits and investigations. Please let us know if you have any questions.

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