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Client Alert Commentary

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Amarin Settles Off-Label Promotion Case Against the FDA

The Amarin settlement represents another important development in the FDA's enforcement of off-label promotion.

On March 8, 2016, US District Court Judge Paul A. Engelmayer entered a Stipulation & Order of Settlement in the off-label promotion case, *Amarin Pharma, Inc. v. US Food and Drug Administration*,[1] finalizing the much-anticipated settlement that the parties had proposed to the court earlier that day.[2] The *Amarin* case garnered close attention in the life sciences industry after Judge Engelmayer granted the plaintiffs' motion for preliminary injunction on August 7, 2015, holding that the First Amendment does not permit the US Food and Drug Administration (FDA) to criminalize Amarin Pharma, Inc.'s (Amarin's) truthful and non-misleading speech promoting the off-label use of its FDA-approved drug, Vascepa.[3] This settlement comes on the heels of a string of cases in which the industry has successfully invoked the First Amendment to challenge the FDA's off-label promotion regulatory regime.

Background of the Amarin Case

Amarin manufactures a triglyceride-lowering drug, Vascepa (icosapent ethyl), which is composed of pure eicosapentaenoic acid (EPA), an omega-3 fatty acid found in fish oil. Vascepa was developed to improve cardiovascular health, and the FDA approved the drug in 2012 for the treatment of adult patients with "very high" triglycerides (above 500 mg/dL of blood).

Following its new drug application (NDA) approval, Amarin sought FDA approval to market Vascepa for patients with "persistently high" triglycerides (between 200 and 499 mg/dL of blood) who are already on statin therapy. To support this second indication, Amarin conducted a clinical trial to study the effect of Vascepa on patients with persistently high triglyceride levels (the ANCHOR study). Amarin conducted the ANCHOR study under the FDA's Special Protocol Assessment (SPA), in which the FDA agreed to the study design and objectives. The ANCHOR trial met all of the objectives set out in the SPA, and Amarin submitted a supplemental NDA (sNDA) to the FDA seeking approval for the expanded indication.

Rather than approve Amarin's application, however, the FDA rescinded the SPA and issued a complete response letter for the sNDA, citing new results from clinical trials involving other drugs that were also intended to reduce triglyceride levels. The FDA explained that the ANCHOR study was premised on the clinical rationale that reducing triglyceride levels in patients with persistently high triglycerides would reduce the risk of cardiovascular events; however, data from these related clinical trials called the premise into question. The FDA stated that, given the uncertainty regarding the cardiovascular benefits of lowering triglycerides in this patient population, Amarin would need to provide evidence that Vascepa indeed reduces the risk of major cardiovascular events in order to obtain the expanded indication. The FDA also refused Amarin's request to include the ANCHOR study results in the approved Vascepa

labelling and expressly warned the company that the FDA may consider Vascepa misbranded under the Federal Food, Drug, and Cosmetic Act (FDCA) if Amarin were to market the drug for use in patients with persistently high triglycerides.[4]

In response, on May 5, 2015, Amarin filed suit against the FDA and the United States seeking declaratory and injunctive relief to, among other things, prevent the FDA and the Department of Justice from taking any action under the FDCA or the False Claims Act, respectively, against Amarin for engaging in certain speech about the use of Vascepa to reduce persistently high triglycerides.[5] Amarin asserted that the proposed communications were truthful and non-misleading commercial speech protected by the First Amendment.

On August 7, 2015, Judge Engelmayer granted Amarin's motion for preliminary injunction.[6] Judge Engelmayer held that truthful and non-misleading speech promoting the off-label use of Vascepa may not form the basis of a prosecution for misbranding. He also agreed that the specific speech Amarin cited in the complaint — Amarin's statements, materials and disclosures about the use of Vascepa to treat persons with persistently high triglycerides — was truthful and non-misleading, subject to particular modifications detailed in the opinion.[7]

Judge Engelmayer, however, highlighted the unusually extensive regulatory history in this case and cited that history as the reason behind his decision to make a determination about the truthfulness of Amarin's proposed speech at such an early stage in the case. He noted specifically that the FDA had already reviewed the off-label use at issue, agreed to the endpoints of the ANCHOR study, confirmed in writing that Vascepa was proven effective for lowering triglycerides in the particular patient population and did not contest the safety of Vascepa for that use. Judge Engelmayer also found persuasive that certain statements Amarin proposed were statements that the FDA already permitted in the dietary supplement context by manufacturers of supplements that are chemically similar to Vascepa. He was unpersuaded by the FDA's argument that dietary supplement manufacturers' statements should be held to a different standard because a lesser showing is required for health claims on supplement labelling.

Shortly after the preliminary injunction was granted, the parties sought a stay of the proceedings to engage in settlement discussions.[8]

Stipulation and Order of Settlement

On March 8, 2016, the parties filed the anticipated proposed Stipulation & Order of Settlement with the court, which the court entered the same day. The parties agreed to be bound by the court's conclusions in the preliminary injunction order and to establish a special procedure for Amarin to obtain FDA clearance of communications regarding Vascepa's off-label use prior to using the communications in promoting Vascepa to doctors in the future.

The procedure, which the Stipulation notes is being made available to Amarin *in addition* to the optional procedures for feedback on promotional materials that the FDA makes available to all drug applicants, permits Amarin to obtain feedback on two proposed communications per calendar year through 2020. Under the procedure, Amarin may submit the communications to the FDA for comment prior to using them in promotion to doctors. If the FDA has concerns with a proposed communication, it will contact Amarin with the agency's specific concerns or objections within 60 calendar days. Amarin will then have 45 calendar days to provide a response. If any dispute remains 30 days later, either party has the option of filing a motion with the *Amarin* court requesting judicial resolution of the dispute. The agreement specifies that each interchange will be accompanied with supporting data, and that the timelines may be extended upon both parties' agreement.

The Stipulation also provides that the FDA retains the right to communicate to doctors after identifying a dispute about a particular communication, and that nothing in the order shall be construed as limiting Amarin's constitutional rights to free speech concerning Vascepa. The Stipulation specifies, however, that Amarin bears the responsibility going forward of ensuring that its communications to doctors regarding off-label use of Vascepa remain truthful and non-misleading.

Implications of the Settlement

The *Amarin* settlement is the latest in a series of cases in which industry has successfully raised the First Amendment to challenge the government's use of promotional speech as evidence of criminal misbranding. Judge Engelmayer relied heavily on a 2012 Second Circuit decision in *United States v. Caronia*, which held that the FDA may not bring a criminal action based on "truthful promotional speech alone, consistent with the First Amendment."[9] And in December 2015, Pacira Pharmaceuticals, Inc. (Pacira), with regulatory counsel from Latham, reached a favorable settlement with the FDA in a lawsuit challenging the FDA's off-label enforcement under the First Amendment, the Fifth Amendment and the Administrative Procedure Act.[10]

However, the extent to which the *Amarin* resolution will impact the FDA's enforcement of its off-label promotion regulations going forward remains unclear. The FDA may view the form of the resolution — settlement — as a means of avoiding precedential significance. In addition, the FDA may view the significance of the case narrowly because of its unusual facts — the FDA had previously conceded that the drug was safe and effective for the off-label use in question and had actually permitted the dietary supplement industry to communicate the very information it was prohibiting Amarin from communicating. Indeed, news outlets have reported that the FDA released a statement shortly after the entry of the Stipulation and Order, which emphasized that the settlement "is specific to this particular case and situation, and does not signify a position on the First Amendment and commercial speech."[11]

This landscape casts substantial uncertainty on the standards that the FDA will now apply to enforce against off-label promotion. Although the FDA has stated its intent to update its policies and guidance to account for First Amendment considerations on numerous occasions over the last several years, it has yet to do so. In December 2014, in response to a citizen petition filed by the Medical Information Working Group, the FDA stated that it planned to issue guidance during the first part of 2015 that that addresses manufacturer dissemination of information regarding unapproved uses.[12] However, no such guidance has been issued to date. Most recently, the FDA Center for Drug Evaluation and Research (CDER) included "evaluating drug advertising and promotion regulation in light of current First Amendment jurisprudence" among its general priorities for 2016.[13] CDER also promised specific guidance for industry on "manufacturer communications regarding unapproved, unlicensed, or uncleared uses of approved, licensed, or cleared human drugs, biologics, animal drugs and medical devices" among the new and revised draft guidance it plans to publish during calendar year 2016.[14]

With the recent stream of judicial resolutions involving the FDA's off-label promotion enforcement authority, including the *Amarin* settlement, we expect that the FDA will not be able to delay revising its off-label promotion policies and guidance much longer, and the changes the FDA makes could be extensive. In light of the current uncertainty and potential regulatory changes, we urge the industry to consult with counsel about any advertising and promotion of FDA-regulated products.

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Endnotes

[1] Stipulation & Order of Settlement, *Amarin Pharma, Inc. v. FDA*, No. 1:15-cv-03588 (S.D.N.Y. Mar. 8, 2016), ECF No. 84.

[2] Proposed Stipulation & Order of Settlement, *Amarin Pharma, Inc. v. FDA*, No. 1:15-cv-03588 (S.D.N.Y. Mar. 8, 2016), ECF No. 83.

[3] *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196 (S.D.N.Y. 2015).

[4] *Id.* at 211-12.

[5] Complaint, *Amarin Pharma, Inc. v. FDA*, No. 1:15-cv-03588 (S.D.N.Y. May 7, 2015), ECF No. 1.

[6] *Amarin*, 119 F. Supp. 196.

[7] The court found that Amarin's request for preliminary relief in connection with potential claims under the False Claims Act was unripe and, accordingly, did not rule substantively on the issue.

[8] Letter Motion, *Amarin Pharma, Inc. v. FDA*, No. 1:15-cv-03588 (S.D.N.Y. Aug. 28, 2015), ECF No. 75.

[9] *Amarin*, 119 F. Supp. 3d at 224.

[10] Stipulation & Order of Settlement, *Pacira Pharmaceuticals, Inc. v. FDA*, No. 1:15-cv-07055 (S.D.N.Y. Dec. 15, 2015), ECF No. 45.

[11] *See U.S. FDA to Allow Amarin to Promote Fish Oil Pill for Off-Label Use*, Reuters, Mar. 8, 2016, http://www.reuters.com/article/us-amarin-fda-settlement-idUSKCN0WA2PK.

[12] Letter from Leslie Kux, Associate Commissioner for Policy, FDA, Docket No. FDA-2011-P-0512-0010 (Dec. 22, 2014), http://www.regulations.gov/#!documentDetail;D=FDA-2011-P-0512-0010.

[13] Janet Woodcock, CDER 2016 Priorities, http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM477299.pdf.

[14] Guidance Agenda: New & Revised Draft Guidances CDER is Planning to Publish During Calendar Year 2016, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm417290.pdf.