Amarin Settlement Erodes Off-Label Promotion Enforcement

Jennifer L. Bragg

Law360, New York (March 11, 2016, 11:34 AM ET) -- In an apparent first, the U.S. Food and Drug Administration has conceded that a pharmaceutical company may engage in truthful and nonmisleading speech promoting the off-label use of a prescription drug. This concession comes as part of the proposed stipulation and order of settlement submitted to the U.S. District Court for the Southern District of New York in Amarin Pharma Inc. v. FDA on March 8. (View the order here.) The proposed order reflects an agreement by the FDA that appears to embrace all of the principles outlined in the district court's Aug. 7, 2015, opinion, chief of which was that truthful and nonmisleading speech promoting the off-label use of an FDA-approved drug cannot form the basis for a criminal misbranding charge. 119 F.Supp.3d 96 (S.D.N.Y. 2015).

While the settlement represents a significant final chapter in a case that has dramatically impacted the FDA enforcement landscape, it also leaves open the possibility that the FDA and the U.S. Department of Justice will pursue off-label cases based on false or misleading speech or conduct. This possibility lends additional significance to the government's recent unsuccessful off-label prosecution of Vascular Solutions Inc. and its president and CEO Howard Root.

Background of the Amarin Case[1]

Amarin manufactures Vascepa, a single-molecule product consisting of the omega-3 acid EPA, which was approved by the FDA in 2012 for the treatment of adult patients with "very high" triglycerides. To support Vascepa's approval, Amarin undertook several clinical trials, including two conducted pursuant to special protocol assessments (SPAs) with the FDA.[2] The FDA subsequently rescinded one of the SPAs (for the "ANCHOR" study) after an advisory committee found "substantial uncertainty" regarding whether the "reductions in triglycerides" demonstrated in the study "would reduce cardiovascular risk." 119 F.Supp.3d at 211. The FDA then (1) refused to approve Amarin's supplemental ANCHOR study-based new drug application seeking approval of Vascepa for treatment of adult patients with "persistently high" triglyceride levels, (2) refused to allow Amarin to include the ANCHOR study efficacy results in the Vascepa label, and (3) warned Amarin that Vascepa would be "considered to be misbranded" if it was marketed for treating "persistently high" triglyceride levels. Id. at 211-12.

In response, Amarin, together with several physician plaintiffs, sued the FDA, seeking to ensure its ability to make truthful, nonmisleading statements about unapproved uses of Vascepa. Id. at 198. Amarin sought protection for its speech at both a general and statement-specific level. To that end, Amarin proposed specific "carefully 'circumscribed,

truthful and scientifically' accurate statements," id. at 214, as well as a number of disclaimers to be used to ensure the truthful information it sought to communicate was not misleading, id. at 214. Amarin then moved for an injunction preventing the FDA from bringing a misbranding action against it, or alternatively, a declaration that its speech was protected against a misbranding action under both the First Amendment and the Fifth Amendment's prohibition on vague laws. On Aug. 7, 2015, the court issued a detailed opinion granting a preliminary declaration in favor of Amarin. Shortly thereafter, the FDA and Amarin agreed to stay the action to explore settlement.

Analysis of the Amarin Case and Settlement Order

The Amarin opinion devoted significant attention to analyzing and explaining the U.S. Court of Appeals for the Second Circuit's 2012 opinion in United States v. Caronia, which held that the Federal Food, Drug and Cosmetic Act neither prohibits nor criminalizes truthful, nonmisleading speech that may constitute off-label promotion of FDA-approved prescription drugs. The Amarin court rejected the FDA's position that Caronia was narrowly applicable to the facts of that case. Instead, the court reiterated: "Where the speech at issue consists of truthful and nonmisleading speech promoting the off-label use of an FDA-approved drug, such speech, under Caronia, cannot be the act upon which an action for misbranding is based." 119 F.Supp.3d at 226. The court also conducted a detailed evaluation of each of Amarin's proposed claims and disclaimers, and declared that, consistent with the First Amendment, Amarin could make certain truthful and nonmisleading off-label statements specified in the opinion.[3]

The proposed Amarin settlement order embraces the district court's findings. Most notably, the settlement order provides that the FDA agrees "to be bound by the court's conclusion that Amarin may engage in truthful and nonmisleading 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." Order ¶ 1. This broad agreement appears to cover any truthful and nonmisleading speech relating to the use of Vascepa for this as-yet unapproved use. The FDA also agrees to be bound by the district court's conclusions on the truthful and nonmisleading nature of specific statements and disclosures examined by the court. Id. ¶ 2. In addition, the settlement order provides Amarin with a fast-track procedure for seeking FDA preclearance of up to two proposed off-label communications per calendar year through the end of 2020, with an option to seek the district court's review of any resulting disputes in that process.[4] The proposed stipulation and settlement order remain subject to the district court's approval.

Amarin's Impact on FDA-Regulated Industry

The approval of the settlement order would bring an end to the Amarin litigation, a case that has unquestionably impacted the off-label promotion regulatory and enforcement landscape, but would also leave open questions regarding whether, and how, the FDA and DOJ will pursue misbranding cases involving off-label promotion. On the one hand, the stated basis for entry of the settlement order is not limited to the facts of the Amarin case; this is significant given that Amarin's rescinded SPA and other key factual circumstances are unlikely to recur in future cases.

Indeed, the proposed settlement order appears to reflect a broad concession by the FDA that Caronia precludes the agency from pursuing criminal misbranding charges based solely on truthful, nonmisleading speech. See Order ¶ 1. At the same time, the settlement order's precise language — pursuant to which the FDA "agree[s] to be bound" by the Amarin court's conclusion that under Caronia, truthful and nonmisleading speech "may not form the basis of a prosecution for misbranding," id. — leaves some latitude for the FDA to argue that Caronia and Amarin do not apply to future cases that (1) involve false or misleading speech, (2) involve conduct rather than speech, or (3) arise outside of the Second Circuit.

All three of these distinctions characterized the DOJ's and FDA's recent unsuccessful prosecution of Vascular Solutions Inc. and Howard Root in the U.S. District Court for the Western District of Texas (case No. 5:14-cr-00926-RCL, W.D. Tex.). The government charged Vascular Solutions and Root with selling medical devices — in particular "Vari-Lase" laser ablation devices used to treat varicose veins — without FDA approval and conspiring to defraud the United States by concealing this allegedly illegal activity (Superseding Indictment, ECF 130, Dec. 2, 2015).

The government alleged that Vascular Solutions and Root engaged in a campaign to promote the Vari-Lase devices for ablation of perforator veins when the devices were only approved for use in superficial veins. Id. The government further alleged that this campaign continued after the FDA failed to clear a specific 510(k) premarket notification covering the use of Vari-Lase devices in perforator veins, and after a clinical trial failed to establish that the devices were safe and effective for this use. Id. Based on these allegations, the government charged that the Vari-Lase devices were misbranded because (1) Vascular Solutions and Root failed to secure clearance of a 510(k) premarket notification covering the use of the Vari-Lase devices in perforator veins, and (2) the devices' labeling lacked adequate directions for this use.

Although the Vascular Solutions case was charged prior to the Amarin decision, Caronia and Amarin were featured prominently in — but did not preclude — the subsequent litigation. First, Vascular Solutions and Root moved to dismiss the indictment against them, arguing under Caronia and Amarin that the indictment sought to criminalize truthful statements regarding the off-label use of the Vari-Lase devices. The court rejected this argument, finding that the government had charged Vascular Solutions and Root with false and misleading — as opposed to "solely truthful" — off-label promotion (ECF 128, Nov. 16, 2015). And, as their trial approached, Vascular Solutions and Root again sought to curtail the government's ability to rely on truthful, nonmisleading speech (ECF 158, Jan. 1, 2016).

The court denied the defendants' motion, finding that the government had represented that it would use evidence of conduct, rather than speech, to establish the defendants' intent to promote the Vari-Lase devices off-label (ECF 213, Jan. 27, 2016). The court further found that while the government planned to use speech to establish an overt act in furtherance of the alleged conspiracy, doing so would not run afoul of the First Amendment because a lawful act may serve as the necessary overt act in furtherance of a conspiracy. Id.

The government ultimately lost the Vascular Solutions case when Vascular Solutions and Root were acquitted on all counts on Feb. 26, 2016. Nevertheless, the government's willingness to pursue this prosecution — and its efforts to distinguish Caronia and Amarin in doing so — suggest that the FDA and DOJ harbored a continued belief that a conduct rather than speech-based off-label prosecution might succeed. For this reason, a broad reading of the Amarin settlement order may be overly optimistic.

Caronia and Amarin, combined with the government's statements in Vascular Solutions, suggest that it is unlikely that the FDA and DOJ will choose — even outside the Second Circuit — to prosecute cases involving solely truthful, nonmisleading speech or conduct. The Amarin settlement order, however, leaves the door open for the government to pursue off-label cases based on objectively false or misleading speech, as it sought to do in Vascular Solutions. In this regard, the unsuccessful Vascular Solutions prosecution may have an equally important impact on the government's future exercise of its enforcement discretion relating to off-label cases.

—By John T. Bentivoglio, Jennifer L. Bragg, Michael K. Loucks, Gregory M. Luce, Maya P. Florence and Alexandra M. Gorman, Skadden Arps Slate Meagher & Flom LLP

John Bentivoglio, Jennifer Bragg and Gregory Luce are partners in Skadden's Washington D.C. office. Michael Loucks is a partner in Skadden's Boston office. Maya Florence and Alexandra Gorman are counsels in Skadden's Boston office. Bentivoglio has previously served as associate deputy attorney general and special counsel for health care fraud at the DOJ. Bragg has previously served in the FDA's Office of Chief Counsel as associate chief counsel for enforcement, where she provided advice to the FDA's Office of Criminal Investigations.

[1] For further factual background regarding the Amarin case, as well as analysis of the case and its potential impact, please see "The Future of Government Regulation, Enforcement of Off-Label Promotion" (Sept. 28, 2015).

[2] The SPA process is designed to provide a sponsor with "regulatory predictability: Provided that the manufacturer follows the procedure set in the SPA agreement and the drug proves [and] meets the benchmarks for effectiveness set in the agreement, the FDA must approve the drug." The FDA may rescind an SPA only if there is an identified and presumably as-yet unresolved "substantial scientific issue essential to determining the safety or effectiveness" of the drug for the additional proposed uses. Amarin, 119 F. 3d at 210 (quoting FDA, "Guidance for Industry: Special Protocol Assessment" (2002), at 10.

[3] Shortly after the Amarin opinion, a second pharmaceutical company, Pacira Pharmaceuticals Inc., and two physicians filed suit against the FDA in the Southern District of New York district court. Pacira's action concerned EXPAREL, Pacira's local anesthetic product, which was only studied in bunionectomies and hemorrhoidectomies but was broadly approved for "administration into the surgical site to produce post-surgical analgesia." Nevertheless, the FDA had issued a warning letter to Pacira warning the company that providing physicians with information about the use of EXPAREL outside of bunionectomies and hemorrhoidectomies constituted misbranding and subjected Pacira to potential criminal prosecution. Pacira broadly challenged the FDA's ability under the First Amendment to limit the company's communications with physicians regarding the approved uses of Exparel. The Pacira case resolved through a settlement in which the FDA rescinded its warning letter to Pacira and clarified that the EXPAREL approval was not limited to bunionectomies and hemorrhoidectomies.

[4] This review is in addition to the optional procedures available to all pharmaceutical companies to solicit FDA comment on proposed advertisements. See 21 C.F.R. Part 202.1 (j)(4).