FDA and Amarin Pharma Reach Milestone Settlement Allowing Off-Label Drug Promotion

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A milestone Settlement Agreement was reached March 8, 2016 between the Food and Drug Administration and Amarin Pharma, Inc. that expressly allows Amarin to promote its drug product, Vascepa®, for unapproved – i.e., "off-label" – uses. Vascepa® is approved only for the treatment of severe hypertriglyceridemia, meaning patients with triglyceride levels at or above 500 mg/dL of blood. The settlement allows Amarin to promote Vascepa® to treat patients on statin therapy with persistently high triglycerides, a less severe condition describing patients with triglyceride levels ≥ 200 and ≤ 499 mg/dL of blood, so long as statements and disclosures are used to ensure such promotion is not false or misleading. This combination of statements and disclosures along with the use of a voluntary procedure for Amarin to pre-clear future promotional claims with the FDA marks a turning point for the regulation of drug advertising and promotional activity in the United States by easing FDA's long held and staunchly defended restrictions on drug marketing.

The Agreement resolves a lawsuit brought by Amarin against FDA for violation of its First Amendment right to Commercial Free Speech. Thus, the Agreement contains an acknowledgement by the FDA that under the decision in *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012), off-label promotion that is truthful and not misleading "may not form the basis of a prosecution for misbranding" against a pharmaceutical manufacturer.

Unique Aspects of the *Amarin* Case

The *Amarin* case, it should be noted, involved a unique set of facts that strongly supported statements the Court considered not misleading about Vascepa's unapproved uses. Amarin successfully completed a phase 3 clinical study demonstrating the effectiveness of Vascepa in lowering triglyceride levels in patients with persistently high triglycerides who were still on statin therapy. This study was conducted under a Special Protocol Agreement entered with the FDA, under which FDA agreed to approve Vascepa for this indication if Amarin satisfied certain requirements. These requirements included meeting pre-specified endpoints and enrolling at least 50 % of patients for an outcomes trial to examine whether Vascepa would also reduce cardiovascular event in patients with persistently high triglycerides. Amarin met the pre-specified endpoints for the SPA trial and met the enrollment criteria for the outcomes trial. Thus, Amarin believed it had satisfied FDA's SPA requirements for approval of Vascepa for the second indication. However, with the affirmation of an Advisory Committee, FDA concluded the endpoints previously agree upon did not establish the lower triglyceride levels in patients with persistently high triglycerides lead to fewer cardiovascular event. FDA thus rescinded its SPA, a rare occurrence, and refused to approve Amarin's supplemental application for the expanded indication; instead, FDA asked for more data.

In addition, the FDA warned Amarin that any promotion of Vascepa for the treatment of persistently high triglycerides would render Vascepa misbranded. Based on this "threat", Amarin brought its suit against FDA. It was with this background that the Court came to examine whether Amarin's proposed statements and disclosures to accompany promotion of Vascepa for this unapproved use would be false or misleading. After a detailed review, the Court agreed that most of Amarin's proposed statements would ensure that its promotion of Vascepa would not be false or misleading. In the Settlement Agreement, Amarin agreed to be bound by its proposed statements and disclosures as reviewed by the Court. Specifically, Amarin agreed to disseminate the results of the studies supporting the unapproved uses with the statement:

> *"Supportive but not conclusive research shows that consumption of EPA and DHA ** * omega-3 fatty acids may reduce the risk of coronary heart disease"*

Amarin also agreed to distribute reprints of relevant peer-reviewed scientific publications. More importantly, Amarin agreed to make relevant "contemporaneous disclosures" to physicians, including:

- *FDA has not approved Vascepa to reduce the risk of coronary heart disease.*
- *FDA has not approved Vascepa for the treatment of statin-treated patients with mixed dyslipidemia and high triglyceride levels.*
- *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, to reduce the risk of coronary heart disease or for treatment of statin-treated patients with mixed dyslipidemia and high (> 200 mg/dL and < 500 mg/dL) triglyceride levels. We encourage you to check that for yourself. Impact of the Amarin Settlement on Off-Label Prosecutions*

FDA Accepts *Caronia* Case Outcome

The Amarin Settlement Agreement also signals the acceptance by federal authorities that *Caronia* establishes that off-label promotion through truthful and non-misleading verbal statements, standing alone, cannot form the basis of criminal charges for misbranding. In *Caronia*, the Second Circuit reversed the misdemeanor criminal conviction of a pharmaceutical sales representative, Alfred Caronia, for misbranding as a result of his verbal statements relating to off-label uses of the drug Xyrem®. That prosecution, consistent with some earlier government prosecutions, was premised upon the allegation that Caronia's promotional statements showed an intended use for Xyrem and the Xyrem label had inadequate directions for that use and therefore caused the drug to be "misbranded."

On appeal, the defendant argued that he was convicted purely based upon his truthful and non-misleading statements about off-label uses of Xyrem, in violation of his right of free speech under the First Amendment. The government's opposition was that "Caronia was not prosecuted for his speech, but that Caronia's promotion of Xyrem for off-label use served merely as 'evidence of intent,' or evidence that the 'off-label uses were intended ones[] for which Xyrem's labeling failed to provide any directions.'" *Id*. at 160-61. The Second Circuit rejected this opposition because the government's consistent arguments at trial were that Caronia violated the law through his off-label promotion and marketing of Xyrem – not that this promotion merely served as evidence of intended use of the drug. Thus, "[t]he government never suggested, for example, that Caronia conspired to place false or deficient labeling on a drug. Rather, the record makes clear that the government prosecuted Caronia *for* his promotion and marketing efforts." *Id*. at 161 (citations omitted). The Second Circuit then went on to find that the government's restriction on Caronia's speech was not consistent with the First Amendment under the four-part test set forth in *Central Hudson Gas & Electric Corp. v. Public Service Commission*, 447 U.S. 557 (1980).

The Amarin Settlement Agreement takes the next step from *Caronia*: Not only are Amarin sales representatives free from prosecution for truthful and non-misleading off-label promotion of Vascepa®, the FDA has agreed to review such off-label communications up to twice a year upon Amarin's voluntary submission to confirm as much.

Pacira Pharmaceuticals Follows *Amarin*

Since the *Amarin* Court sent FDA and Amarin into its settlement negotiations, two cases have been brought and resolved in which the companies' off-label promotion has been permitted. First, Pacira Pharmaceuticals settled its lawsuit against FDA by reaching an agreement on a labeling change that effectively affirmed Pacira's promotion of its analgesic drug, Exparel®, for use in various surgeries rather than in only the two specific surgeries studied in the clinical trials supporting Exparel's approval. Pacira, like Amarin, had unique and compelling facts supporting Pacira's expanded promotion. Specifically, FDA had approved Exparel as a surgical analgesic without specifying the types of surgeries in the indications for use. Instead, the directions for use of the drug covered only the two types of surgeries. Upon being sued, with the Amarin case having just been decided, FDA agreed to revise the labeling to provide directions for use for various surgeries and thus permit promotion for such uses.

Medical Device Maker, Vascular Solution Inc, Follows *Caronia*

Most recently, a Texas jury found Vascular Solution Inc, a manufacturer of a medical device intended for ablation of superficial veins, not guilty on criminal charges of off-label promotion based on a conclusion that the promotion was true and not misleading.

So where will off-label prosecution go from here? While only time will tell, a good guess would be that criminal misbranding prosecutions

will focus on blatantly false statements and non-speech evidence of intent to misbrand – such as internal marketing plans showing intended uses of a drug (that do not match the label directions), and incentive compensation plans that are designed for uses of a drug that do not match label directions. However, to avoid misleading promotion, statements about off-label uses should be carefully crafted with disclosures and qualifying statements. As the *Amarin* court noted, "[p]rior consultation with the FDA may prove a helpful prophylactic, and may avert misbranding charges where the FDA and the manufacturer would take different views of a statement in the end…."

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