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Food, Drug & Device Law Alert - Federal Court Authorizes Pharmaceutical Firm To Engage In Off-label Promotion Using Certain Specific Information And Statements

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On August 7, a federal district court in New York preliminarily resolved a closely-watched dispute between the FDA and an affiliate of Amarin Corporation plc in favor of Amarin. *Amarin Pharma, Inc. v. FDA*, Case No. 15-3588, 55 (S.D.N.Y. Aug. 7, 2015) (opinion and order granting preliminary injunction). The dispute concerned proposed truthful and non-misleading, but off-label promotion, of an Amarin drug, Vascepa®. Citing Amarin's First Amendment rights, the court issued a preliminary injunction authorizing Amarin to make several specific statements or disclosures to doctors and to disseminate 13 scientific publications concerning Vascepa®.

Some factual background is important to understanding the court's ruling. FDA previously approved Vascepa® as an adjunct to diet to reduce triglyceride levels in patients with severe (? 500 mg/dL) hypertriglyceridemia. This approval was based on a single phase 3 clinical trial conducted in patients with "very high" triglycerides pursuant to an agreement with FDA.

After Vascepa®'s approval, Amarin learned that physicians were also using it to treat patients with "persistently high" triglycerides (? 200 and ? 500 mg/dL) and planned to seek approval for its use in this expanded patient population. Similar to its approach with the initial indication, Amarin designed a single phase 3 clinical trial to examine the effect of Vascepa® on triglyceride levels among statin-treated patients with persistently high triglycerides (the ANCHOR trial) and entered into another agreement with FDA. Amarin also agreed to conduct a cardiovascular outcomes trial (the REDUCE-IT trial) to study whether Vascepa® would be effective in reducing cardiovascular events.

Amarin completed the ANCHOR study and believed it had satisfied all of FDA's requirements to obtain approval of Vascepa® for persistently high triglycerides. Thus, Amarin submitted a supplemental NDA (sNDA) for the persistently high triglyceride indication in February, 2013, and anticipated a timely approval. Instead of approving the sNDA, however, FDA convened an Advisory Committee. After the FDA and Amarin had agreed to the ANCHOR and REDUCE-IT trials, several cardiovascular outcomes studies had called into question whether a reduction in triglyceride levels would translate into a reduction in cardiovascular events. Accordingly,

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FDA asked the Advisory Committee whether Vascepa®'s triglyceride lowering effect was sufficient to approve the drug for use in patients with persistently high triglycerides. The Advisory Committee voted against approval of Vascepa® and FDA declined to approve it. According to Amarin, when FDA conveyed its decision to Amarin FDA stated that "any effort by Amarin to market Vascepa® for the proposed supplemental use could constitute 'misbrand[ing] under the Federal Food, Drug, and Cosmetic Act [(FDCA)].'"

Shortly after receiving the FDA's letter, Amarin filed its complaint with the court and sought the preliminary injunction authorizing the specific statements or disclosures and the dissemination of the scientific articles mentioned above. In ruling for Amarin, the court relied heavily on the relatively recent decision in *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012). In Caronia, the U.S. Court of Appeals for the Second Circuit reversed the criminal conviction of a pharmaceutical sales representative for the off-label promotion of a prescription pharmaceutical based on the First Amendment. The Second Circuit summarized its decision as follows: "We construe the misbranding provisions of the FDCA as not prohibiting and criminalizing the truthful off-label promotion of FDA approved prescription drugs…. We conclude simply that the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug."

FDA argued for a narrow interpretation of *Caronia*, limited to its facts, and for the position that it could pursue Amarin for off-label promotion by analogy to other crimes, such as jury tampering, blackmail, and insider trading, where speech constitutes the criminal act. The Amarin court rejected those arguments, however, and concluded "[w]here the speech at issue consists of truthful and non-misleading 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." In other words, "if the speech at issue is found truthful and non-misleading, under Caronia, it may not serve as the basis for a misbranding action."

Towards the end of its lengthy opinion, the court discussed the specific information which Amarin sought to share with doctors. With respect to the 13 scientific publications, the court observed that the FDA did not claim that they were, individually or collectively, false or misleading and therefore approved their distribution. Amarin sought to disseminate a summary of the ANCHOR trial. Again the court stated that the FDA did not argue that the summary is false or misleading, and the court found the summary is "studiously neutral" and approved its distribution.

Amarin also sought to make certain specific "statements" and "disclosures." The court stated that the FDA agreed with two of the statements and four of the disclosures, and the court found they were truthful and not misleading. Amarin agreed to the FDA's proposal to disclose any potential financial or affiliation biases between itself and the people who conducted the ANCHOR study. The court then discussed at some length two disputed disclosures and one disputed statement and, after revising the disclosures somewhat, authorized Amarin to make them.

Although this case likely represents a significant victory for Amarin, firms subject to FDA regulation should tread carefully before engaging

wholesale in off-label promotion of medical devices, pharmaceuticals, or other applicable products. There are certain facts that may limit how this case is applied in the future. It was decided by a district court with jurisdiction over only eight counties in New York. The *Caronia* case, on which the Amarin court heavily relied, was decided by the Second Circuit which, while often influential, technically has jurisdiction only over Connecticut, New York, and Vermont. Other courts may view the issues differently, although it is worth noting that the Supreme Court's decision in Sorrell v. IMS Health Inc., 131 S. Ct. 2653 (2011), also calls into question the FDA's regulation of off-label promotion based on the First Amendment.

Importantly, as noted above in *Amarin* the truthful and non-misleading nature of most of the information Amarin sought to disclose was not disputed. The statements were supported by the results of the ANCHOR study or otherwise and the FDA did not claim several of them were false or misleading. The court noted the case was unusual in this respect:

[T]he Court notes that Vascepa's unusual and extensive regulatory history makes it realistic to determine, at this early stage, the truthfulness of Amarin's proposed statements regarding its off-label use. Here, the FDA has already reviewed the off-label use at issue. It approved the ANCHOR study, which tested Vascepa's effectiveness in reducing triglyceride levels among patients with persistently high triglycerides. And it has confirmed in writing, including in the CRL [Combined Response Letter], that Vascepa has proven effective in doing so. *Amarin has thus been able to base its proposed communications about Vascepa almost entirely on statements by the FDA itself* (emphasis added).

In future cases, important issues may be who has the burden to prove that alleged off-label promotion is truthful and non-misleading and what proof is required to do so. In this case, Amarin's evidence satisfied one of the highest standards, a clinical trial to which FDA had agreed.

Further, the court itself sounded some cautionary notes, such as the following:

A final observation: Although the FDA cannot require a manufacturer to choreograph its truthful promotional speech to conform to the agency's specifications, there is practical wisdom to much of the FDA's guidance, including that a manufacturer vet and script in advance its statements about a drug's off-label use. A manufacturer that leaves its sales force at liberty to converse unscripted with doctors about off-label use of an approved drug invites a misbranding action if false or misleading (e.g., one-sided or incomplete) representations result. *Caronia* leaves the FDA free to act against such lapses. A manufacturer may also conclude that it is prudent to consult with the FDA before promoting off-label use.

In connection with the court's comment that "the FDA is free to act against" false or misleading off-label promotion, it is worth remembering that the potential remedies are severe, including prison and debarment from the industry.

Finally, in another important cautionary note, the court the court stated:

The Court has held that Amarin's proposed communications, as modified herein, are presently truthful and non-misleading. But the dynamic nature of science and medicine is that knowledge is ever-advancing. A statement that is fair and balanced today may become incomplete or otherwise

misleading in the future as new studies are done and new data is acquired. The Court's approval today of these communications is based on the present record. *Amarin bears the responsibility, going forward, of assuring that its communications to doctors regarding off-label use of Vascepa® remain truthful and non-misleading* (emphasis added).

If the facts and circumstances change in the future so that Amarin's statements are no longer truthful and non-misleading, it may be exposed to the remedies noted above. Indeed, since the case was decided on a preliminary basis, it is possible discovery will show some of the statements or disclosures approved by the court were not truthful and non-misleading. If so, Amarin may face a panoply of potential remedies. Of course, the court's decision is subject to appeal as well.

Thus, FDA regulated firms are well-advised to continue to proceed cautiously before engaging in any potentially off-label promotion.

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