

Client Alert



April 2016

The Post-Amarin Age and Its Potential Effect on Off-Label Promotion

In March 2016, Amarin Pharma, Inc. ("Amarin") and the United States Food and Drug Administration ("FDA") filed a proposed stipulation and order of settlement in the U.S. District Court for the Southern District of New York. In sum, when finalized, FDA most likely will be bound by the district court's August 7, 2015 opinion,ⁱ and most notably, FDA would agree to be bound by the court's conclusion that Amarin may engage in truthful and non-misleading commercial speech promoting the off-label use of Amarin's product, and that such speech may not form the basis of a misbranding criminal prosecution. While FDA has had commercial free speech setbacks with other court cases in recent years in attempting to police off-label use promotion, the Amarin case represents FDA explicitly conceding that a pharmaceutical company may engage in truthful and non-misleading commercial speech promoting an unapproved or off-label use of an approved prescription drug.

The Amarin Opinion and Settlement Order

Amarin's drug in question, Vascepa (icosapent ethyl), an ethyl ester of the omega-3 fatty acid eicosapentaenoic acid, is an approved drug indicated as an adjunct to diet to reduce triglyceride levels in adult patients with severe hypertriglyceridemia (triglycerides \geq 500 mg/dL). After receiving its first approved indication from FDA in 2012, Amarin submitted a supplemental new drug application for a second indication in 2013, and anticipated a timely approval for treating patients with persistently high triglyceride levels from 200 to 499 mg/dL who have already received statin therapy. Amarin believed it had satisfied all of FDA's requirements to obtain approval of Vascepa for this indication in accordance with a special protocol assessment with FDA. Nevertheless, FDA rescinded the special protocol assessment and issued a Complete Response Letter to Amarin stating the Agency was not able to approve the indication in light of recent clinical trial data. Most prominently, the Complete Response Letter concluded that "any effort by Amarin to market Vascepa for the proposed supplemental use could constitute 'misbranding' under the Federal Food, Drug, and Cosmetic Act ("FDCA")."ⁱⁱ In response, Amarin, together with four physician plaintiffs, sued FDA seeking, among other things, a declaratory judgment to ensure Amarin's First Amendment right to engage in truthful and non-misleading statements about unapproved uses of Vascepa.ⁱⁱⁱ

The court granted Amarin's motion for preliminary injunction against FDA, with the opinion largely based on the U.S. Court of Appeals for the Second Circuit's 2012 opinion in *United States v. Caronia*, which held that the FDCA's misbranding provisions neither prohibit nor criminalize the promotion of a drug for off-label use based on speech alone.^{iv} In rejecting FDA's argument to apply *Caronia* narrowly to

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the facts of *Caronia* only, the *Amarin* court conducted a thorough analysis of the First Amendment and concluded that the holding in *Caronia* is a definitive statutory construction, instead of being fact-specific.^v According to the *Amarin* court, the holding in *Caronia* applies to all truthful and non-misleading promotional speech, and the promotional statement of unapproved uses made by sales and marketing people remains under the protection of the First Amendment as long as such statements are truthful and non-misleading.^{vi} The *Amarin* court further conducted a detailed evaluation of each of *Amarin*'s proposed claims and disclaimers, and held that *Amarin*'s proposed communications are presently truthful and non-misleading.^{vii} However, *Amarin* explicitly limited the application of its holding. The protection of the First Amendment only covers speech rather than conduct.^{viii} Moreover, a company's speech may be admissible as evidence of intent where the concerned conduct is not purely speech-based. For example, if a company pays for or buys doctors' resort vacations to reward off-label prescribing, a company's truthful statements promoting off-label use could serve as the evidence to prove its intent to promote off-label use.^{ix} Moreover, such speech is not protected if the speech itself is false or misleading.^x The *Amarin* court also noted that circumstances could change the court's approval of *Amarin*'s present statements as truthful and non-misleading, noting that rapid developments in medical science may cause the statements to become unfair or misleading as new studies are done and new data are obtained.^{xi}

The proposed *Amarin* settlement order, which is still subject to the district court's approval, adopts the *Amarin* court's key findings. The settlement order also provides *Amarin* with a pre-approval procedure for seeking FDA approval of up to two proposed off-label communications regarding Vascepa per calendar year through the end of 2020, with an option to seek the district court's review of any resulting disputes in this process.

Navigating the uncharted waters of the post-*Amarin* age

If the court approves the settlement order, the *Amarin* litigation will come to the end. FDA's explicit surrender of part of its regulatory and enforcement power over off-label promotion eventually could change the landscape of future enforcement against pharmaceutical or medical device companies. The decisions in *Caronia* and *Amarin* may cast doubts on FDA's ability to regulate off-label use promotion as the Agency did in the past. Furthermore, additional courts may follow the *Caronia* and *Amarin* courts, given the opportunity. However, in taking a closer look, it may be premature to declare FDA's total defeat in this regulatory area.

The proposed *Amarin* settlement does not mean that drug and device companies should immediately start to aggressively promoting beyond their approved labeling. Obviously, FDA and the Department of Justice ("DOJ") will continue to prosecute companies' off-label promotion when their promotions involve false or misleading speech. Moreover, what constitutes "non-misleading" is not entirely clear. While it may be straightforward to determine the scope of truthfulness in a promotional claim, the scope of non-misleading can be rather difficult. For example, clinical results of adequate and well-controlled studies may sufficiently fall into the non-misleading information category, but there remains less guidance as to how companies discern if objective information about studies, other than adequate and well-controlled studies, can be asserted as non-misleading. (See discussion of substantiation further below). This consequence may give FDA an opportunity to pursue actions based on its own judgment as to what is non-misleading information or not. FDA and DOJ most likely will continue to focus on conduct-based prosecution if the speech-based promotion

creates a higher bar. Furthermore, the proposed *Amarin* settlement does not shed light on the substantiation issue. It is likely that FDA and DOJ still could challenge a company' promotional claim if the company is unable to properly substantiate its claim even if such claim initially seems truthful and non-misleading and worthy of the First Amendment protection. Finally, there is also a possibility that FDA and DOJ could find a way to initiate cases outside of the Second Circuit. It could possibly get different results in other U.S. circuits if it found a way to pursue this avenue.

As a consequence, the *Amarin* holding, which is likely to be adopted into the official settlement, should not create an overly aggressive outlook that FDA and DOJ's days of challenging off-label promotion are over. A pharmaceutical or medical device company should still maintain its review and approval of promotional communication in accordance with the product's prescribing information and labeling. If pursued, statements about an off-label use should still be subject to a very high level of internal scrutiny. They will truly need to be "bullet-proof" and beyond any reproach to avoid enforcement risk. We recommend discussing plans for off-label promotion with FDA before commencement. The characterization of study results of an unapproved use may pose higher risks than disseminating an objective statement of the study results. A company should not leave its sales force at liberty to converse with doctors about off-label use of an approved drug without a script or written statement carefully reviewed by the company's regulatory and legal personnel assuming such an approach is pursued. A company still should monitor and pay close attention to the development of the science and revise any promotional claims accordingly in a timely manner for better assurance of the truthful and non-misleading nature of an off-label promotional statement. This measure may be particularly critical for a novel product which has a risk-benefit profile that cannot be ascertained substantially without continuous trials and studies after the approval of its first indication. In addition, to the same end, it is advisable for a company with such a novel product to seek advance guidance from FDA. In many instances, communication between FDA and the company during the development and approval of the product, as well as in any post-marketing discussions, may prove useful. These may be presented or found in official meeting minutes, regulatory correspondence; or contact reports. They may provide abundant clues for the company to understand and appreciate FDA's views on appropriate claims that may be made within and outside the scope of the approved labeling for a particular product. The understanding of FDA's views through the analyses of such communication may be helpful to construct a communication of off-label use for presentation to and discussion with FDA

Overall, in the post-*Amarin* age, FDA's ability to regulate off-label promotion may be more limited, but it will at the very least demand more of companies' efforts at the organization level to adopt a compliance practice, across multiple functions in medical affairs, development, pharmacovigilance, and legal and compliance, to assure every off-label message's truthful and non-misleading nature. Claims will have to be fully justified if the company elects to take advantage of any promotional openings created by *Amarin*. While the trend of limiting FDA's ability to regulate truthful and non-misleading statements concerning off-label use may continue, there will always be a need to develop truthful and non-misleading messages with proper support, justification, and substantiation.

ⁱ 119 F. Supp. 3d 96 (S.D.N.Y. 2015).

ⁱⁱ Complaint at 27, *Amarin Pharma, Inc. v. FDA*, No. 15-3588 (S.D.N.Y. May 7, 2015).

ⁱⁱⁱ 119 F. Supp. 3d at 198.

^{iv} 703 F.3D 149 (2d Cir. 2012).

^v *Amarin Pharma, Inc. v. FDA*, No. 15 Civ 3588, Slip op. 48 (S.D.N.Y. Aug. 7, 2015).

^{vi} *Id.* at 51.

^{vii} *Id.* at 53-56.

^{viii} *Id.* at 52.

^{ix} *Id.*

^x *Id.*

^{xi} *Id.* at 66.