Another One Bites the Dust: FDA Doesn't Like the Fishy Smell of the Latest Court Decision on Off-Label Dissemination

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The Food and Drug Administration (FDA) has lost yet another court decision challenging its ability to restrict a company's commercial free speech rights. To quote the rock band Queen, Another One Bites the Dust.

In the most recent court decision, Amarin Pharma, Inc. v. United States Food and Drug Administration, No. 15 Civ. 3588 (PAE) (S.D. N.Y. August 5, 2015), a U.S. District Court granted Amarin's preliminary injunction to prohibit FDA from taking enforcement action against the company's distribution of information about an unapproved use of its FDA-approved fish oil, triglyceride-lowering prescription drug product, Vascepa® (icosapent ethyl).

In this Bulletin, we will summarize the facts of the case, highlight key elements of the 70-page decision, and offer several observations.

I. Summary of Facts

- Vascepa is approved as an adjunct to diet to reduce triglyceride levels in adult patients with severe hypertriglyceridemia. These patients would also be treated with statins. The product is composed of pure eicosapentaenoic acid (EPA), an omega-3 fatty acid.

- Amarin wanted to promote the product for a wider group of patients than approved, e.g., patients treated with statins with high but not very high triglyceride levels. This use is an "off-label" use.

- The company sought to make healthcare professionals aware of clinical study results concerning the efficacy of the drug in certain patients, which FDA had questioned, but with qualified statements, such as: "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 was prepared to provide additional information, such as a selection of peer-reviewed scientific articles on the potential effect of EPA on the reduction of the risk of coronary heart disease. It was also willing to include disclosures and disclaimers to doctors, such as the drug had not been approved for certain uses, among other qualifiers.

- According to Amarin, FDA intimated that the dissemination of such information would be off-label (because the drug was only approved to treat very high triglyceride levels) and would misbrand the drug product, potentially resulting in enforcement action. FDA (after convening an advisory panel) did not approve the drug product for the additional indication. Thus, Amarin took the preemptive step of seeking a preliminary injunction.

- Amarin claimed that the statements were truthful and non-misleading speech, and thus should be protected by the First Amendment, citing a previous U.S. Court of Appeals for the Second Circuit decision (the 2012 United States v. Caronia case, which we summarized[1] previously).[2]

1 http://www.agg.com/files/uploads/Client-Alerts/Kitchens-Minsk-Second-Circuit-Rules-Off-Label-Promotion-is-Protected-Speech.pdf

2 The Second Circuit dismissed a misbranding conviction on the basis of the off-label promotion by a sales representative conveying truthful and non-misleading information to doctors. *See* 703 F.3d 149 (2d Cir. 2012).

- In a June 5 letter, perhaps intended to make the case moot, FDA noted during the court proceeding that it would not consider the dissemination to be evidence of misbranding if the company met certain conditions. FDA indicated it did not have concerns with much of the information the company proposed to communicate. Amarin was willing to agree to some, but not all, of the FDA-requested disclosures.

II. Highlights of Court Decision

- The District Court said that the FDA June 5 letter did not make the case moot, because Amarin had not agreed to all of the company's conditions and, thus, the letter continued to expose the company to potential FDA enforcement action. The court noted, "Because Amarin faces a non-extinguished threat of a misbranding prosecution for speech it proposes to undertake as to Vascepa, there remains a live case or controversy."

- The court, citing Caronia, said that the government cannot prosecute companies and their representatives under the Federal Food, Drug, and Cosmetic Act for truthful, non-misleading discussion, even if about off-label uses: "The Court's considered and firm view is that, under *Caronia*, the FDA may *not* bring such an action based on truthful promotional speech alone, consistent with the First Amendment." The court also wrote that, unlike FDA's contention, the Caronia decision was not limited to the facts of that specific case.

- The court held:

  > Amarin may engage in truthful and non-misleading speech promoting off-label use of Vascepa … such speech may not form the basis of a prosecution for misbranding … the combination of statements and disclosures that Amarin proposes to make to doctors relating to the use of Vascepa to treat persons with persistently high triglycerides, as such communications have been modified herein, is truthful and non-misleading.

- FDA failed to persuade the court that its regulation of off-label promotion should be exempt from First Amendment scrutiny.

- The court recognized that FDA has a substantial interest in protecting consumers from potentially ineffective drugs and encouraging companies to utilize the drug approval process to include new uses in the product label. However, the court said FDA could have used less restrictive approaches to accomplish its goals. In this case, Amarin's proposed statements and disclaimers, with possible tweaks to explain the status and limitations of the research, might have made the statement not misleading. As a result, the court enjoined FDA from considering the off-label communications to be evidence of misbranding.

- The District Court rejected FDA's position that, for prescription drugs, any such communications should be supported by "significant scientific agreement."

- The decision made clear that false or misleading statements are not protected speech. In addition, the government could prosecute non-communicative, unlawful promotional activities (e.g., rewarding doctors for prescribing a product for off-label uses). The court said that Caronia protects off-label promotion "where it wholly consists of truthful and non-misleading speech."

- Because the agency can take enforcement action against misleading statements (e.g., one-sided or incomplete), companies should consider voluntary restrictions or appropriate qualifiers. The Court offered 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 and 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. Reasonable minds may differ over whether a given statement is misleading in context; and developments in science or medicine may make a once-benign statement misleading. Prior 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.

III. AGG Observations

- The case is, of course, notable for limiting FDA's ability to restrict off-label promotion. The decision is clearly a win for industry to communicate proactively truthful and non-misleading information about clinical trial results. This goes beyond FDA's 2014 draft guidance on disseminating off-label communications, which favors more independently-produced information. We have prepared a Bulletin[3] on that draft guidance.

- However, at this time, the case has applicability only to those jurisdictions in the Second Circuit (covering Connecticut, New York, and Vermont).

- It is not clear whether FDA will appeal the court's decision. It might choose not to appeal for fear of another loss, and it would be appealing to the Second Circuit, i.e., the same circuit that decided Caronia, which was the primary basis for this court's decision. However, FDA might be concerned that, without appealing, it will implicitly allow manufacturers to distribute off-label information, thereby circumventing the regulatory process. That is, the agency might be fearful of the public policy ramifications if it does not appeal.

- It is noteworthy that FDA has lost other First Amendment cases (e.g., dietary supplements, pharmacy compounding). So, with this loss, we can expect FDA to act gingerly and prosecute those cases only where the information is clearly false or misleading.

- There remains the question of who decides what is truthful and not misleading: the company, FDA, or the courts. Without an objective definition of the "truthful and non-misleading" standard, it appears to remain a subjective standard that is not likely to be resolved anytime soon.

- Related to the aforementioned issue, the case focused on dissemination to healthcare professionals and not direct-to-consumer (DTC). While the court did not address DTC specifically, and perhaps the analysis might remain the same, it will be interesting to see whether FDA will adopt a more paternalistic, conservative approach to protect patients, which could result in a more narrow definition of "truthful and non-misleading."

- Separate from FDA enforcement, companies should also consider other regulatory agencies' scrutiny; the Justice Department or State Attorneys General might consider action. In addition, product liability claims arising out of injuries due to off-label uses are not negated by the court decision.

- Some analyses of the decision have called it "precedent-setting." We will leave such characterizations to others, particularly because of its potential limited application (e.g., preliminary injunctive relief, Second Circuit) and FDA's apparent reluctance to pick a fight. The agency has indicated it intends to hold a public meeting on off-label promotion. However, the case is important, because it shows, yet again, that FDA is not invincible, and the First Amendment presents a significant limitation of an attempt by FDA to curtain truthful and non-misleading promotion. One court at least has found that off-label promotion may be protected by the First Amendment. This case has left a bad odor for FDA or, in keeping with the fish theme, "it stinks" (for FDA, not the industry).

3 http://www.agg.com/files/Publication/cfd18246-b514-4d17-9557-cf3c69e87cd7/Presentation/PublicationAttachment/68b82e32-8125-46a4-9f04-061b8fc0d2e6/Minsk-Nduom-What-We-Meant-To-Say-FDA-Provides-A-Recent-Guidance-On-Dissemination-o.pdf

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