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Amarin Case Tests Limits of FDA Regulation of Off-Label Promotion

By David C. Gibbons and Jeffrey N. Wasserstein

In May 2015, Amarin Pharma, Inc. (Amarin or the Company) filed a complaint against the U.S. Food and Drug Administration (FDA) in U.S. District Court for the Southern District of New York seeking declaratory and injunctive relief that would prevent FDA from taking action against the Company for disseminating off-label information relating to its hypertriglyceridemia drug, Vascepa®.[1] Shortly after filings its complaint, Amarin filed a motion for preliminary injunction to prevent the same. On August 7, 2015, the court granted Amarin's request for preliminary relief. This case posed the most significant test regarding FDA regulation of a pharmaceutical manufacturer's purported off-label speech since *Caronia*.[2] Also of interest is the posture in this case, where a manufacturer has proactively filed a lawsuit to protect planned promotional statements about its product rather than raising First Amendment free speech protection as a defense to prosecution related to alleged off-label promotion.

Vascepa, icosapent ethyl, is an ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (EPA), obtained from fish oil.[3] FDA approved Amarin's New Drug Application (NDA) for Vascepa for the reduction of triglyceride levels in adults

David C. Gibbons is an associate at Hyman, Phelps & McNamara, PC. His practice focuses on the pharmaceutical and biotechnology industry where he advises on advertising and promotion, product development, and regulatory compliance issues.

Jeffrey N. Wasserstein, Director, Hyman, Phelps & McNamara, PC, focuses his practice on the promotion of therapeutic products, including pharmaceutical, biotech, in vitro diagnostics and medical device companies.

with severe hypertriglyceridemia (triglycerides ≥ 500mg/dL) in 2012.

Context is critical. In order to understand the basis for Amarin's First Amendment claims concerning its promotion of Vascepa, one must first delve into the story behind Vascepa's initial approval, the Company's subsequent plans for the development and marketing of the product, and FDA's reactions and responses to the same.

History of Vascepa's Initial Approval and Amarin's Subsequent Interaction with FDA

Vascepa's approval was based on a single phase 3 clinical trial—the MARINE trial—conducted in patients with "very high" triglycerides (≥ 500 mg/dL).[4] Vascepa's approved indication carries with it two limitations of its use. Specifically, the indication statement in Vascepa's label states that the effect of Vascepa on the risks for pancreatitis and cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined.[5] Following the completion of MARINE, Amarin planned to obtain approval for use of Vascepa in patients with "persistently high" triglycerides (≥ 200 and ≤ 500 mg/dL).[6]

As the Company had done with MARINE, 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 a Special Protocol Assessment (SPA) agreement prior to study initiation.[7] Generally, an SPA indicates FDA agreement that the study will support approval of the product's marketing application if it is conducted according to the protocol and it achieves its agreed-upon objectives. In the ANCHOR SPA agreement, FDA agreed with the design and planned analysis of the ANCHOR trial as "adequately address[ing] the objectives necessary to support a regulatory submission."[8] Amarin had also planned to conduct a cardiovascular outcomes trial to examine whether Vascepa would be effective in reducing major adverse cardiac events—the REDUCE-IT trial, which is expected to be completed in 2017 with results available in 2018.[9] As part of the ANCHOR SPA, FDA required, and Amarin agreed, that the REDUCE-IT trial would have at least 50% of the planned enrollment completed before FDA would accept Amarin's supplemental new drug application (sNDA) for use of Vascepa in patients with persistently high triglycerides.[10]

The ANCHOR study results showed statistically significant reductions in triglyceride levels with Vascepa, compared to placebo, achieving its primary endpoint as agreed with FDA.[11] Vascepa also achieved statistically significant reductions in other lipid parameters and did not raise low-density lipoprotein cholesterol (LDL-c or bad cholesterol).[12] Based on these results, combined with the enrollment of the REDUCE-IT trial, Amarin believed it had satisfied all of FDA's requirements to obtain approval of Vascepa for persistently high triglycerides, as the Company had agreed with FDA in the SPA agreement.[13] Thus, Amarin submitted its sNDA for the persistently high triglyceride indication in February 2013[14] and anticipated a timely approval for this additional indication.[15]

Instead, FDA convened an advisory committee during which the agency called into question the clinical validity of the agreed upon ANCHOR endpoint of triglyceride lowering and whether it would translate into reduced major adverse cardiovascular events—a question that was intended to be answered by the ongoing REDUCE-IT trial. Based in part on the advisory committee vote, FDA rescinded the ANCHOR SPA[16] and eventually issued a Complete Response Letter to Amarin. In a securities filing, Amarin stated that it "had proposed to FDA multiple alternative indications, data presentations, disclaimers and other regulatory pathways to approval under the sNDA, but FDA determined not to approve [the] label expansion reflecting the ANCHOR clinical trial efficacy data . . . ."[17] Amarin stated that FDA concluded the Complete Response Letter "with a warning 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")]'"[18]

Promotion of Vascepa for Persistently High Triglycerides: FDA Regulation and Amarin's Proactive Challenge

FDA has, historically, heavily regulated the promotion of prescription drug products based on the authority granted to it under the FDCA. First, FDA has relied on the FDCA's provision that prohibits the misbranding of drug products.[19] A drug is misbranded if its labeling is "false or misleading in

any particular."[20] The FDCA defines labeling as "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article."[21] The term "accompanying" has been interpreted broadly. The U.S. Supreme Court held that "[o]ne article or thing is accompanied by another when it supplements or explains it . . . No physical attachment one to the other is necessary. It is the textual relationship that is significant."[22]

Second, the FDCA defines a drug, in part, based on its intended use.[23] Intended use means:

> [T]he objective intent of the persons legally responsible for the labeling of drugs. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives.[24]

The "intended use" provision has been used by FDA to assert jurisdiction over manufacturers and their products based on the content of product-specific communications, even when FDA's jurisdiction over the communications themselves is questionable.[25] Where the intended use of a prescription drug, as established by the objective intent of legally-responsible persons, differs from the use approved by FDA as indicated in the product's approved labeling, FDA has asserted that the product is a "new drug" for which FDA approval is required.[26] Placing a new drug in interstate commerce without FDA approval is a violation of the FDCA.[27]

Furthermore, any drug is misbranded according to the FDCA if its labeling does not bear "adequate directions for use."[28] FDA regulations define adequate directions for use as those under which a lay person can "use a drug safely and for the purposes for which it was intended."[29] Labeling for prescription drugs, which are not safe for use except under supervision by a licensed health care provider, cannot bear adequate directions for use by a lay person, but can be subject to an exemption from this statutory requirement.[30] FDA regulations require that, to satisfy the conditions for this exemption, prescription drugs must have labeling that contains "adequate information for [] use . . . under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all conditions for which it is advertised or represented."[31] Such labeling must be authorized under an approved NDA.[32]

Thus, without an approved sNDA for the persistently high triglyceride indication, Amarin did not have FDA sanction to promote Vascepa for that indication. Amarin stated in its complaint that it would be prevented from speaking about the successful ANCHOR trial or any of the study's results.[33]

Amarin went on the offensive. In light of the aforementioned regulatory scheme used by FDA to tightly control the promotion of prescription drug products, Amarin's strategy was to obtain protection for its proposed statements and claims as truthful, non-misleading commercial speech. Amarin filed a civil complaint against FDA seeking declaratory and injunctive relief that would prevent FDA prosecution against the Company for truthful, non-misleading speech concerning Vascepa and certain off-label promotional content regarding Vascepa that the Company proposed to disseminate, stating:

> [I]t has now been over four years since April 2011 when Amarin demonstrated the effect of Vascepa® on patients with persistently high triglycerides and Amarin still cannot freely communicate the results of the ANCHOR trial in a truthful and non-misleading manner without fear of criminal prosecution and civil liability due to FDA's regulatory regime.[34]

Interestingly, Amarin put before the court examples of the types of truthful and non-misleading speech the Company had in mind. Specifically, Amarin stated, in its complaint, that the Company sought to disseminate the following information to health care providers:

- Research showing that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease;
- The ANCHOR study primary efficacy data demonstrating that Vascepa lowered triglycerides in patients with persistently high triglyceride levels not controlled by diet and statin therapy;
- Positive secondary endpoint data from the ANCHOR trial showing that Vascepa reduced non-high density lipoprotein cholesterol, Apolipoprotein B, very-low-density lipoprotein cholesterol, and total cholesterol levels from baseline relative to placebo in patients with persistently high triglyceride levels not controlled by diet and statin therapy; and

- The reduction in triglycerides observed with Vascepa was not associated with elevations in low-density lipoprotein cholesterol, or bad cholesterol, relative to placebo.[35]

In addition, Amarin also wanted to provide health care professionals with "peer-reviewed scientific publications relevant to the potential effect of EPA on the reduction of the risk of coronary heart disease . . . ."[36]

Amarin further stated in its complaint that, in order to ensure that its promotional materials and statements were not misleading, the Company would "contemporaneously disclose" statements that FDA has not approved Vascepa to reduce the risk of coronary heart disease or for the treatment of statin-treated patients with mixed dyslipidemia and persistently high triglyceride levels; the effect of Vascepa on the risk of cardiovascular mortality and morbidity has not been determined; the REDUCE-IT trial was underway; and a disclaimer that Vascepa may not be eligible for reimbursement under government health care programs, for coronary heart disease risk reduction or for treatment of statin-treated patients with mixed dyslipidemia and persistently high triglycerides.[37]

Amarin also raised a unique dichotomy it faced in the promotion of Vascepa given the apparent inconsistent approach taken by FDA related to EPA-containing products. Amarin noted, in its complaint, that dietary supplement manufacturers who market products containing EPA are permitted by FDA to make a "qualified health claim" that "[s]upportive but not conclusive research shows that consumption of EPA and [Docosahexaenoic Acid] DHA omega-3 fatty acids may reduce the risk of coronary heart disease."[38] Amarin has argued that its inability, under FDA's regulatory scheme, to make similar statements about Vascepa is misleading to health care professionals because they cannot be informed about Vascepa's use in a broader patient population, even though Vascepa contains the same ingredient, EPA, but is of pharmaceutical-grade quality and has clinically proven benefits.[39]

Raising First Amendment Defenses to FDA Regulation of Off-Label Promotion

There is little dispute today that a pharmaceutical manufacturer's off-label promotion constitutes commercial speech. While not expressly proposing a commercial transaction, which generally distinguishes commercial speech from pure speech, the economic interests of the speaker disseminating promotional statements or materials are sufficient to classify such speech as commercial, and thereby subject it to lesser constitutional protection than other forms of speech.

Commercial speech cases under the First Amendment are evaluated according to the principles articulated in *Central Hudson*.[40] Under *Central Hudson*, the government may suppress commercial speech that does not "accurately inform the public about lawful activity" and it "may ban forms of communication more likely to deceive the public than to inform it."[41] However, in *Central Hudson*, the Supreme Court held that government restrictions on truthful and non-misleading commercial speech must directly serve a substantial government interest and such restrictions may be no more extensive than necessary to serve that interest.[42] The Court said that "excessive restrictions cannot survive" where more limited restrictions can serve the government's interest.[43] The Supreme Court has struck down content- and speaker-based restrictions in the context of pharmaceutical marketing where it found those restrictions were not proportional to the government's interests.[44] Speaker- or content-based restrictions on speech to advance the government's policy objectives where it disfavors the message of the speaker does not withstand constitutional scrutiny.[45] In *Sorrell*, a state government's restraint on pharmaceutical manufacturers from influencing a health care provider's prescribing choices was held unconstitutional.[46] Also, FDA-imposed restrictions on off-label promotion, in and of itself, have been struck down.[47]

To get around the problem posed by *Central Hudson*, FDA has argued that its regulations, and enforcement thereof, do not restrict *speech*, but rather are aimed at *conduct* properly regulated by FDA pursuant to the FDCA. In a recent high-profile First Amendment case, *United States v. Caronia*, the government argued that it had not prosecuted the speaker, a pharmaceutical sales representative, for his speech, but merely used his speech as evidence of the intent to misbrand the drug (as defined by FDCA) and of its off-label use; therefore the First Amendment was not implicated by its restrictions on off-label promotion.[48] Although it is well-settled law that the evidentiary use of speech is constitutionally permissible, the line between the government's permissible

evidentiary use of commercial speech and impermissible restrictions on commercial speech can be difficult to draw. The Supreme Court held in *Wisconsin v. Mitchell* that the "evidentiary use of speech to establish the elements of a crime or to prove motive or intent" does not run afoul of the First Amendment.[49] Under this precedent, FDA can properly use speech as evidence of the intended use of a product, as it relates to whether such product can be classified as a drug under the FDCA.[50] In contrast, The Second Circuit held, in *Caronia*, that the FDCA does not criminalize truthful and non-misleading off-label promotion of a drug product.[51] The court found that Caronia's speech "was itself the proscribed conduct" and rejected the government's arguments to the contrary, while leaving the door open to the possibility that evidence of intent could be argued successfully.[52]

Amarin argued that FDA, by way of its regulatory scheme concerning off-label promotion, criminalized its truthful and non-misleading commercial speech regarding off-label uses, which are otherwise protected by the First Amendment. Amarin stated, in its complaint, that FDA has created a "web of regulations" that conflict with the FDCA and "criminalize virtually all manufacturer communication to healthcare professionals about the off-label use" of its products.[53] Amarin argued that FDA's "expansive interpretation" of the labeling provisions of the FDCA "effectively captures all manufacturer speech concerning off-label uses . . . regardless of how truthful, non-misleading, and beneficial to the medical community the speech may be . . . ."[54] Similar to arguments made in successful First Amendment challenges to FDA regulation of pharmaceutical promotion, the Company asserted that FDA regulations, generally and as applied to Amarin, place a ban on truthful and non-misleading commercial speech, which does not withstand scrutiny under the First Amendment. Such arguments have been successful in challenging FDA's restrictions on the dissemination of information concerning unapproved uses. Over a decade prior to *Caronia*, the Washington Legal Foundation challenged FDA's enforcement of its guidance documents as well as provisions in the Food and Drug Administration Modernization Act of 1997[55] restricting the dissemination of medical and scientific journal articles

and medical reference textbooks and also limiting pharmaceutical manufacturer support for continuing medical education courses.[56]

Perhaps in the face of another potential blow to its regulation of off-label promotion, FDA took a new tack in the Amarin case. Prior to submitting its response to Amarin's motion for preliminary injunction, FDA attempted to moot Amarin's case in a letter provided to Amarin and filed with the court. In its communication to Amarin, FDA stated that it "does not intend to object to Amarin's proposed communications" if made in a truthful, non-misleading, and balanced manner.[57] Essentially, FDA agreed that many of Amarin's proposed communications were consistent with FDA policy on dissemination of reprints and other medical communications.

FDA has, in recent years, developed, released, and updated nonbinding, draft guidance documents expressing the agency's position on when and how pharmaceutical and medical device manufacturers can disseminate information concerning off-label uses of their products. FDA first released its guidance concerning the distribution of scientific and medical publications regarding unapproved uses in 2009 and updated it in 2014.[58] In this revised draft guidance document, FDA provides a number of recommendations on how journal articles, reference textbooks, and clinical practice guidelines should be distributed when they concern the safety or effectiveness of an unapproved use of an approved drug.[59] In its draft guidance to pharmaceutical and medical device manufacturers on responding to unsolicited requests for off-label information, FDA states that it has "long taken the position that firms can respond to unsolicited requests for information about FDA-regulated medical products by providing *truthful, balanced, non-misleading, and non-promotional* scientific or medical information that is responsive to the specific request . . . ."[60] FDA's policy, as expressed in these draft guidance documents, has been to limit communication by manufacturers concerning unapproved uses of their approved products and to condition its exercise of enforcement discretion to bring an action under the FDCA on compliance with its recommendations in the guidance documents.[61]

FDA also agreed that Amarin's proposed contemporaneous disclosures regarding Vascepa's regulatory status, approval limitations, and the status of the REDUCE-IT trial would help to balance Amarin's presentation of Vascepa efficacy data in patients with persistently high triglycerides.[62] However, FDA required Amarin to make additional disclosures, including providing the current FDA-approved prescribing information, limiting the dissemination of such information to "educational or scientific settings," and not distributing the proposed materials with marketing materials or by individuals without the "appropriate background or training" to discuss such information (e.g., sales representatives).[63]

FDA continued to reject Amarin's ability to make claims similar to the qualified health claims of EPA-containing dietary supplements. Following the D.C. Circuit's ruling in *Pearson v. Shalala*, makers of dietary supplements were permitted to make certain health claims that were not supported by significant scientific agreement when accompanied by specific disclaimers or qualifications to correct the inherent misleadingness of such claims.[64] However, health- or disease-related dietary supplement claims, in general, are subject to a different statutory and regulatory scheme and held to a lower level of required scientific evidence than are claims associated with prescription drugs.[65] In refuting Amarin's ability to make qualified health claims for Vascepa, FDA justified its exercise of enforcement discretion regarding these claims in the dietary supplement context, while holding to the statutory standard of substantial evidence for cardioprotective claims associated with Vascepa, even when such claims were qualified.[66]

Following its attempt to narrow the scope of the dispute, FDA responded to Amarin's motion for preliminary injunction by arguing that: (1) even post-*Caronia*, the government can use off-label speech as evidence of intent to promote a product for an unapproved use and that this evidentiary use does not implicate *Central Hudson* since it is not a restriction on speech itself;[67] (2) the government can prohibit false or misleading statements, which would include summaries of studies that are biased or omit material information, such as the idea that "drug-induced decreases in triglyceride levels lead to a reduction in the risk of cardiovascular events in patients on statin therapy";[68] and (3) even if the challenged provisions are found to be restrictive of speech, rather than merely used for their evidentiary value, they nonetheless meet the *Central Hudson* test for restrictions on commercial speech, pointing to the substantial

government interest in protecting the public with regard to drug safety through the new drug approval process.[69] Notably, with regard to this last point, FDA argued that Congress required FDA to review the safety and effectiveness of "*each* intended use . . . *before* the product is introduced into interstate commerce for that use," and that this substantial governmental interest is directly advanced by FDA regulation of speech related to unapproved uses of FDA-approved products.[70]

The Court's Grant of Preliminary Relief to Amarin

On August 7, 2015, the court rejected FDA's arguments and granted preliminary relief to Amarin. The court first determined that Amarin's proactive, or "pre-enforcement," challenge to FDA's regulation of its speech presented a live case or controversy, ripe for adjudication. In order to meet this threshold requirement in First Amendment cases, a plaintiff must allege a "real and imminent fear" of prosecution based on the statute as well as prosecution history under the statute.[71] The court found that Amarin had satisfied this requirement given FDA's threat of bringing a misbranding action against the Company as FDA related in the Complete Response Letter it issued to Amarin regarding Vascepa's marketing application for use in patients with persistently high triglycerides.[72] Applying the principles articulated by the Second Circuit in *Caronia*, the court next addressed Amarin's request for relief, for specific statements and also generally.[73]

In granting Amarin's statement-specific request for relief, the court evaluated and ruled on each of Amarin's proposed off-label statements concerning Vascepa along with FDA's responses to the same. The court pointed to the "extensive regulatory history" of Vascepa that made it possible for the court to establish the truthfulness of Amarin's proposed statements concerning off-label use of Vascepa.[74] The court held that Amarin's dissemination of a summary of the ANCHOR study results, the reprints regarding the potential cardioprotective effect of EPA, and Amarin's proposed communication of detailed ANCHOR study results, when presented with certain disclosures, were neither false nor misleading.[75] The court went on to consider other "contested disclosures" that Amarin proposed to make contemporaneously with certain off-label statements concerning Vascepa. Here, the court proceeded to provide a revised disclosure and held that its own revision was truthful and non-misleading, but noted that Amarin and FDA were "at liberty to pursue further refinements . . . ."[76]

Finally, the court considered Amarin's proposed cardiovascular disease claim, which FDA had rejected in both its letter to Amarin and in its brief on the motion before the court.[77] The court held that Amarin's cardiovascular disease claim, given its qualified nature along with FDA's acceptance of its use for dietary supplements, was truthful and non-misleading and could not expose Amarin to liability for misbranding.[78] To FDA's concerns that doctors may derive errant conclusions from the claim or misunderstand the uncertainty regarding the effect of triglyceride lowering on cardiovascular disease, the court said, "[d]octors can grasp that point" and are not likely to confuse the language indicating a lack of certainty.[79]

Having upheld Amarin's proposed statements, as modified in the court's opinion, the court noted that circumstances could change its "approval" of those statements. The court stated:

> [T]he 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.[80]

In addition to its rulings on the specific statements proposed by Amarin, the court also addressed Amarin's general request for First Amendment protection for truthful and non-misleading speech concerning unapproved uses of an approved drug. The court applied the principles of law in *Caronia* to which it was bound by the Second Circuit, although this court amplified *Caronia's* central holding. Specifically, the court rejected FDA's position that the Second Circuit's holding in *Caronia* was fact-specific and not broadly applicable, finding that *Caronia's* holding was "a definitive one of statutory construction."[81]

FDA argued that it could lawfully use speech to establish both the

intent and the act of misbranding,[82] a refinement of its long-standing position that it would use Amarin's speech as evidence of misbranding, which does not prosecute the speech itself. FDA stated that it "may bring a misbranding action where Amarin's only acts constituting promotion of Vascepa for an off-label use are its truthful and non-misleading statements about that use, provided that these acts support an inference that Amarin intended to promote that off-label use."[83] FDA went on to argue that "it does not read Caronia to preclude a misbranding action where the acts to promote off-label use consist solely of truthful and non-misleading speech, provided that the evidence also shows that the drug had been introduced into interstate commerce and that the FDA had not approved it as safe and effective for the off-label use."[84] To bolster its point, FDA likened misbranding to other crimes where speech constitutes the act, such as jury tampering, blackmail, and insider trading.[85]

The court rejected FDA's interpretation of *Caronia* and stated that its "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."[86] The court also rejected FDA's position that criminal misbranding is analogous to jury tampering, blackmail, or insider trading. In the end, the court's opinion in *Amarin* appears to close the door on FDA's line of reasoning by holding, "[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."[87]

FDA made three counter-arguments, none of which persuaded the court. First, FDA argued that Amarin's proactive challenge constituted a "frontal assault" on FDA's new drug approval process to which Congress gave effect in the 1962 amendments to the FDCA.[88] Second, FDA argued that Caronia's holding should only apply to certain types of truthful and non-misleading off-label promotion, consistent with FDA policy as expressed in its guidance documents. For example, off-label promotion in the context of a solicited request for such information is permissible while the unsolicited provision of such information is not.[89] Finally, FDA reprised its argument that *Caronia* does not prohibit the use of speech as evidence of intent to promote a drug for off-label uses.[90] The court rejected each of FDA's counterarguments in turn. The court stated that the 1962 amendments predate First Amendment jurisprudence protecting commercial speech[91] and those cases finding that pharmaceutical speech qualifies for such protection.[92] The court reiterated that *Caronia* applies "across-the-board to all truthful and non-misleading promotional speech."[93] As to FDA's argument that *Caronia* does not preclude the use of speech as evidence of intent, the court found this argument "beside the point" since Amarin's lawsuit concerned only the situation in which FDA prosecuted the Company for misbranding based on its truthful and non-misleading speech.[94] The court stated that the "construction [of the misbranding provision in the FDCA in accord with *Caronia*] applies no matter how obvious it was that the speaker's motivation was to promote such off-label use."[95] The court concluded by stating: "[i]n the end, however, if the speech at issue is found truthful and non-misleading, under *Caronia*, it may not serve as the basis for a misbranding action."[96]

Conclusion

Amarin represents a significant decision for the pharmaceutical industry and further erodes FDA's ability to tightly control off-label promotion. However, there are important limitations to the court's decision in *Amarin* that must frame its applicability. While the court went deeply into the merits of the case, the opinion reflects a ruling only on Amarin's motion for preliminary injunction. The opinion provides, however, a great deal of insight into the court's thinking on the matter and its eventual ruling, should the case proceed. The government has a number of options at this point, one of which is to file an interlocutory appeal. The government's next move may have a significant impact on this ruling.

While this ruling in *Amarin*, coupled with the Second Circuit's decision in *Caronia*, appear to foreclose FDA from prosecuting a pharmaceutical manufacturer for truthful and non-misleading off-label promotion, it is important to note that this precedent has only been established in the Second Circuit to date and there is considerable uncertainty as to how sister circuits would rule if faced with the same set of facts. The venue for future litigation concerning off-label promotion, whether initiated by a pharmaceutical manufacturer or FDA, will be a matter of strategic importance for future litigants, whether on the side of industry or the government.

The *Amarin* victory was won with a particular set of facts that favored the Company. Amarin had a completed clinical trial on the specific use it desired to promote, the design and analysis of which were agreed upon prospectively by FDA. Furthermore, the Company had, in hand, peer-reviewed medical journal articles discussing the active ingredient in Vascepa. Importantly, the speech at issue was only directed at healthcare providers, not at the lay public, which limits the ruling's applicability to consumer-directed advertising. The unapproved use that Amarin wanted to discuss with healthcare providers was very close to the approved indication—both concerned triglyceride-lowering, with the difference being the patient population for which the benefit was sought. Finally, Amarin was cognizant of and agreed to disclosures that communicated essential contextual information that, in addition to the truthful scientific information, rendered its promotion non-misleading, according to the court's analysis.

Also, the limitation of First Amendment protection to truthful and non-misleading speech is not to be missed. Truthful information can mislead, depending on the context and the totality of information presented. Indeed, the court gave very practical advice to manufacturers when it said:

> 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.[97]

This is certainly not the end of the story. We not only await the parties' next moves in the *Amarin* case but we are also eager to see FDA's approach to working with industry stakeholders and formulating policy on the dissemination of information regarding unapproved uses of approved drugs.

On August 28, 2015, the parties jointly requested the proceedings be stayed until October 30 to explore settlement of the matter.

1. Amarin Pharma, Inc. v. FDA, No. 15-3588 (S.D.N.Y. 2015). Four physicians who prescribe Vascepa for both on- and off-label uses joined Amarin as co-plaintiffs. *See* Complaint at 8-9, Amarin Pharma, Inc. v. FDA, No. 15-3588 (S.D.N.Y. May 7, 2015) (hereinafter Compl.).
2. *See* United States v. Caronia, 703 F.3d 149 (2d Cir. 2012).
3. Vascepa (icosapent ethyl) Label, NDA 202057 (June 23, 2015).
4. Compl. at 17.
5. Vascepa (icosapent ethyl) Label, NDA 202057 (July 26, 2012). These limitations remain in Vascepa's currently approved U.S. label. *See* Vascepa (icosapent ethyl) Label, NDA 202057 (June 23, 2015).
6. Compl. at 17-18.
7. Vascepa (icosapent ethyl), Special Protocol Assessment – Agreement, IND 102457 (July 6, 2009) (the ANCHOR SPA); the ANCHOR SPA was amended in May 2010, but there was no change to FDA's agreement on the design, execution, or analysis of the ANCHOR study. Compl. at 21-22. The protocol was amended to change the threshold for the minimum TRIGLYCERIDE level in the study from 150 mg/dL to 200 mg/dL. FDA Endocrinologic and Metabolic Drugs Advisory Committee, Tr. at 75, (Oct. 16, 2013) (FDA Ad Com).
8. ANCHOR SPA at 1.
9. Compl. at 21.
10. *Id.*
11. *Id.* at 22.
12. *Id.*
13. *Id.*
14. Press Release, Amarin, Amarin Announces Submission of Supplemental New Drug Application (sNDA) for Vascepa® for the Treatment of Patients with High Triglycerides with Mixed Dyslipidemia: Submission for Indication Studied in the ANCHOR Phase 3 Clinical Trial under Special Protocol Assessment Agreement with FDA (Feb. 26, 2013), http://investor.amarincorp.com/releasedetail.cfm?ReleaseID=743096.
15. Compl. at 22.
16. Vascepa (icosapent ethyl), Special Protocol Assessment – Rescind Agreement, IND 102457 (Oct. 29, 2013) (SPA Rescission).
17. Amarin, Form 8-K, Sec. 8.01 (Apr. 27, 2015), http://www.sec.gov/Archives/edgar/data/897448/000119312515150702/d916310d8k.htm.
18. Compl. at 27.
19. FDCA § 301(b).
20. *Id.* § 502(a).
21. *Id.* § 201(m).
22. Kordel v. United States, 335 U.S. 345, 350 (1948).
23. *See* FDCA § 201(g)(1).
24. 21 C.F.R. § 201.128.
25. William W. Vodra et al., *The Food and Drug Administration's Evolving Regulation of Press Releases: Limits and Challenges*, 61 Food & Drug L.J. 623, 627 (2006).
26. *Id.*
27. FDCA § 505(a); *see also id.* § 201(p).
28. *Id.* § 502(f).
29. 21 C.F.R. § 201.5.
30. FDCA §§ 503(b), 502(f).
31. 21 C.F.R. § 201.100(d)(1).
32. *Id.* § 201.100(d); *see also* Memorandum of Law in Opposition to Plaintiff's Motion for Preliminary Injunction at 13, n.4, *Amarin*, No. 15-3588 (S.D.N.Y. June 23, 2015) (hereinafter Memo in Opp.).
33. Compl. at 28.
34. *Id.*
35. Compl. at 41-42.
36. *Id.* at 42.
37. *Id.* at 42-43.

38. *Id.* at 34, 41.
39. *Id.* at 39.
40. *See* Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n, 447 U.S. 557, 561-63 (1980); *see also* Krista Hessler Carver, *A Global View of the First Amendment Constraints on FDA*, 63 Food & Drug L.J. 151, 169-70, 209-10 (2008).
41. *Cent. Hudson*, 447 U.S. at 563.
42. *Id.* at 566.
43. *Id.* at 564.
44. Sorrell v. IMS Health, Inc., 131 S.Ct. 2653, 2672 (2011).
45. *Id.* at 2670.
46. *See id.* at 2670-71.
47. Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51 (D.D.C. 1998).
48. *Caronia*, 703 F.3d 149 at 160-61 (2d Cir. 2012).
49. Wisconsin v. Mitchell, 508 U.S. 476, 489 (1993).
50. Whitaker v. Thompson, 353 F.3d 947, 953 (D.C. Cir. 2004)
51. *Caronia*, 703 F.3d at 162.
52. *Id.* at 161.
53. Compl. at 47.
54. *Id.* at 48 (emphasis omitted).
55. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997).
56. *See* Wash. Legal Found. v. Henney, 202 F.3d 331, 333-334 (D.C. Cir. 2000).
57. Exhibit A, Letter from Ellen London to Judge Paul A. Engelmayer at 6, Amarin Pharma, Inc. v. FDA, No. 15-3588 (S.D.N.Y. June 8, 2015).
58. FDA, Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices: Guidance for Industry and Food and Drug Administration Staff(Reprint Guidance), 2 (Feb. 2014).
59. *See id.* at 7-17.
60. FDA, Responding to Unsolicited Requests for Off-Label Information about Prescription Drugs and Medical Devices: Guidance for Industry and Food and Drug Administration Staff (Off-Label Requests Guidance), 6 (Dec. 2011) (emphasis added).
61. Reprint Guidance at 6; Off-Label Requests Guidance at 3.
62. Letter from Ellen London to Judge Paul A. Engelmayer at 7.
63. *Id.* at 9.
64. 164 F.3d 650, 652 (D.C. Cir. 1999); *see also* Whitaker v. Thompson, 248 F. Supp. 2d 1, 10-11 (D.D.C. 2002).
65. FDCA § 403(r)(3)(B).
66. Letter from Ellen London to Judge Paul A. Engelmayer at 8-9.
67. Memo. in Opp. at 18, 22.
68. *Id.* at 23.
69. *Id.* at 27 (citing *Caronia*, 703 F.3d at 166 and Thompson v. Western States Med. Ctr., 535 U.S. 357, 369 (2002)).
70. Memo. in Opp. at 27-28.
71. Opinion and Order, Amarin Pharma, Inc. v. FDA, No. 15-3588, 39-40 (S.D.N.Y. Aug. 7, 2015) (opinion and order granting preliminary injunction) (hereinafter Amarin Order).
72. *Id.* at 40.
73. *Id.* at 28.
74. *Id.* at 54.
75. *Id.* at 55, 57.
76. *Id.* at 60.
77. *See* Letter from Ellen London to Judge Paul A. Engelmayer at 10; Memo. in Opp. at 8-9.
78. Amarin Order at 64.
79. *Id.* at 65.
80. *Id.* at 66.
81. *Id.*at 48.
82. *Id.* at 44.
83. *Id.*
84. *Id.* at 44-45.
85. *Id.* at 45.
86. *Id.*
87. *Id.* at 49.
88. *Id.*
89. *Id.* at 50.
90. *Id.* at 51.
91. *See, e.g., Cent. Hudson.*
92. *See Sorrell.*
93. Amarin Order at 51.
94. *Id.*
95. *Id.*
96. *Id.*at 53.
97. *Id.*