The Future of Government Regulation, Enforcement of Off-Label Promotion

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Three years ago, in *United States v. Caronia*, the U.S. Court of Appeals for the Second Circuit held that the Federal Food, Drug and Cosmetic Act (FDCA) neither prohibits nor criminalizes truthful, nonmisleading speech that may constitute off-label promotion of prescription drugs approved by the Food and Drug Administration (FDA). Hoping to narrow the impact of this ruling, the Department of Justice (DOJ) and FDA chose not to appeal *Caronia*, publicly asserting that the ruling would not impact regulatory and enforcement efforts regarding off-label promotion.

Recently, the consequences of the failure to appeal *Caronia* became apparent. On August 7, 2015, the U.S. District Court for the Southern District of New York granted a preliminary injunction in favor of Amarin Pharma, Inc. and several physician plaintiffs, permitting affirmative off-label promotional activities in connection with the company's already-approved drug, Vascepa. (Click here to view the opinion.) And a second pharmaceutical company, Pacira Pharmaceuticals, Inc., along with two physicians, adopted Amarin's playbook and filed suit against FDA in the Southern District of New York, seeking, *inter alia*, a ruling that FDA's regulation on prescription drug advertising, 21 C.F.R. § 202.1, violates the First Amendment.

When evaluated in the context of DOJ's decision *not* to appeal the *Caronia* decision, the *Amarin* decision, its procedural history and the subsequent developments — including Pacira's suit — have profound implications for FDA-regulated companies. We explore some of those implications for pharmaceutical and medical device manufacturers and their counsel in the following review.

Summary

- The government's decision not to appeal *Caronia* created a fertile forum for Amarin — and now Pacira — to challenge FDA's enforcement policies. In granting Amarin's motion for preliminary relief, the district court acted to "ensure [Amarin's] ability to engage in truthful and nonmisleading speech free from the threat of a misbranding action." Unless and until other circuits reject the *Caronia* holding, *Amarin* substantially limits FDA's ability to prohibit truthful and nonmisleading speech outside a product's approved labeling. Moreover, *Amarin* is likely to have significant persuasive impact on Pacira's case, which was brought in the same court.
- To cabin *Caronia*'s holding, the government in *Amarin* sought to limit its holding to the facts and circumstances of that case — "a ticket good for one day only." The district court "firm[ly]" disagreed and "refute[d]" the notion that the Second Circuit's ruling was limited to the facts of *Caronia*. The *Amarin* district court concluded that "[w]here the speech at issue consists of truthful and nonmisleading 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."
- The *Amarin* district court further rejected the government's stated interest in "deter[ing] manufacturers from evading the FDA's review process for additional uses of approved drugs." It noted that *Caronia* "identified alternative, and less speech-restrictive, means for the FDA to achieve its objectives," yet the government never sought rehearing or petitioned for *certiorari* in *Caronia*.
- The district court declined to limit *Caronia*'s holding to only reactive statements made by nonsales personnel, stating "[i]ndeed, the speech on which the *Caronia* prosecution itself was based involved the very types of statements promoting off-label use that the FDA most disfavors: proactive oral statements to a doctor by a manufacturer's sales representative."

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- The *Pacira* litigation takes the *Amarin* litigation one step further and includes a First Amendment challenge to FDA action in a Warning Letter demanding that "Pacira immediately cease" engaging in speech with physicians about uses of Pacira's product that FDA considered to be off-label.
- FDA and the industry should expect to see a continued flow of litigation challenging FDA's ability to engage in any regulatory enforcement activities that infringe on truthful and nonmisleading speech.

Background of the *Amarin* Case

Amarin manufactures Vascepa, a triglyceride-lowering drug approved in 2012 for the treatment of adult patients with "very high" triglycerides. The approval was based on a study known as the MARINE study. While completing the MARINE study, Amarin entered into a special protocol assessment (SPA) with FDA to conduct a second study, called the ANCHOR study, which was designed to assess the efficacy of Vascepa for patients with "persistently high" triglyceride levels. Amarin and FDA later entered into another SPA for the "REDUCE-IT" study, which remains ongoing and is designed to evaluate whether Vascepa is effective in "helping prevent major cardiovascular events in high-risk patients."

The SPA process is designed to provide a sponsor with "regulatory predictability: Provided that the manufacturer follows the procedure set in the SPA agreement and the drug proves [and] meets the benchmarks for effectiveness set in the agreement, the FDA must approve the drug." FDA may rescind an SPA only if there is an identified and presumably as yet unresolved "'substantial scientific issue essential to determining the safety or effectiveness'" of the drug for the additional proposed uses.

The ANCHOR trial met all of the prespecified endpoints required for approval, and Amarin submitted a supplemental new drug application seeking approval of Vascepa for treatment of adult patients with "persistently high" triglyceride levels in February 2013. In October 2013, FDA convened a public Advisory Committee on Vascepa "to determine if [the] reductions in triglycerides levels, as demonstrated in the ANCHOR study ... would reduce cardiovascular risk." The committee determined that there was "'substantial uncertainty'" in answering this question, and FDA thereafter rescinded the SPA, a decision that was sustained upon additional agency review.

On April 27, 2015, FDA issued a complete response letter (CRL) refusing (1) to approve Vascepa for treating patients with "persistently high" triglyceride levels and (2) to allow Amarin "to include the ANCHOR results in the Vascepa label."[1] FDA also warned Amarin that Vascepa would be "'considered to be misbranded ... if it is marketed'" for treating "persistently high" triglyceride levels.

Ten days later, Amarin, together with several physician plaintiffs, filed a complaint. Claiming that "FDA's threat of a misbranding action [as articulated in the April 27 CRL] is chilling it from engaging in constitutionally protected truthful speech," Amarin sought relief to ensure its ability to make truthful, nonmisleading statements about Vascepa. Amarin argued that it wanted to provide truthful information about its drug. The physicians argued that FDA's "current regime for regulating the flow of 'off-label' information to doctors about prescription drugs ... severely restricts medical professionals' access to information from the source most knowledgeable about the drugs: the drug manufacturers." The complaint sought protection for Amarin's speech at both a general and statement-specific level, including for the following "carefully 'circumscribed, truthful and scientifically' accurate statements":

- That "[s]upportive but not conclusive research shows that" consumption of certain substances "may reduce the risk of coronary heart disease";
- That the ANCHOR study demonstrates that for a certain category of patients, "Vascepa lowers triglyceride levels"; and
- That the ANCHOR study showed that Vascepa achieved certain specifically enumerated outcomes.

In addition, Amarin sought approval to distribute 13 specific peer-reviewed publications and a written summary of the ANCHOR study that includes a chart reporting efficacy data. To assure the information was not misleading, Amarin also proposed making a set of five disclosures regarding the status of FDA's review and conclusion regarding the ANCHOR study.

On May 22, 2015, Amarin moved for preliminary relief under the First Amendment, and alternatively under the due process clause, claiming that FDA's regulations did not "fairly notify Amarin of what off-label promotion is permitted and what is forbidden." Amarin sought an injunction preventing FDA from bringing a misbranding action against it, or alternatively, a declaration that its speech was protected against a misbranding action. Amarin also sought protection from civil claims under the False Claims Act.

On June 5, 2015, Dr. Janet Woodcock, FDA's director of the Center for Drug Evaluation and Research (CDER), sent Amarin a letter that "attempted to moot the dispute altogether" by agreeing in part to statements Amarin proposed to make and by

[1] FDA anticipated, however, that the final results of the REDUCE-IT study expected in 2018 might address the uncertainty and support approval.

proposing defined conditions under which Amarin could pursue its promotion efforts. FDA thereafter filed its brief opposing preliminary relief, arguing that the dispute would be moot if Amarin would accept the terms of its letter. It also argued that Amarin's plan to make proactive statements about Vascepa's off-label use amounted to a "frontal assault ... on the framework for new drug approval that Congress created in 1962." FDA argued that *Caronia* did not block FDA from using truthful and nonmisleading speech as evidence of a manufacturer's intent to engage in misbranding.

In its June 30, 2015, reply memorandum, Amarin declined the FDA's proposal to moot the controversy, asserting a right to "engage in a full and truthful dialogue with healthcare professionals."

The *Amarin* Opinion

The court's opinion is insightful for two reasons. First, the court spent considerable time analyzing and explaining the *Caronia* decision. Second, the court conducted a detailed evaluation of each of Amarin's proposed claims and disclaimers, enabled by the specificity in Amarin's complaint and the detailed responses in FDA's briefing.

As to the scope of the *Caronia* decision, the court rejected FDA's position that *Caronia* applied only to the facts of that case, stating:

> 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. A fair reading of that decision refutes the FDA's view that the Second Circuit's ruling was limited to the facts of Caronia's particular case. To be sure, the Circuit closely reviewed the record of Caronia's trial ... But the Circuit did so to isolate the acts upon which Caronia's conviction had rested —specifically to determine whether Caronia's speech had "served merely as 'evidence of intent'" or whether Caronia had been "prosecuted for his speech." The Circuit found the latter, holding that the record revealed that "the government did prosecute Caronia for his speech." ... Where 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.

With respect to Amarin's proposed disclosures, the court reviewed each in turn to determine whether it was "necessary to make Amarin's overall communications about Vascepa non-misleading. ... err[ing] on the side of caution, meaning in favor of giving doctors more, not less, information." The court concluded that Amarin can:

- Disseminate reprints of 13 peer-reviewed scientific publications that address the effect of Vascepa for an unapproved use.
- Disseminate a "studiously neutral" overview of its study that is neither false nor misleading, and can accompany that with specific truthful and non-misleading statements about the study.
- Make certain agreed statements and disclosures, including an assertion that "supportive but not conclusive research" suggests that Vascepa helps to prevent cardiovascular disease. In evaluating a proposed statement concerning FDA's refusal to approve the second use for Vascepa, "the Court agree[d] with the FDA that an explanation for the FDA's decision not to approve Vascepa for off-label use is warranted, to give doctors a context in which to understand the agency's decision. Unexplained, the FDA's decision would be, potentially, a mystery. It might foster any number of unhelpful misconceptions. ... a fair and neutral statement of the present state of scientific knowledge and of the basis for the FDA's decision not to approve Vascepa to treat patients with persistently high triglycerides."

While the court approved Amarin's requested injunction, it cautioned that the "First Amendment does not protect false or misleading commercial speech" and that "[a] manufacturer that engages in non-communicative activities to promote off-label use cannot use the First Amendment as a shield." The court also declined to grant preliminary relief in conjunction with the FCA because FDA's CRL did not mention the FCA and thus the court did not find a ripe controversy. The court entered the following preliminary relief:

> Specifically the Court declares that: (1) Amarin may engage in truthful and non-misleading speech promoting the off-label use of Vascepa, i.e., to treat patients with persistently high triglycerides, and under Caronia, such speech may not form the basis of a prosecution for misbranding; and (2) Based on the information presently known, 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.

On August 31, 2015, Judge Paul Engelmayer approved a 60-day stay to allow the parties to explore settlement. According to the docket, FDA has not yet appealed the order.

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Significance of the Procedural Posture in *Amarin*

Unlike *Caronia*, where the judicial review occurred in the context of an appeal by a pharmaceutical sales representative from a criminal conviction, *Amarin* involved an affirmative challenge to FDA's enforcement scheme and included four doctors as plaintiffs. In *Caronia*, the record was based on the government's theory of wrongdoing as found in the indictment, evidence it presented at trial and jury instructions for which it advocated. Because Caronia was convicted at trial, the record also included a jury's finding of guilt. While the impact on free speech was the core basis for the appeal of the criminal conviction, the case did not involve an in-depth review of the challenged speech as occurred in *Amarin*.

In *Amarin*, the record, and thus the battleground, was tailor-made for an in-depth analysis of the speech in question. The court reviewed numerous forms of speech, including the dissemination of scientific articles, specific study summaries, and specific statements and disclosures concerning a drug's efficacy. Because the plaintiffs drafted their complaint to include specific claims and other speech, FDA was forced to take specific positions on the proposals in a public forum, which resulted in a highly specific opinion that provided greater judicial guidance than *Caronia* could offer.

Amarin also is notable for the court's willingness to render a legal opinion for injunctive relief in an area that many thought might be susceptible to a government argument for deference to agency expertise under *Chevron* principles.[2] Instead, the district court focused on the First Amendment rights and agency intrusion on speech. Still, future courts may be reluctant to displace agency reasoning where there is less scientific clarity in FDA's record and the seeming arbitrariness of its decision.

The *Pacira* Litigation

Perhaps encouraged by the *Amarin* court's willingness to consider a judicial challenge to FDA's administrative actions, on September 8, 2015 — just a month after *Amarin* — Pacira Pharmaceutical, Inc. and two physicians filed a complaint against FDA in the Southern District of New York concerning EXPAREL, Pacira's local anesthetic product. Although preapproval clinical trials only involved bunionectomies and hemorrhoidectomies, Pacira sought, and FDA granted, approval of EXPAREL for "administration into the surgical site to produce postsurgical analgesia." While EXPAREL's label does not specify the "surgical site," the dosage and administration instructions are for only two surgeries, bunionectomies and hemorrhoidectomies. The label also states that the drug had only been tested for use in those two surgeries and has "not been demonstrated to be safe and effective in other procedures."[3] Pacira alleges that when FDA approved the indication language for EXPAREL without any reference or limitation to a surgical site, it approved a broad indication for the drug, allowing it to be used in any surgical site.

Following approval, Pacira alleges that it "spoke with physicians, surgeons, and anesthesiologists" about using EXPAREL "in different surgical sites" and shared with physicians "the actual experiences that other physicians had administering EXPAREL in different surgical sites." Pacira further alleges that "FDA has thus been on notice since April 2012 that Pacira was properly promoting EXPAREL as approved for surgeries other than hemorrhoidectomy and bunionectomy."

Yet in September 2014, FDA issued a Warning Letter to Pacira "demanding that 'Pacira immediately cease' sharing with surgeons, anesthesiologists and other sophisticated audiences certain information about using EXPAREL outside a bunionectomy or hemorrhoidectomy," the specific procedures in which EXPAREL was studied in the clinical trials supporting its approval. FDA further warned Pacira that its conduct rendered EXPAREL misbranded and subjected Pacira to potential criminal prosecution. Describing "an extensive promotional campaign by Pacira to promote the use of EXPAREL in surgical procedures other than those for which the drug has been shown to be safe and effective," FDA demanded that Pacira formulate "a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audiences that received these promotional materials."[4]

Like the *Amarin* litigation before it, Pacira now seeks federal court review[5] of FDA's efforts to "forbid Pacira's truthful and non-misleading speech to [physicians] about their lawful use" of Pacira's product, relying on the U.S. Supreme Court's First Amendment precedent, the Second Circuit's ruling in *Caronia*, and the district court's *Amarin* opinion from August 2015. Pacira asks the court to declare (1) "that FDA may not, under the FDCA and consistent with the First Amendment, limit Pacira's communications to health care providers regarding FDA approved uses of Exparel," 2) "that 21 C.F.R. § 202.1(l)(2) is invalid under the FDCA and the First Amendment, insofar as it

[2] *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*

[3] http://www.exparel.com/pdf/EXPAREL_Prescribing_Information.pdf.

[4] *See* Department of Health and Human Services, Warning Letter, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM416513.pdf.

[5] Pacira alleges that before it filed its complaint, it "repeatedly sought to meet with the FDA to discuss its position" but the FDA refused to meet and instead issued a "close-out" of its Warning Letter on July 24, 2015.

would restrict Pacira's truthful and non-misleading speech," and (3) "that FDA's attempt to modify Pacira's approved Indication through a Warning Letter is arbitrary, capricious, [and] in excess of the Agency's statutory authority."

We make no comment on the merits of this litigation in its earliest stages, but we find the following noteworthy: (1) the speed with which Pacira filed its action — within a month of the Amarin ruling and less than two months after the FDA's close-out of the Warning Letter, (2) Pacira's decision to file its action in the same Second Circuit federal district court that decided *Amarin*, and (3) the breadth of the relief sought.

Skadden Commentary

The *Amarin* opinion fundamentally alters the present regulatory and enforcement landscape for off-label promotion in several respects.

Will DOJ appeal the ruling? We believe it is unlikely. The appeal necessarily would be to the Second Circuit that decided *Caronia* by a three-judge panel. While a different panel likely would decide the *Amarin* appeal, the prior *Caronia* opinion most likely will govern the outcome. At this point, however, it is possible that DOJ may conclude it has no choice but to appeal. An appeal may pose substantially greater risk for DOJ than did the *Caronia* appeal (which would have involved seeking *en banc* review of the panel's decision or filing a petition for *certiorari* to the U.S. Supreme Court). The recent request for a stay while the parties explore settlement suggests that DOJ would like to avoid further appellate rulings on the point.

What happens if DOJ does not appeal the Amarin decision? DOJ and FDA will be bound by the rulings in the Second Circuit. We also believe that any DOJ decision not to appeal the Amarin decision, coupled with its decision not to appeal *Caronia*, will hasten acceptance of the ruling in other circuits. While a court in another circuit could reach a contrary conclusion, the greater likelihood is that other judges will adopt the reasoning expressed in these two opinions, in light of the Supreme Court's recent decision in *Sorrell* and other First Amendment decisions.

In *Amarin*, the court specifically noted that the government never sought rehearing nor petitioned for *certiorari* in *Caronia*. ("… despite a vigorous dissent to the effect that the panel majority had 'call[ed] into question the very foundation of our century-old system of drug regulation.'") Further, when discussing public interest concerns, the court observed that "[h]ad the FDA believed that *Caronia* gravely undermined the drug approval process, it should have sought review of that decision." Courts outside the Second Circuit are likely to view any DOJ decision not to appeal *Amarin* in a similar light.

We also think there will be a steady flow of litigation similar to *Amarin* and *Pacira* until FDA issues guidance to the industry that demonstrates a commitment not to engage in regulatory conduct or enforcement actions that necessarily or consequentially abridge the First Amendment rights of manufacturers. It is likely that FDA moved quickly, after the court's ruling in *Amarin*, to try to settle the case to limit further damage; the filing of the *Pacira* litigation demonstrates that after failing to appeal *Caronia,* the government may have already lost the ability to limit *Caronia*'s reach.

Will DOJ curtail its off-label investigations and prosecutions? Despite public statements to the contrary, *Caronia* appears to have had some impact on DOJ's pursuit of off-label enforcement actions where there is no evidence of false or misleading statements by a manufacturer. While *qui tam* relators will mourn any loss of ability to leverage a criminal investigation for off-label conduct to a handsome monetary recovery, and may choose to proceed in civil cases, the lack of any criminal enforcement hammer will discourage the high-dollar settlement achieved in the past. The *Amarin* decision should continue this shift in focus. To avoid direct First Amendment challenges to the FDCA and its provisions, DOJ likely will direct its efforts toward cases with evidence of false and misleading statements. Companies and employees should expect heightened scrutiny on the accuracy of any statements made on off-label uses and should anticipate that DOJ will look closely at any omissions, with an eye on whether an omission has rendered an otherwise truthful statement misleading.

How will these rulings impact FDA's use of Warning Letters? The potential exists for a substantial impact on how FDA uses its Warning Letters. FDA rarely has had to defend its power to issue Warning Letters or what it says as a regulator in those letters. That power is under direct attack in *Pacira* in the same inhospitable forum that decided *Amarin*. A ruling by the Southern District of New York against FDA in *Pacira* likely would have a profound impact on the number and content of future Warning Letters.

Can my company begin to engage in off-label promotion? As regards any particular promotional campaign, this is a complex question that cannot be adequately addressed within the scope of this article. Even *Amarin* continues to hold that truthful statements can be misleading, either in context or because of material omissions, so an understanding of the overall context is critical. We do believe, however, that truthful, nonmisleading statements about the company's products are more likely to be protected by a court's consideration of the First Amendment, and at least in the Second Circuit, the company has strong precedent to defend its action. Such conduct engaged outside the Second Circuit, while probably also protected, carries an increased risk of enforcement or regulatory action. Based upon these legal developments, for example, companies now can give more consideration to the affirmative distribution of scientific

information outside a product's approved labeling where such information is accurate and complete. For example, under strict internal controls and review processes, companies may consider the distribution of peer-reviewed reprints or accurate summaries of such studies to health care professionals. At the same time, companies would be well advised to exercise restraint in encouraging sales representatives to engage in extensive off-label discussion, given the practical difficulty of ensuring that all representatives communicate such information only in accordance with the company's guidance. Restraint also would be prudent in communicating off-label information where inappropriate use of the product would carry significant risks.

Despite the breadth of its ruling, the *Amarin* court emphasized that there remains "practical wisdom to much of FDA's guidance." Noting that FDA remained free to pursue misbranding claims for false or misleading promotion, including one-sided or incomplete representations, the court warned manufacturers of their potential liability for sales forces' unscripted conversations about off-label uses. It also noted that where FDA and a manufacturer might disagree as to the truthfulness of a particular representation, the manufacturer may be wise to consult with FDA and resolve any ambiguities before promoting the off-label use. The court emphasized that Amarin's motion involved a unique fact pattern, whereby it was able to base its proposed off-label communications almost exclusively upon FDA's own statements. Cases that lack such "unusual and extensive regulatory history" and drugs that lack Vascepa's high safety profile might present stronger grounds for FDA to establish false or misleading representations. The court also warned that "[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. … Amarin bears the responsibility, going forward, of assuring that its communications to doctors regarding off-label use of Vascepa remain truthful and non-misleading."

What impact does the *Amarin* opinion have on direct-to-consumer advertising? Because Amarin's complaint sought only to engage in discussions with health care professionals, the opinion never addresses direct-to-consumer advertising. The court did make clear that *Caronia* applies to all truthful and nonmisleading speech and not just to proactive (versus reactive) requests or requests from health care professionals (versus patients).

What is meant by the *Amarin* court's statement that a company cannot use the First Amendment as a shield for "non-communicative activities"? Companies should expect that DOJ and FDA, as both agencies begin to accept the First Amendment limitations imposed on FDA's regulatory and DOJ's enforcement powers, will examine a company's conduct designed to promote a product for an unapproved use very closely. Companies should be careful regarding nonspeech activities related to unapproved indications.

When will we see FDA's guidance and how will *Sorrell, Harkonen, Caronia,* and now *Amarin* influence that guidance? It is impossible to predict when FDA may issue guidance. We believe there is substantial pressure on it to do so quickly following the Amarin opinion, and that pressure was ratcheted up with the filing of the *Pacira* litigation. There is a conflict between the regulations that restrict promotion for unapproved uses and the First Amendment right of manufacturers and their employees to engage in truthful, nonmisleading speech. For now, the *Amarin* opinion is filled with useful guidance for FDA and industry alike.

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