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EXPERT ANALYSIS

Considerations for Device Firms in the Wake of a String of Successful First Amendment Challenges to FDA's Regulation of Off-Label Speech

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Over the past few years, we have witnessed an erosion of the Food and Drug Administration's restriction of off-label speech through several court cases that have challenged the constitutionality of these restrictions on manufacturers' speech. Distilling the implications of these decisions for medical device companies raises some complex questions and considerations as they consider engaging in this type of protected speech.

RECENT CHALLENGES TO THE FDA'S RESTRICTION OF OFF-LABEL SPEECH

While a detailed accounting of the facts and procedural aspects is beyond the scope of this analysis, a few of the more recent decisions and settlements are discussed below. The critical thread that is woven throughout these First Amendment challenges, beginning with the 2011 Supreme Court decision *Sorrell v. IMS Inc.*,[1] is the holding that truthful and non-misleading off-label speech cannot be the basis for prosecution under the misbranding provisions of the Federal Food, Drug and Cosmetic Act.

In *United States v. Caronia* the government alleged that sales representatives knowingly and intentionally conspired to misbrand a prescription drug by marketing it for off-label uses.[2] Following a conviction in the U.S. District Court for the Eastern District of New York, Alfred Caronia appealed. He argued that the First Amendment prohibits the criminalization of a manufacturer's truthful and non-misleading promotional speech of an FDA-approved drug for off-label use, where such use is not itself illegal and others are permitted to engage in such speech.

On appeal, the 2nd U.S. Circuit Court of Appeals focused on the basis of the FDA's case, which was that Caronia's speech alone was the prohibited conduct. The court found that the prohibition of off-label promotion did not meet the scrutiny applied to content- and speaker-based speech restrictions, noting, "The government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug." In other words, the court distinguished between off-label promotional speech as the basis for prosecution under the misbranding provisions of the FDCA versus off-label promotional speech as evidence of the intended use of the drug.

In addition to the decision that lawful off-label promotional speech alone cannot be the basis for prosecution under the FDCA, *Caronia* is also notable in that within this construct of protected off-label speech, it discussed the concept of distinguishing between truthful discussion of off-label uses versus fraudulent speech (i.e., misleading doctors about the lawful use of a product or stating falsehoods).

Recent rulings clearly signal a major shift in the FDA's traditional approach to regulating off-label speech.

The court was clear that false and misleading speech is not protected. The FDA's interpretation of the court's holding was that pursuant to the FDCA, promotional statements by a company about an off-label use can serve as evidence of a drug's intended use. The court's holding, however, did not specifically address whether off-label speech could be used as evidence of intent to misbrand a product.

There was a general sense in the industry that *Caronia* would be seen as limited to the facts of the case. The court in *Amarin Pharma Inc. v. FDA* thought otherwise, citing *Caronia* as binding precedent and using it as the basis to grant Amarin's motion for a preliminary injunction against the FDA.[3] Specifically, the court found that the off-label promotion the company planned to engage in was lawful or could be made so with the addition of certain disclosures.

Specifically, the court held, "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." Thus, building upon the *Caronia* holding and that court's discussion of the distinction between truthful versus fraudulent speech, *Amarin* specifically calls out truthful and non-misleading speech promoting an off-label use as protected speech.

In addition, the court further expounded on the idea of what constitutes "truthful and non-misleading" information, noting that it evolves. The court explained, "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."

On March 8 the parties in *Amarin* proposed a settlement. Under the terms of the settlement, the FDA waived its right to appeal the court's earlier decision and agreed to be bound by the holding that Amarin may engage in truthful and non-misleading speech promoting the cholesterol drug Vascepa off-label. In addition, the parties agreed that per *Caronia*, such speech may not trigger prosecution for misbranding and that Amarin's proposed statements, as modified by the ruling, were truthful and non-misleading.

Interestingly, as part of the settlement, in addition to the existing pre-clearance procedures available to drug companies for FDA review of promotional materials, Amarin may submit two communications per year (through 2020) about Vascepa's off-label use for pre-review. The FDA will be required to respond with any concerns within 60 days. Furthermore, disagreements the parties cannot resolve may be resolved through the court without the need to file anew. The court has approved the settlement.

In *Pacira Pharmaceuticals Inc. v. FDA* the company brought suit against the FDA following a 2014 warning letter contesting Pacira's distribution of materials describing a prescription drug's use in two surgeries that were not studied in the premarket clinical trials.[4] The FDA took the position that the drug had not been shown to be safe and effective in those procedures. Pacira relied on *Caronia* and *Amarin* to support its position that certain speech it wanted to disseminate to healthcare providers, if considered off-label, is constitutionally protected because it is truthful and non-misleading.

The case settled Dec. 15, 2015, and the settlement terms are notable. Specifically, the FDA agreed to drop restrictions on the drug's marketing and to approve labeling changes clarifying that the drug is indicated for treating pain at any surgical site. Furthermore, the FDA acknowledged that the broader indications date retroactively to the 2011 approval, so any marketing for other surgeries since then was not off-label promotion. Most notably, the FDA formally retracted its 2014 warning letter, which is exceedingly rare.

Last but not least, the *United States v. Vascular Solutions Inc.* case involved a prescription medical device, the Vari-Lase, which was 510(k) cleared for laser ablation of varicose veins.[5]

Vascular Solutions Inc. marketed a special "short kit" that was designed for use with the Vari-Lase devices for ablation/removal of "perforator" veins, a type of vein not specifically spelled out in the cleared indications for use. Indeed, VSI had previously submitted a separate marketing application for the Vari-Lase system for ablation of perforator veins. The application was backed by data from a company-sponsored clinical trial, which failed to support Vari-Lase's safety and effectiveness compared to a competing device cleared for perforator vein treatment.

VSI's marketing application for perforator veins was ultimately denied, and the FDA specifically told it not to sell Vari-Lase for this use.

Internal VSA documents urged sales personnel to suggest that the devices could be used to treat perforator veins. After learning of the government's investigation, sales personnel used the term "short vein segments." Sales representatives were also provided with reference citations to studies discussing the device's effectiveness for the uncleared use.

Based on the above, in November 2014, the U.S. Department of Justice charged VSI and CEO Howard C. Root with conspiracy to introduce unapproved devices into interstate commerce and defraud the U.S. by concealing such sale and illegal promotion of a medical device for a new intended use (off-label) with inadequate directions for use in the product's labeling.

Relying on *Caronia* and *Amarin*, VSI argued that the First Amendment's protection of truthful, non-misleading speech about off-label uses protected the speech at issue. What is notable in this case is the instruction provided to the jury. Specifically, the jury was instructed that if it found that VSI's promotional speech to doctors was solely truthful and not misleading, that speech could not be the basis for a misbranding conviction.

VSI and Root were acquitted of all off-label promotion charges. Thus, based on the jury instruction, it would appear that the decision turned on a finding that the speech was indeed truthful and non-misleading.

An interesting aspect of the VSI case is the dual role played by the data on device's off-label use. The FDA found the data inadequate to support a finding of substantial equivalence, which was the basis of a "not substantially equivalent" decision and a specific warning to the company not to promote the device for this use. These same data were likely considered by the jury in support of its decision that the promotional off-label speech at issue met the truthful and non-misleading standard and thus was protected.

The cases discussed above each presented unique facts and circumstances that played into the courts' specific analyses and ultimate decisions (or the parties' decision to settle). While we must be sensitive to the factually driven nature of these decisions, the central tenet of the court's decision in *Caronia* has been consistently reinforced and more clearly defined with each of these cases.

These rulings opened the door for companies to consider use of truthful and non-misleading off-label communications with health care providers.

CONSIDERATIONS MOVING FORWARD

Where do medical device companies go from here? These cases clearly signal a major shift in the FDA's traditional approach to regulating off-label speech, and they have opened the door for companies to consider pursuing truthful and non-misleading off-label communications with health care providers in accordance with these decisions.

However, in looking to implement such communication practices, the need to have a clearly defined standard for what constitutes "truthful and non-misleading" becomes critical, particularly when considering the potential fallout if the standard is deemed unmet.

WHAT CONSTITUTES 'TRUTHFUL AND NON-MISLEADING'

"Truthful" and "non-misleading" are not new concepts to the medical device industry. They are actually central concepts at the heart of the FDA's requirements for promotional labeling. The Federal Trade Commission also relies on the terms "truthful" and "non-misleading" when assessing advertisements, endorsements and testimonials.

There is subjectivity involved in assessing any given speech, particularly as it relates to what may be considered misleading. How do we define this standard in the context of assessing off-label speech about medical devices to determine whether the speech is protected and thus immune from prosecution under the misbranding provisions of the FDCA?

In *Amarin*, the court tied the concept of "truthful and non-misleading" to scientific data and studies, highlighting that the availability of new studies and data can impact whether speech

that previously met the standard remains truthful and non-misleading over time. A level-of-evidence standard to assess what is "truthful and non-misleading" in the context of off-label speech seems reasonable.

But where should that level of evidence be set? The FDA statutes and regulations set forth a number of different evidentiary standards for supporting marketing permission. There are, however, differences in such levels of evidence required for devices versus drugs in the premarket approval setting.

Indeed, we don't need to go outside the device center to find different levels of evidence required for PMA approval versus substantial equivalence via the 510(k) notification pathway. Outside the premarket setting, however, it is unclear whether these same levels of evidence would be appropriate for assessing whether off-label speech is "truthful and non-misleading."

Defining "truthful and non-misleading" in the context of what is or is not protected speech raises complex issues that have not yet been fully vetted. Further guidance from the agency would be helpful to provide a framework within which manufacturers can reasonably assess contemplated off-label speech.

HIGH STAKES IN THE ABSENCE OF A CLEAR FRAMEWORK

In looking to implement such communication practices, the need to have a clearly defined standard for what constitutes "truthful and non-misleading" is critical.

Unfortunately, in the absence of a clear standard, companies' appetites for pursuing such off-label communications after these court decisions may be dampened. In particular, the stakes are significant for companies when gambling with considerable ambiguity surrounding what the FDA considers "truthful and non-misleading" in the context of off-label speech about a particular medical device.

The FDCA is a strict liability statute, meaning a violation of the adulteration and misbranding provisions does not require intent for a misdemeanor violation. In addition, the FDA has an arsenal of enforcement tools it can use to target what it regards as prohibited activities. Furthermore, a resurgence of application of the Park doctrine, which allows individuals to be held accountable for off-label marketing, may also be of concern in this context.[6]

Under the Park doctrine, responsible corporate officers have an affirmative duty to seek out and remedy violations and implement measures to prevent them. As such, executives could be individually prosecuted for misdemeanors for failing to prevent or correct a violation of the FDCA stemming from off-label communications that were found to be false and/or misleading. In sum, a strict liability statute plus the potential for individual accountability are weighty considerations for medical device companies considering dissemination of off-label promotional speech.

PRE-REVIEW OF OFF-LABEL SPEECH

The *Amarin* settlement raises interesting issues in the context of application of truthful and non-misleading off-label speech for medical devices. Specifically, the settlement sets forth a process that relies on the existing avenue for pre-clearance of promotional materials for pharmaceutical drugs as well as a dispute resolution process that ends in judicial resolution should the parties not be able to resolve the dispute amongst themselves.

Adapting use of this existing pre-review process would appear to be a reasonable approach to afford companies the opportunity to present proposed off-label speech and obtain the FDA's feedback as to whether it passes the "truthful and non-misleading" test. However, such a regulation establishing a pre-clearance process for promotional materials does not exist in the medical device statute or regulations.

The FDA's Center for Devices and Radiological Health reviews labeling as part of marketing submissions. But once labeling is approved, the FDA leaves it to the company to apply the given standard and decide if promotional labeling is within the scope of the cleared indications and satisfies the other requirements for such labeling.

If the agency were to move in the direction of the Amarin settlement and allow the use of the pre-clearance process to review proposed off-label promotional speech, wouldn't a similar avenue be warranted for medical devices to afford device firms the same opportunity to reduce their exposure through a pre-clearance process?

The medical device industry generally abhors more regulation, so it is unclear if it would welcome the introduction of such a process within this context to bring greater certainty and achieve parity with the drug center.

CONCLUSION

As exciting as these developments are in terms of opening the door for firms to consider pursuing truthful and non-misleading off-label communications with healthcare providers, industry may be slow to jump in initially because critical questions remain about fundamental aspects of such an approach.

The specific level of evidence needed to satisfy the "truthful and non-misleading" standard needs definition, and a viable framework for these assessments does not yet exist. Relying on the courts to make such determinations as a long-term approach is not a tenable (or desirable) solution.

Should the FDA take the lead and adapt the drug center's existing pre-clearance process for review of off-label speech, what will this mean for the medical device industry, which does not have such a process? Health policy experts have convened and are brainstorming other possible approaches, including the idea of pre-review panels administered by third parties outside the agency. Industry awaits the release of promised guidance on these issues, although the timeframe for issuance remains unknown.

There is no doubt that creating a transparent, workable framework and process will take time. Further dialogue between the FDA and all stakeholders is needed on these complex issues. Until then, it is unlikely that firms will pursue wholesale changes in approach to their promotional practices.

NOTES

[1] 131 S. Ct. 2653 (2011).

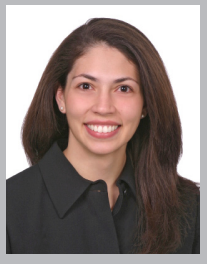
[2] 703 F.3d 149 (2d Cir. 2012).

[3] *Amarin Pharma Inc. v. FDA,* 119 F. Supp. 3d 196 (S.D.N.Y. 2015).

[4] Complaint for Declaratory and Injunctive Relief, *Pacira Pharmaceuticals Inc. et al. v. FDA et al.,* No. 15-cv-7055, 2015 WL 5256628 (S.D.N.Y. Sept. 8, 2015).

[5] *United States v. Vascular Solutions Inc.,* No. 14-cr-926, *verdict returned* ,2016 WL 806265 (W.D. Tex. Feb. 26, 2016.

[6] *See United States v. Park,* 21 U.S. 658 (1975).



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