UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

AMARIN PHARMA, INC., DR. JONATHAN HERBST, DR. ERIC RISHE, DR. PETER GOTTESFELD, and DR. RALPH YUNG,	:	
Plaintiffs,	:	15 CV 3588 (PAE)
-against-	:	
U.S. FOOD AND DRUG ADMINISTRATION, UNITED STATES OF AMERICA, STEPHEN OSTROFF, M.D., in his official capacity as Acting Commissioner of Food and Drugs, and SYLVIA MATHEWS BURWELL, in her official capacity as Secretary of the Dep't of Health and Human Services,	:	
Defendants.	:	

AMICUS CURIAE WASHINGTON LEGAL FOUNDATION'S MEMORANDUM OF LAW IN SUPPORT OF PLAINTIFFS' MOTION FOR PRELIMINARY INJUNCTION

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CORPORATE DISCLOSURE STATEMENT

Pursuant to Fed.R.Civ.P. 7.1, the Washington Legal Foundation (WLF) states that it is a corporation organized under § 501(c)(3) of the Internal Revenue Code. WLF has no parent corporation, and no publicly-held company has a 10% or greater ownership interest.

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

Cases:

Page(s)

Statutes and Constitutional Provisions:

Miscellaneous:

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INTERESTS OF *AMICUS CURIAE*

The interests of Washington Legal Foundation (WLF) are set out more fully in the accompanying motion for leave to file this brief.[1] In brief, WLF is a public interest law and policy center with supporters in all 50 states. WLF regularly appears before federal and state courts to promote economic liberty, free enterprise, a limited and accountable government, and the rule of law.

In particular, WLF has devoted substantial resources over the years to promoting the free speech rights of the business community, appearing before numerous federal courts in cases raising First Amendment issues. *See, e.g., Sorrell v. IMS Health Inc*., 131 S. Ct. 2653 (2011); *Nike v. Kasky*, 539 U.S. 654 (2003). WLF has successfully challenged the constitutionality of FDA restrictions on speech by pharmaceutical manufacturers. *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998), *appeal dism'd*, 202 F.3d 331 (D.C. Cir. 2000). As a result of that litigation, FDA is subject to a permanent injunction limiting FDA authority to suppress manufacturer dissemination of certain journal articles/medical texts discussing off-label uses of their FDA-approved products.

More recently, WLF lawyers played a key role in overturning—on First Amendment grounds—the criminal conviction of a pharmaceutical representative for conspiring to violate the Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 301 *et seq.*; the representative's "crime" consisted of speaking truthfully about off-label uses of a drug manufactured by his company.

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[1] WLF states that no counsel for a party authored this brief in whole or in part; and that no person or entity, other than WLF and its counsel, contributed monetarily to the preparation and submission of this brief.

United States v. Caronia, 703 F.3d 149 (2d Cir. 2012).

WLF believes that health care improves when doctors are provided unrestricted access to truthful information about the safety and effectiveness of FDA-approved drugs. WLF is concerned that FDA restrictions on truthful speech are denying doctors access to the best available information about FDA-approved drugs and thereby are interfering with delivery of state-of-the art medical care.

INTRODUCTION AND STATEMENT OF THE CASE

FDA has a long history of seeking to suppress manufacturer speech regarding FDA-approved drugs. FDA has repeatedly asserted that: (1) *anything* a drug manufacturer says about the uses of its products should be deemed an effort to promote the product for those uses, without regard to the context within which the statements are made; (2) such "promotional" statements render the drug in question "misbranded" to the extent that the statements discuss uses that are not included on the FDA-approved label; and (3) the subsequent distribution of the misbranded drug is a federal criminal offense. It has issued numerous Warning Letters and guidance documents that warn manufacturers that they face severe sanctions for discussing such off-label product uses, without regard to the truth of any statements they might make.

Because government suppression of truthful speech has obvious First Amendment implications, one would expect FDA—in the documents it has issued regarding off-label speech—to include some discussion of steps it takes to ensure that its regulatory actions conform with constitutional limitations on government power. Surprisingly, however, FDA guidance documents and Warning Letters uniformly make no mention of the First Amendment. Moreover, when litigants raise First Amendment challenges to FDA regulations in court

proceedings, FDA in almost every instance has responded by asserting that the challenged agency action does not even implicate the First Amendment because FDA is regulating commercial conduct, not speech. Numerous courts have rejected that conduct-not-speech argument and, if FDA raises it in this case, it should be rejected here as well. As the motion explains, FDA seeks to suppress speech that it has not shown to be false or misleading. Under those circumstances, an injunction is warranted in the absence of evidence from FDA demonstrating that suppression of the speech furthers a substantial government interest in a narrowly tailored manner.

Plaintiff Amarin Pharma, Inc., in its motion for a preliminary injunction, sets out the details of its multi-year effort to obtain FDA approval of a supplemental indication for Vascepa to treat patients with persistently high triglycerides. WLF will not repeat that history here, except to note that an April 27, 2015 letter from FDA to Amarin (the Complete Response Letter) denied Amarin's request for approval. The letter also denied Amarin's request to include in its Vascepa labeling the efficacy data from its ANCHOR trial, an extensive trial whose findings FDA does not challenge. Most importantly for purposes of this motion, the letter concluded with a warning that any effort by Amarin to market Vascepa for its proposed supplemental use could constitute "misbrand[ing]" under the FDCA—thereby exposing Amarin to criminal prosecution.

Amarin responded to that warning by filing suit on May 7, 2015 and by filing this motion for a preliminary injunction on May 22, 2015. Amarin seeks, among other things, a declaration that FDA regulations prohibiting manufacturer speech about off-label uses of an FDA-approved product are unconstitutional as applied to Amarin's truthful speech about Vascepa, and an injunction preventing FDA from taking any action against Amarin on the basis of such speech.

SUMMARY OF ARGUMENT

Both the Supreme Court and the Second Circuit have repeatedly upheld the rights of drug manufacturers to speak truthfully about their products. The Supreme Court has stated unequivocally that "speech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment." *Sorrell*, 131 S. Ct. at 2659. The Second Circuit has invoked the First Amendment to uphold the right of a drug manufacturer to promote all lawful uses of its products, even uses for which FDA has not granted labeling authority. *Caronia*, 703 F.3d at 169.

Despite widespread judicial recognition of drug manufacturer speech rights, FDA for decades has sought to silence drug manufacturers by threatening severe sanctions against any manufacturer that dares to discuss the efficacy of one of its products when put to a use not explicitly sanctioned by FDA. In particular, FDA has flatly rebuffed Amarin's request that it be permitted to discuss with doctors the "supportive but not conclusive evidence" that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease. In a June 5, 2015 letter to Amarin (the "Woodcock Letter"), FDA made clear that it would deem Vascepa "misbranded" if Amarin suggests to doctors that Vascepa may be effective in reducing the risk of coronary heart disease in statin-treated patients who have (or are at risk for) cardiovascular disease. Woodcock Letter at 10.

FDA's efforts to silence Amarin are inconsistent with the First Amendment. While conceding that the ANCHOR trial demonstrated that Vascepa use lowers triglyceride levels in the targeted population, FDA contends that the available scientific data do not adequately support the conclusion that lowering triglyceride levels in the subject population translates into a

reduction in the risk of cardiovascular disease ("CVD"). But FDA concedes that there is scientific uncertainty in this area and simply contends that the evidence is not yet sufficiently compelling to conclude that Amarin's application for the implied indication under its supplemental labeling authority satisfies FDA's high approval standards. FDA's efforts to suppress entirely the supportive scientific evidence runs head-long into the First Amendment because of the ready availability of a more narrowly tailored alternative: requiring the inclusion of Amarin's proffered disclaimers.

Indeed, FDA cannot plausibly argue that there is *no* scientific evidence to support Amarin's proposed discussions regarding the efficacy of omega-3 fatty acids in reducing the risk of coronary heart disease, given both the evidence offered by Amarin and the uncontradicted evidence that FDA continues to permit such claims to be made by dietary supplement manufacturers. FDA has provided no coherent explanation for its apparent position that the First Amendment somehow provides fewer speech protections for drug manufacturers than for dietary supplement manufacturers. FDA states that its differing treatment of drug labeling and dietary supplement labeling "is a consequence of the different regulatory regimes, established by statute and regulation, for these products." Woodcock Letter at 9. That statement is incorrect. FDA permits dietary supplement manufacturers to make health claims regarding the consumption of omega-3 fatty acids because it was effectively ordered to do so by the D.C. Circuit; and that court based its ruling against FDA on the First Amendment, not on statutory grounds. *Pearson v. Shalala*, 164 F.3d 650, 657-58 (D.C. Cir. 1999).

Pearson's First Amendment analysis is equally applicable here. A government agency violates the First Amendment when it seeks to suppress credible evidence of a drug's

effectiveness when the possibility that listeners might be misled can be minimized by requiring the speaker to include disclaimers explaining any shortcomings in the evidence. *Id.* at 658 ("[W]hen government chooses a policy of suppression over disclosure—at least where there is no showing that disclosure would not suffice to cure misleadingness—government disregards a 'far less restrictive' means" of achieving the government's objectives).

Moreover, FDA's efforts to suppress non-misleading speech about off-label uses of FDA-approved drugs swim against the tide of modern medicine. Off-label use of FDA-approved drugs is widespread precisely because doctors recognize that the medical community's knowledge regarding the safety and effectiveness of FDA-approved products inevitably outpaces FDA-approved labeling. In some fields such as oncology, the great majority of medically-accepted treatments involves off-label uses of FDA-approved drugs and devices. Doctors will be unable to treat their patients optimally unless they have access to all credible information about such off-label uses, and FDA does not contest that a drug's manufacturer generally knows more than anyone else about the drug's safety and effectiveness in treating both on-label and off-label conditions. The government may, of course, prohibit prescriptions for an off-label use if it determines that the use raises particular safety concerns. But in the absence of such a prohibition, FDA's selective suppression of non-misleading speech—whereby everyone except Amarin and manufacturers of similar products is permitted to discuss the association between consumption of omega-3 fatty acids and a reduction in the risk of coronary heart disease—does not advance any substantial government interest and thus cannot withstand First Amendment scrutiny.

Courts have repeatedly struck down federal government efforts to suppress speech about

off-label uses of FDA-approved products. Indeed, since 1998 FDA has been subject to a permanent injunction issued by a federal district court in litigation brought by WLF on behalf of doctors who complained that FDA was violating their First Amendment rights by interfering with their receipt of medical information about safe and effective off-label uses. *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998), *appeal dism'd*, 202 F.3d 331 (D.C. Cir. 2000). Yet, FDA has largely ignored its judicial defeats. Its warnings to manufacturers against promoting products for off-label uses include no hint that FDA deems its regulation of such promotion to be subject to First Amendment constraints. Under those circumstances, Amarin has good reason to fear that it will face severe FDA sanctions if it communicates with doctors in the manner it contemplates. Accordingly, Amarin's standing to sue and the ripeness of its claims cannot seriously be questioned.

ARGUMENT

I. THE FIRST AMENDMENT PROHIBITS FDA'S EFFORTS TO TOTALLY SUPPRESS NON-MISLEADING INFORMATION ABOUT OFF-LABEL USES OF VASCEPA, AN FDA-APPROVED PRODUCT

The federal courts have long recognized that the First Amendment, subject only to narrow and well-understood exceptions, does not countenance governmental control over the content of speech. *Bartnicki v. Vopper*, 532 U.S. 514, 527 (2001) ("As a general matter, state action to punish the publication of truthful information seldom can satisfy constitutional standards.") (citations omitted). Even if FDA restrictions on conversations between Amarin employees and doctors about the latest scientific evidence regarding legal uses of Vascepa are adjudged under the intermediate standard of scrutiny applicable to *commercial speech* restrictions, they cannot withstand First Amendment review. FDA's restrictions on non-

misleading speech do not directly advance any substantial government interest, nor are they sufficiently narrowly tailored in light of the availability of alternative measures that would infringe on speech rights to a far lesser degree. FDA's content-based restrictions on Amarin's non-misleading speech are particularly objectionable, given that the speech relates to a common medical practice: the off-label prescription by doctors of Vascepa to reduce the risk of coronary heart disease in statin-treated patients who have (or are at risk for) cardiovascular disease. Because off-label use of Vascepa and other FDA-approved drugs is so common, it is all the more important that doctors have unrestricted access to the latest scientific information about the safety and effectiveness of such off-label use.

A. Off-Label Use of FDA-Approved Drugs Plays a Vital Role in Medical Care

When it approves a drug or medical device for introduction into interstate commerce, FDA reviews the product label. The label sets forth the indications approved by FDA. FDA requires that the label list approved uses and prohibits listing any use that FDA has not approved. But because FDA does not regulate the practice of medicine, doctors are free to write prescriptions for uses that are not listed on a drug's label.

The medical community's knowledge regarding the safety and efficacy of FDA-approved products inevitably outpaces FDA-approved labeling. Researchers who regularly work with approved drugs and devices undertake studies that demonstrate safe and efficacious uses for the drugs/devices that are not included within the labeling. In some fields such as oncology, the great majority of medically-accepted treatments involves off-label uses of FDA-approved drugs and medical devices. Accordingly, were doctors limited to using therapeutic products only as labeled, doctors would be providing sub-optimal care to their patients. In many cases, doctors

simply could not treat their patients in accordance with widely accepted standards of care without resorting to off-label uses.

Indeed, the U.S. Supreme Court has officially recognized off-label treatments as an important part of medical care in this country. *See Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341, 350, 351 n.5 (2001) ("'[O]ff-label' usage of medical devices (use of a device for some other purpose than that for which it has been approved by the FDA) is an accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medicine. . . . Off-label use is widespread in the medical community and often is essential to giving patients optimal medical care, both of which medical ethics, FDA, and most courts recognize.").

Congress similarly recognizes the importance of off-label uses. For example, it imposed an outright prohibition on previous FDA efforts to limit the authority of physicians to put FDA-approved products to off-label uses. *See* 21 U.S.C. § 396 (providing that "nothing in [the FDCA] shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.").

A corollary to the prominent position that off-label drug use occupies within the practice of medicine is that doctors must be able to learn which off-label uses are medically recognized. The need for knowledge does not stop with graduation from medical school; new drugs and devices are constantly entering the market, and new uses for these products are constantly being recognized as safe and effective. The discovery that an approved product is beneficial in treating an off-label condition is of no help to a patient unless his/her physician knows about that use.

Accordingly, effective health care delivery requires that information about new uses be widely disseminated within the medical community. Disseminating this information takes both effort and resources. Manufacturers—who have both the necessary resources and the incentive to exert the necessary effort—have traditionally played a large and beneficial role in disseminating information about efficacious new uses of FDA-approved products.

FDA's 2009 guidance document on manufacturer distribution of medical literature[2] purports to recognize the important role in health care played both by off-label uses and by dissemination of truthful information about such uses:

> These off-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care. Accordingly, the public health may be advanced by healthcare professionals' receipt of medical journal articles and medical or scientific reference publications on unapproved or new uses of approved or cleared medical products that are truthful and not misleading.

2009 Guidance at 3.[3]

B. The First Amendment Imposes Significant Restrictions on the Government's Authority to Regulate Non-Misleading Speech Regarding Off-Label Uses

The Supreme Court has stated unequivocally that "speech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment." *Sorrell*, 131 S. Ct. at 2659. Putative regulators of such speech must overcome

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[2] FDA Final Guidance, "Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices" (Jan. 2009).

[3] *See also* FDA Draft Guidance, "Distributing Scientific and Medical Publications on Unapproved New Uses," at 6, 79 Fed. Reg. 11793 (March 3, 2014) ("this draft guidance, like the 2009 guidance, recognizes the value to health care professionals of truthful and non-misleading scientific or medical publications on unapproved new uses.")

significant First Amendment issues even if their regulations are subject to the somewhat relaxed standards generally applicable to commercial speech restrictions.

At a minimum, the Supreme Court requires that the government prove that the restriction "directly advances" a "substantial government interest" and is "narrowly tailored" to achieve a reasonable "fit" between an agency's stated goals and its means of achieving them. *Central Hudson Gas & Electric Corp. v. Public Serv. Comm'n*, 447 U.S. 557 (1980).[4] For the *Central Hudson* test to be satisfied, the Court must be persuaded that the cost of the regulation has been "carefully calculated." *City of Cincinnati v. Discovery Network, Inc.*, 507 U.S. 410, 416 n.12 (1993). The burden of justifying speech restrictions rests squarely with government regulators. *Thompson v. Western States Medical Center*, 535 U.S. 357, 373 (2002).[5]

FDA has on occasion argued that its regulation of manufacturer promotional activity does not implicate the First Amendment because FDA is regulating manufacturers' conduct, not their speech. It argues that it is not regulating speech *per se* but rather is merely using speech as evidence of manufacturers' intent to market their products for an unapproved new use and/or as

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[4] Under the four-part *Central Hudson* test, courts consider as a threshold matter whether the commercial speech concerns unlawful activity or is inherently misleading. If so, then the speech is not protected by the First Amendment. If the speech concerns lawful activity and is not inherently misleading, then the challenged speech regulation violates the First Amendment unless government regulators can establish that: (1) they have identified a substantial government interest; (2) the regulation "directly advances" the asserted interest; and (3) the regulation "is no more extensive than is necessary to serve that interest." *Central Hudson*, 447 U.S. at 566.

[5] The evidentiary burden is not light. For example, the government's burden of showing that a commercial speech regulation advances a substantial government interest "in a direct and material way . . . is not satisfied by mere speculation or conjecture; rather, a government body seeking to sustain a restriction on commercial speech must demonstrate that the harms it recites are real and that its restrictions will alleviate them to a material degree." *Rubin v. Coors Brewing Co.*, 514 U.S. 476, 487 (1995) (citations omitted).

evidence that the manufacturer is illegally distributing a misbranded drug (*i.e.*, "misbranded" because the product label does not contain adequate directions for the alleged intended new use). Federal courts have overwhelmingly rejected these the-First-Amendment-is-inapplicable arguments. *See, e.g.*, *Caronia*, 703 F.3d at 160-62; *Western States*, 535 U.S. at 365-68 (holding that Congress was regulating pharmacists' speech when it adopted a statute declaring that any pharmacy that advertised its drug compounding capabilities thereby transformed its otherwise unregulated compounded drugs into unapproved "new drugs" subject to FDA regulation). When FDA's only evidence that a manufacturer is marketing a new and misbranded drug consists of manufacturer speech about an FDA-approved product, it is disingenuous for FDA to assert that it is not regulating speech. As the Second Circuit explained in rejecting government claims that prosecutors were merely using off-label speech as evidence of illegal commercial conduct, "The government never suggested that Caronia engaged in any form of misbranding other than the promotion of the off-label use of an FDA-approved drug." *Caronia*, 703 F.3d at 161.

C. FDA's Speech Restrictions as Applied to Amarin Cannot Survive *Central Hudson* Scrutiny Because They Are Not Narrowly Tailored

The principal "substantial interest" that FDA asserts in support of its speech suppression is an interest in preventing doctors from being misled into believing that scientific evidence strongly supports the effectiveness of Vascepa for its proposed supplemental indication in treating patients with persistently high triglyceride levels. According to FDA:

> Amarin has not demonstrated with substantial evidence that Vascepa is effective to reduce the risk of coronary heart disease in statin-treated patients who have CVD or are at risk for CVD. Yet, the qualified health claim that Amarin seeks to use for Vascepa will suggest to physicians that Vascepa may be effective for that use in those patients. To the extent that a physician misapprehends the evidence underlying the qualified health claim Amarin seeks to use for Vascepa and prescribes Vascepa instead of a more effective treatment, the patient—already with CVD or at risk for

> CVD—could be harmed. For example, although it may not be Amarin's intent, the use of the qualified health claim could lead physicians to prescribe Vascepa in lieu of promoting healthy dietary and lifestyle changes or prescribing statin therapy, which is proven to reduce the risk of cardiovascular events. Thus, including the qualified health claim in connection with your distribution of Vascepa would be potentially harmful to the public health, and *FDA would consider such conduct to be potentially misleading or potential evidence of intended use*.

Woodcock Letter at 10 (emphasis added).

Even accepting that FDA could demonstrate that its speech suppression "directly advances" its interest in preventing statements that might mislead some doctors, FDA has not and cannot demonstrate that its policy satisfies the fourth prong of the *Central Hudson* test (narrow tailoring). There is no basis for concluding that appropriate disclaimers (which Amarin has offered to make) would be insufficient to eliminate any potential for doctors to be misled by Amarin's proposed health claim. As *Pearson* explained, "when government chooses a policy of suppression over disclosure—at least where there is no showing that disclosure would not suffice to cure misleadingness—government disregards a 'far less restrictive' means" of achieving the government's objectives. *Pearson*, 164 F.3d at 658.

FDA has chosen a policy of suppression over disclosure in this instance without any indication that it has engaged in a "careful[ ] calculat[ion]," *Discovery Network*, 507 U.S. at 416 n.12, to determine whether a policy of compelled disclosures would serve its interests equally well. FDA asserts, "[T]he use of the qualified health claim could lead physicians to prescribe Vascepa in lieu of promoting healthy dietary and lifestyle changes or prescribing statin therapy, which is proven to reduce the risk of cardiovascular events." But FDA's concern that some doctors might be misled could be fully addressed by requiring disclaimers such as, "Statin therapy has been proven effective in reducing the risk of cardiovascular events; consumption of

omega-3 fatty acids should be viewed as a supplement to, not a replacement for, statin therapy in patients already diagnosed with CVD or at risk for CVD"; or "Patients should be reminded that consumption of Vascepa or other products containing omega-3 fatty acids should not be viewed as a substitute for healthy dietary and lifestyle changes, both of which have been proven to reduce the risk of cardiovascular events." Doctors are a highly educated audience; FDA has demonstrated no basis for suspecting that doctors would misapprehend the import of disclaimers of that nature.

There are instances, of course, in which a health claim is so unsupported that no disclaimers would be sufficient to eliminate the possibility that doctors might be misled, because *any* reliance on an outlandish health claim is unwarranted. But FDA has never attempted to put Amarin's proposed health claim in that category, nor could it. Even FDA recognizes that there is *some* reliable scientific evidence that supports the proposed health claim. Indeed, as Amarin has explained, for over a decade FDA has permitted manufacturers that sell dietary supplements containing EPA and/or DHA to convey to *consumers* (a group much more prone to misunderstanding medical information than are doctors) the very same qualified health claim that Amarin now proposes to make to doctors. FDA asserts that Amarin has not demonstrated Vascepa's effectiveness with respect to the proposed supplemental indication with "substantial evidence" (Woodcock Letter at 10)—by which FDA means a double-blind, placebo-controlled study of the sort that Amarin is now undertaking. But FDA does not contest that the numerous peer-reviewed scientific publications listed in Exhibit A to the Complaint provide at least some "supportive" research that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease.

Nor has FDA supplied a coherent explanation for its apparent position that the First Amendment somehow provides fewer speech protections for drug manufacturers than for dietary supplement manufacturers. FDA states that its differing treatment of drug labeling and dietary supplement labeling "is a consequence of the different regulatory regimes, established by statute and regulation, for these products." Woodcock Letter at 9. That statement is incorrect. FDA permits dietary supplement manufacturers to make health claims regarding the consumption of omega-3 fatty acids because it was effectively ordered to do so by *Pearson*, which based its ruling against FDA on the First Amendment, not on statutory grounds. The D.C. Circuit concluded that FDA's ban on a dietary-supplement health claim—that "consumption of omega-3 fatty acids may reduce the risk of coronary heart disease"—flunked *Central Hudson*'s narrow tailoring requirement because any danger that consumers would be misled could be alleviated with disclaimers. *Pearson*, 164 F.3d at 658-59. FDA has supplied no evidence suggesting that disclaimers would be less effective when directed at doctors than when directed at consumers.[6]

In sum, in the absence of any demonstration by FDA that disclaimers would be ineffective in preventing doctors from being misled, Amarin is entitled to a preliminary injunction against FDA's blanket ban on Amarin's proposed qualified health claim. The Supreme Court has repeatedly held that blanket speech bans run afoul of the fourth *Central Hudson* prong when the government could satisfy its substantial interests by imposing disclaimer

[6] FDA argued in *Pearson* that outright suppression of the omega-3 fatty acid claim was warranted in part because consumers were particularly susceptible to being misled given that "the consumer would have difficulty in independently verifying" health claims. *Id.* at 655. That argument suggests that despite its current litigating position, FDA actually believes that more stringent speech restrictions are warranted when dietary supplement manufacturers convey health claims directly to consumers than when drug manufacturers convey health claims to well-trained medical professionals.

requirements on would-be speakers. *Western States*, 535 U.S. at 376; *44 Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 507 (1996); *In re R.J.M.*, 455 U.S. 191, 203 (1982).

D. FDA's Speech Restrictions as Applied to Amarin Cannot Survive *Central Hudson* Scrutiny for the Additional Reason That They Do Not Directly Advance FDA's Interest in Preventing Doctors from Being Misled

FDA's efforts to suppress speech about off-label uses of FDA-approved drugs swim against the tide of modern medicine. FDA's suppression of manufacturer speech is motivated by its desire to reduce the likelihood that doctors will inappropriately prescribe an FDA-approved drug for an off-label use as a result of potentially misleading information conveyed to them by the drug's manufacturer. FDA undoubtedly has a strong interest in preventing doctors from being misled. But given the prevalence of off-label prescriptions in virtually all areas of medicine and the widespread availability of information about the safety and effectiveness of numerous off-label indications, there is strong reason to conclude that FDA's concerted efforts at speech suppression do nothing to improve the quality of information that reaches doctors. Accordingly, FDA's speech suppression also fails the third prong of the *Central Hudson* test: it does not directly advance FDA's interest in preventing doctors from being misled.

FDA has approved Vascepa for use as an adjunct to diet to reduce triglycerides in adult patients with "very high triglycerides." But recent data show that approximately half of all Vascepa prescriptions are for off-label uses, *e.g.*, to treat patients with "high triglycerides" or "persistently high triglycerides." Pltf. Br. 4. The prevalence of such off-label prescriptions indicates that many doctors, after reviewing the available literature and using their best medical judgment, have concluded that prescribing Vascepa provides a medical benefit to their patients with "high triglycerides" or "persistently high triglycerides" (the latter being a subset of the

former). Accordingly, FDA suppression of Amarin's speech has not prevented doctors from receiving and acting on information regarding the health benefits of lowering triglyceride levels among patients with high and/or persistently high triglycerides.

That doctors have ready access to such information is not surprising, given the highly targeted nature of FDA's speech suppression: it applies to Amarin and manufacturers of similar drugs but to no one else. Whether FDA can satisfy the third prong of the *Central Hudson* test (*i.e.*, whether its speech suppression directly advances its interests in preventing doctors from being misled) thus depends on whether FDA can demonstrate that the quality of information doctors receive is improved by preventing Amarin from weighing in on the issue. The evidence available to date suggests that FDA cannot make that demonstration.

Amarin proposes telling doctors that "[s]upportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease." In order to ensure that such statements do not mislead doctors, Amarin has promised to append numerous disclaimers to the statements, such as that "FDA has not approved Vascepa to reduce the risk of coronary heart disease." It is difficult to understand how FDA's rejection of that proposal reduces the likelihood that doctors will be misled regarding the safety and effectiveness of off-label use of Vascepa. The data indicate that numerous doctors are already prescribing Vascepa off-label in order to reduce the risk of coronary heart disease among those with high and/or persistently high triglycerides. They are doing so on the basis of information from sources other than Amarin (such as clinical guidelines and medical compendia that endorse use of Vascepa to treat patients with persistently high triglycerides) but not from Amarin itself. Given the large number of doctors who currently prescribe Vascepa for patients with persistently

high triglycerides, it stands to reason that the quality of their decision-making with respect to future prescriptions is likely to improve if they are granted access to non-misleading information from Amarin.

FDA will have an opportunity, when it files its opposition brief, to present evidence that its speech suppression directly advances its substantial interest in preventing doctors from being misled. WLF wishes to emphasize, however, that FDA's burden of proof is weighty. It must demonstrate that its speech suppression advances the government's interest in "a direct and material way." *Edenfield v. Fane*, 507 U.S. 761, 767 (1993). The Supreme Court has emphasized that this requirement cannot be satisfied with mere speculation and conjecture. Rather, the burden is on FDA to "demonstrate that the harms it recites are real and that its restrictions will in fact alleviate them to a material degree." *Coors Brewing*, 514 U.S. at 486. FDA has not to date made any such demonstration.

II. AMARIN IS ENTITLED TO IMMEDIATE JUDICIAL REVIEW OF ITS FIRST AMENDMENT CLAIMS GIVEN THE LIKELIHOOD THAT IT WILL BE SANCTIONED IF IT COMMUNICATES WITH DOCTORS IN THE MANNER THAT IT PROPOSES

The June 5, 2015 Woodcock Letter strongly hints that FDA's opposition brief will argue that the lawsuit should be dismissed because it is premature. Any such argument is not well taken. Given the likelihood that Amarin will be sanctioned if it conveys its proposed health claims to doctors, Amarin can demonstrate both that it has standing to assert its claims and that this case is ripe for review.

To establish Article III standing, a plaintiff must show: (1) an injury in fact; (2) a sufficient causal connection between the injury and the conduct complained of; and (3) a likelihood that the injury will be redressed by a favorable decision. *Lujan v. Defenders of*

Wildlife, 504 U.S. 555, 560-61 (1992). The mere threat of government enforcement of the law against an individual or entity is enough to satisfy the injury-in-fact requirement, provided that the threatened enforcement is sufficiently imminent. *Susan B. Anthony List v. Druehaus*, 134 S. Ct. 2334, 2342 (2014). The Supreme Court recently explained the imminence requirement as follows:

> [A] plaintiff satisfies the injury-in-fact requirement where he alleges an intention to engage in a course of conduct arguably affected with a constitutional interest, but proscribed by a statute, and there exists a credible threat of prosecution thereunder.

Ibid. (citation omitted).

Amarin satisfies the injury-in-fact prerequisites set forth in *Susan B. Anthony List*. It is proposing to exercise its constitutionally protected freedom of speech. Its speech is arguably prohibited by the FDCA. And the threat of prosecution under the FDCA is "credible" given FDA's threats—in both the Complete Response Letter and the Woodcock Letter—that Amarin could be subject to prosecution if it goes ahead with its proposed speech. *See, e.g.*, Woodcock Letter at 10 ("[I]ncluding the qualified health claim in connection with your distribution of Vascepa would be potentially harmful to the public health, and FDA would consider such conduct to be potentially misleading or potential evidence of intended use.").

Amarin's case is also ripe for review. The ripeness doctrine is designed to protect government agencies from "premature judicial interference" and to delay review until "an administrative decision has been formalized and its effects felt in a concrete way by the challenging party." *Abbott Labs. v. Gardner*, 387 U.S. 136, 149 (1967). There is nothing "premature" about Amarin's lawsuit, which challenges FDA speech suppression policies that have been consistently articulated by the agency for at least 25 years. Moreover, the Woodcock

Letter is unequivocal in its rejection of Amarin's proposed health claim. The Second Circuit has made clear that a claim is particularly likely to be deemed ripe when, as here, it raises First Amendment claims and when the plaintiff challenges the government's speech restrictions as applied to specific statements the plaintiff wishes to make. *Nutritional Health Alliance v. Shalala*, 144 F.3d 220, 225-27 (2d Cir. 1998).

FDA's June 5, 2015 letter hinted that the agency may seek dismissal of the complaint on ripeness grounds, stating, "FDA is currently engaged in a comprehensive review of its regulations and guidance documents regarding manufacturers' dissemination of information regarding their medical products, and new guidance will be forthcoming." Woodcock Letter at 5-6. But given FDA's unequivocal rejection of Amarin's proposed health claim, FDA's assertion that it is engaged in a "comprehensive review" of its restrictions on manufacturer speech does not justify postponing consideration of Amarin's First Amendment claims.

Moreover, FDA has declared on a number of occasions over the past several decades that it was undertaking a review of its speech policies in the aftermath of court decisions striking down agency actions on First Amendment grounds. *See, e.g.*, FDA, *Request for Comments on First Amendment Issues*, 67 Fed. Reg. 34942 (May 16, 2002). Despite such FDA declarations, WLF is unaware of any FDA documents that address First Amendment limitations on FDA's regulation of manufacturer speech. None of the FDA guidance documents issued over the past two decades that discuss manufacturer dissemination of off-label information include any reference to the First Amendment. The glaring absence of indications that FDA takes First Amendment constraints into account when formulating its speech regulation policies provides all the more reason for Amarin to fear that it will face severe FDA sanctions if it communicates with

doctors in the manner it contemplates—and thus why consideration of its First Amendment claims should not be deferred.[7]

WLF's own litigation history with FDA indicates that the agency will not let its past defeats in First Amendment litigation stand in the way of its efforts to restrain manufacturer dissemination of information about off-label product uses. WLF filed suit against FDA in 1995 on behalf of doctors who complained that the agency was violating their First Amendment rights by interfering with their receipt of medical information about safe and effective off-label uses. The court granted summary judgment for WLF in 1998, ruling that FDA violated the First Amendment by adopting a policy that severely restricted manufacturer dissemination of medical texts and peer-reviewed journal articles. *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998). The court entered an injunction that provided in pertinent part:

> Defendants SHALL NOT in any way prohibit, restrict, sanction or otherwise seek to limit any pharmaceutical or medical device manufacturer or any other person:
>
> a) from disseminating or distributing to physicians or other medical professionals any article concerning prescription drugs or medical devices previously published in a bona fide peer-reviewed professional journal, regardless of whether such article includes a significant or exclusive focus on uses of drugs or medical devices other than those approved by FDA and regardless of whether such article

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[7] One can also infer from the Woodcock Letter that FDA also intends to argue that much of the complaint should be dismissed on mootness grounds. The letter suggests that FDA does not object to significant portions of what Amarin intends to say, and that FDA would have told Amarin as much had Amarin bothered to ask before filing its lawsuit. *See, e.g.*, Woodcock Letter at 1 (""[Y]ou did not ask for our views before filing the complaint. . . . [W]e do not have concerns with much of the information you proposed to communicate."). A close comparison of the complaint and the Woodcock Letters reveal, however, that the parties' positions are widely divergent. For example, while agreeing that Amarin should be permitted to distribute the results of the ANCHOR study, FDA seeks to impose major restrictions on the means of distribution. *See* Woodcock Letter at 7 (FDA calls on Amarin to distribute this information "in educational or scientific settings only."). The language of the complaint suggests that Amarin asserts a First Amendment right to disseminate the results of the study in a far less restricted manner.

> reports the original study on which FDA approval of the drug or device in question was based;
>
> b) from disseminating or redistributing to physicians or other medical professionals any reference textbook (including any medical textbook or compendium) or any portion thereof published by a bona fide independent publisher and otherwise generally available for sale in bookstores or other distribution channels where similar books are normally available, regardless of whether such reference textbook or portion thereof includes a significant or exclusive focus on uses of drugs or medical devices other than those approved by FDA.

Id. at 73-74. While other portions of the court's injunction were subsequently vacated as moot, the portions quoted above remain in force.

FDA later argued that the injunction applied only to two FDA guidance documents issued in 1996[8] and did not apply to later agency action addressing manufacturer dissemination of medical texts and journal reprints containing off-label information. In a February 1999 order the district court denied that its injunction was so narrow in scope. *Washington Legal Found. v. Friedman*, 36 F. Supp. 2d 16, 18 (D.D.C. 1999). The court explained that it had not intended merely to address the validity of the two 1996 guidance documents but rather to address the validity of "the policies underlying the Guidance Documents," and thus that FDA was enjoined from adopting similar restrictions on manufacturer speech in the future. *Id.* FDA appealed, but the D.C. Circuit dismissed the appeal after determining that FDA had largely abandoned it. *Washington Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000). The appeals court vacated a portion of the injunction as moot, but stated explicitly that the remainder of the injunction (including the portions quoted above) remained in place. *Id.* at 334 n.4 & 337 n.7.

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[8] *See* "Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data," 61 Fed. Reg. 52800 (Oct. 8, 1996); "Guidance for Industry Funded Dissemination of Reference Texts," 61 Fed. Reg. 52800 (Oct. 8, 1996).

Despite the injunction and FDA's other First Amendment defeats (including the Second Circuit's decision in *Caronia*), FDA continues to assert its right to suppress all manufacturer speech concerning off-label use. Under those circumstances, Amarin's fear of prosecution is eminently reasonable, and it has every right to insist that consideration of its First Amendment claims not be deferred.

CONCLUSION

Amicus curiae WLF respectfully requests that the Court grant the motion for a preliminary injunction.

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Respectfully submitted,

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