UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

AMARIN PHARMA, INC., et al., Plaintiffs, v. UNITED STATES FOOD & DRUG ADMINISTRATION, et al., Defendants.	Civil Action No. 1:15-cv-03588-PAE

BRIEF OF *AMICUS CURIAE* PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA IN SUPPORT OF PLAINTIFFS' MOTION FOR PRELIMINARY INJUNCTION

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INTEREST OF *AMICUS CURIAE* [1]

The Pharmaceutical Research and Manufacturers of America ("PhRMA") is a voluntary, nonprofit association representing the Nation's leading research-based pharmaceutical and biotechnology companies. PhRMA's mission is to advocate public policies that encourage the discovery of life-saving and life-enhancing medicines. PhRMA's members are dedicated to discovering medicines that help patients lead longer, healthier, and more productive lives. In 2014 alone, PhRMA's members invested an estimated $51.2 billion in efforts to discover and develop new medicines. *See* PhRMA, 2015 Biopharmaceutical Research Industry Profile, at 36 fig.13 (2015), http://www.phrma.org/sites/default/files/pdf/2015_phrma_profile.pdf. PhRMA frequently files *amicus curiae* briefs in cases raising matters of significance to its members.

PhRMA has a substantial interest in ensuring that the courts fully protect pharmaceutical manufacturers' ability to share truthful, non-misleading information about the medicines that they research and develop – their First Amendment rights – and thus has a significant interest in this case. Like Plaintiff Amarin Pharma, Inc. ("Amarin"), PhRMA members market and sell FDA-approved medicines which doctors also prescribe for additional uses not approved by FDA. PhRMA members want to provide healthcare professionals with truthful, non-misleading information to help them decide whether to treat patients with these drugs, but the threat of civil or criminal liability chills such speech. PhRMA members operate under the same FDA regulations banning promotion of unapproved uses of medicines that Plaintiffs identify in their Complaint.

[1] No counsel for a party authored this brief in whole or in part, and no party or counsel for a party made a monetary contribution intended to fund the preparation or submission of this brief. No one other than PhRMA, its members, or its counsel made a monetary contribution to the preparation or submission of this brief. Amarin Pharma, Inc. ("Amarin") is not a member of PhRMA.

INTRODUCTION

The Government's reading of the Food, Drug, and Cosmetics Act ("FDCA") as applied in this case would potentially make Amarin criminally and civilly liable for providing truthful and non-misleading scientific and medical information to well-trained health care professionals regarding unapproved uses of FDA-approved drugs or data that are not contained in the FDA-approved labeling for such medicines. That reading conflicts with Supreme Court and Second Circuit precedent. Applying Supreme Court rulings regarding communications about drugs, the Second Circuit has recognized First Amendment protection for manufacturers' speech about unapproved uses and has found that the Government's asserted interests in preserving the integrity of FDA's drug approval process does not justify blanket prohibitions against truthful and non-misleading speech. *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012). Instead, patients benefit when their healthcare professionals receive more—not less—truthful, non-misleading information about the medicines they prescribe.

The Government's justifications for censoring truthful speech ring particularly hollow as applied to the Plaintiffs in this case. Even though the Government would bar manufacturers from sharing information about unapproved uses of FDA-approved drugs with doctors, those healthcare professionals—exercising their own independent medical judgment—may lawfully prescribe the drugs for those same unapproved purposes. *See Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001). In fact, unapproved uses of prescription drugs are integral to the practice of medicine, and many such uses reflect the standard of patient care and are included in medical compendia upon which doctors rely in considering prescribing options. Prescribing Amarin's drug, Vascepa, to treat patients with persistently high triglycerides is a medically accepted, unapproved use that is integral to the practice of medicine. The truthful and non-

misleading speech that Amarin and the Physician Plaintiffs have identified in their Complaint, therefore, does not cause or abet illegal acts when it influences a doctor's decision to prescribe the drug for this use. As the Second Circuit has explained, "prohibiting off-label promotion by a pharmaceutical manufacturer while simultaneously allowing off-label use 'paternalistically' interferes with the ability of physicians and patients to receive potentially relevant treatment information; such barriers to information could inhibit, to the public's detriment, informed and intelligent treatment decisions." *Caronia*, 703 F.3d at 166.

Because doctors routinely lawfully prescribe FDA-approved drugs for unapproved uses, informed patient care relies upon doctors having access to accurate, comprehensive, and current information about such uses. Biopharmaceutical manufacturers are an important source of this knowledge. Amarin has a First Amendment right to provide such truthful and non-misleading information. Doctors have a First Amendment right to receive it. And patients have a strong health-related interest in this Court's affirmation of those rights.

FDA's recent made-for-litigation "regulatory letter" to Amarin does not cure the constitutional defects in FDA's content-based restrictions on protected speech. In a footnote, FDA exacerbates and reinforces them: the footnote reiterates in broad strokes the Agency's longstanding position that the FDCA and FDA's implementing regulations prohibit manufacturers from speaking to healthcare professionals about unapproved uses. 06/05/15 FDA Letter at 1 n.1. Beyond that, the letter purports to be an exercise of enforcement discretion, relies on "draft" guidance documents that FDA itself contends do not bind the Agency, and contains significant caveats that preserve the Government's option to pursue criminal and civil enforcement based on manufacturers' protected speech. What is more, the letter is an ad hoc, discretionary implementation of prior draft guidance documents in the context of litigation; it

does not have the force of a regulation and does not provide meaningful guidance to manufacturers. Rather than solve the problem, therefore, the letter only highlights the burden that FDA's regulations regularly impose on manufacturers and the Agency's invocation of its own vague and malleable discretion rather than publication of clear, binding guidance that comports with constitutional requirements.

ARGUMENT

I. Unapproved Uses of FDA-Approved Medicines Are Lawful, Commonplace in Modern Medical Practice, and Critical to Patient Care.

The critical role that alternative, unapproved uses of FDA-approved medicines play in modern medical practice magnifies the harms caused by the threat of liability in this case. An unapproved or "off-label" use is not a *disapproved* use. Those terms merely describe the regulatory status of a particular use of an FDA-approved medication or medical device. *See* James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 Food & Drug L.J. 71, 83 (1998). Typically, FDA has made no qualitative judgment at all regarding an unapproved use. Thus, describing a particular use of a medication as "off-label" or "unapproved" in no way suggests that the use is "medically inappropriate." *See id.* at 83-85.

In fact, FDA does not have authority to deem a particular use of an approved drug "medically inappropriate." Congress explicitly limited FDA's regulatory authority to overseeing issues in the manufacture and commercialization of drugs, and did *not* extend the Agency's authority to the practice of medicine. In particular, the FDCA does not limit or interfere with the ability of physicians to prescribe FDA-approved drugs to any patient to treat any condition or disease, whether or not the drug is approved for that use. *See Buckman Co.*, 531 U.S. at 350 ("'[O]ff-label' usage of medical devices . . . is an accepted and necessary corollary of the FDA's

mission to regulate in this area without directly interfering with the practice of medicine."); *Wash. Legal Found. v. Henney*, 202 F.3d 331, 333 (D.C. Cir. 2000) ("A physician may prescribe a legal drug to serve any purpose that he or she deems appropriate, regardless of whether the drug has been approved for that use by the FDA.").

FDA itself has stated that "[o]nce a drug or medical device has been approved or cleared by FDA, generally, healthcare professionals may lawfully use or prescribe that product for uses or treatment regimens that are not included in the product's approved labeling." FDA, *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), http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm (hereinafter "FDA Good Reprint Practices"); *accord* Nat'l Insts. of Health, Nat'l Cancer Inst., *Off-Label Drug Use in Cancer Treatment* (Jan. 1, 2014), http://www.cancer.gov/about-cancer/treatment/drugs/off-label ("[O]nce the FDA approves a drug, doctors can prescribe it for any purpose that they think makes sense for the patient."). Although FDA determines the overall safety and efficacy of a drug as part of the drug approval process, the Agency does not determine all the uses for which a drug may be safe and effective. Thus, even if FDA had the authority, the Agency is in no position to overrule the medical judgment of a healthcare professional regarding the benefits of a drug in treating his or her patients. The prescribing physician is in the best position to understand the patient's medical history, condition, and potential responsiveness to a prescription drug.

Moreover, federal regulation cannot always keep pace with advances in medical practice. For example, the development of real world evidence concerning a drug's safety and effectiveness for treating a particular condition commonly outpaces the FDA supplemental drug

approval process, which is time-consuming and expensive. As a result, unapproved uses are not only lawful, but also integral to the practice of medicine in the United States. As the American Medical Association has recognized, "[t]he prevalence and clinical importance of prescribing drugs for unlabeled uses are substantial." Joseph W. Cranston et al., *Report of the Council on Scientific Affairs: Unlabeled Indications of Food and Drug Administration-Approved Drugs*, 32 Drug Info. J. 1049, 1050 (1998); *see also* Dep't of Defense, TRICARE; Off-Label Uses of Devices; Partial List of Examples of Unproven Drugs, Devices, Medical Treatments, or Procedures, 77 Fed. Reg. 38,177, 38,177 (June 27, 2012) ("In general, good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics, and devices . . . according to their best knowledge and judgment."); AHFS, Drug Information xiv (2012) ("[A]ccepted medical practice (state-of-the-art) often includes drug use that is not included in FDA-approved labeling."); *More Information for Better Patient Care: Hearing on S. 1477 Before the S. Comm. on Labor and Human Resources*, 104th Cong. 81 (1996) (statement of William B. Schultz, then-FDA Deputy Commissioner for Policy) ("[I]n certain circumstances, off label uses of approved products are appropriate, rational, and accepted medical practice. FDA knows that there are important off label uses of approved drugs.").

The frequency with which doctors rely upon unapproved uses to help their patients substantiates this point. In 2001, approximately 150 million prescriptions—21% of all prescriptions—were for unapproved uses. David C. Radley et al., *Off-label Prescribing Among Office-Based Physicians*, 166 Archives Internal Med. 1021, 1021 (2006). In some medical specialties, such as pediatrics and oncology, the majority of prescriptions are for alternative, unapproved uses of FDA-approved medicines, in part because it is exceptionally difficult to conduct the clinical trials necessary to secure drug approval with children, and cancer patients

often cannot wait for the completion of a multi-year clinical-trial process to secure FDA supplemental approval for a new use. According to the American Academy of Pediatrics, "80 percent of drugs administered to children are given off-label." U.S. Gen. Accounting Office, GAO/T-HEHS-96-212, *Prescription Drugs: Implications of Drug Labeling and Off-Label Use* 3 n.6 (1996). "The off-label use of drugs in oncology has been estimated to reach 50%, or even more." Paolo G. Casali, Editorial, *The Off-Label Use of Drugs in Oncology: A Position Paper by the European Society for Medical Oncology (ESMO)*, 18 Annals Oncology 1923, 1923 (2007).

Alternative, unapproved uses of FDA-approved medicines in these and other specialties can be central to patient care in the most critical situations. A 2012 study showed that when adult critical care patients receive antibiotics, the use is off-label between 19% and 43% of the time, depending on the drug involved. G.S. Tansarli, et. al, *Frequency of the off-label use of antibiotics in clinical practice: a systematic review* (Dec. 2012), http://www.ncbi.nlm.nih.gov/pubmed/23253317. And research presented at the American Academy of Pediatrics National Conference and Exhibition showed that for pediatric patients in the intensive care unit, 96% of prescribed medications were used off-label. *Off-Label Medications Prescribed to Nearly All Pediatric Intensive Care Patients* (Oct. 21, 2012), http://www.aap.org/en-us/about-the-aap/aap-press-room/Pages/Off-Label-Medications-Prescribed-to-Nearly-All-Pediatric-Intensive-Care-Patients.aspx.

Alternative, unapproved uses of FDA-approved medicines are not only widely accepted in the medical profession, but often are the established standard of care that healthcare professionals must meet in treating patients. *See* FDA Good Reprint Practices, *supra* ("[O]ff-label uses or treatment regimens . . . may even constitute a medically recognized standard of

care."). That standard can require doctors to prescribe a drug for an unapproved use where, as commonly occurs, FDA has not approved any drug to treat a patient's disease or condition. The National Cancer Institute, for instance, has explained that "[r]esearch has shown that off-label use of drugs is very common in cancer treatment. Often, usual care for a specific type or stage of cancer includes the off-label use of one or more drugs." Nat'l Insts. of Health, Nat'l Cancer Inst., *supra*.

Reflecting that unapproved uses are often clinically effective and medically necessary, federal law authorizes—and, in some instances, requires—the government to provide reimbursement for such uses. The Medicaid Act, for example, directs the Secretary of Health and Human Services to reimburse states, healthcare professionals, hospitals, and patients for any unapproved use that is "medically accepted." 42 U.S.C. § 1396r-8(d)(1)(B)(i). Congress defined the phrase "medically accepted" to mean *either* that FDA has approved the drug for the prescribed use, *or*, absent FDA approval, that one or more of three specified drug compendia cite the use. *See id.* § 1396r-8(k)(6). Compendia are government-sanctioned bodies composed of clinical experts that conduct evidence-based analyses of treatment options that may be useful for physicians. The compendia then make their evidentiary findings available to health care professionals.

The three compendia specified in the Medicare and Medicaid statutes, *id.* § 1396r-8(g)(1)(B)(i)—American Hospital Formulary Service (AFHS) Drug Information, United States Pharmacopeia-Drug Information (or its successor publications), and the DRUGDEX Information System—are examples of such summaries of drug information compiled by clinical experts who have reviewed the clinical records relating to medicines. For anticancer chemotherapeutic drugs, the Social Security Act, section 1861(t)(2), names an additional authoritative compendium—

American Medical Association Drug Evaluations—and also authorizes the Secretary of Health and Human Services to identify other sources for medically accepted alternative, unapproved uses. *Id.* § 1395x(t)(2)(B). The Medicaid Act also expressly requires states to establish coverage for a particular use of a drug based on broad medical acceptance, whether or not FDA has approved the use. *See id.* § 1396r-8(d)(4)(C). The Medicare Part D prescription-drug benefit program similarly covers unapproved uses that are *neither* FDA-approved *nor* cited in a compendium. *See Layzer v. Leavitt*, 770 F. Supp. 2d 579, 583-84 (S.D.N.Y. 2011) (citing 42 U.S.C. § 1395w-102(e) and holding that federal agency unlawfully refused to provide Part D coverage for alternative uses of medicines that were neither FDA-approved nor listed in any of the statutory compendia).

II. As the Second Circuit Recognized in *Caronia,* Doctors Need Access to Accurate Information About Medically Accepted Unapproved Uses of FDA-Approved Drugs, Including Information That Manufacturers Provide.

Given the widespread, medically accepted, and government-subsidized uses of numerous FDA-approved prescription medicines for unapproved indications, healthcare professionals need accurate, comprehensive, and current information about those uses.

FDA itself has affirmed "[t]he principle . . . that the very latest information that can be of value to physicians, pharmacists, and patients must be made available as soon as possible. Frequently, unlabeled use information is extremely important." Stuart L. Nightingale, then-FDA Associate Commissioner for Health Affairs, *Unlabeled Uses of Approved Drugs,* 26 Drug Info. J. 141, 145 (1992). FDA has further "recognize[d] . . . the important public health and policy justification supporting dissemination of truthful and non-misleading medical journal articles and medical or scientific reference publications on unapproved uses of approved drugs and approved or cleared medical devices to healthcare professionals and healthcare entities." FDA Good Reprint Practices, *supra*. FDA has even conceded that "public health may be advanced by

healthcare professionals' receipt of medical journal articles and medical or scientific reference publications on unapproved new uses of approved or cleared medical products that are truthful and not misleading." *Id.*

Healthcare professionals have finite time they must devote both to treating patients and keeping up with developments in their fields. In most cases, the manufacturer of a medicine—which researched and developed the medicine, tracks and transmits to the government physician reports on their experience with the medicine, and follows closely the medical literature reports on the medicine—will have the most up to date information regarding the manufacturer's own product. In some cases, as with Amarin here, the manufacturer will have designed and carried out the very study that advances medical understanding of the benefits of its drug, putting the manufacturer in the best position to share and explain those findings. Without that information, physicians may overlook useful treatments for their patients.

In *Caronia*, the Second Circuit recognized the need for the free flow of truthful, non-misleading information about lawful uses of FDA-approved drugs, including from the manufacturers of those drugs. It observed that "in the fields of medicine and public health, 'where information can save lives,' it only furthers the public interest to ensure that decisions about the use of prescription drugs, including off-label usage, are intelligent and well-informed." 703 F.3d at 167. The court of appeals clarified that the facts of the case did not involve false or misleading communications, and therefore the drug manufacturer could share its information and let doctors determine the best course of action, taking into consideration information from the manufacturer as well as all other factors, including the drug's FDA-approval status. *Id.* (quoting *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 367 (2002)), for the proposition that "the

speaker and the audience, not the government, assess the value of the information presented"). So too here.

In this case, Amarin's medication Vascepa is listed in a medical compendium (AHFS Drug Information) as a treatment for persistently high triglyceride levels. *See* Decl. of Steven Ketchum in Supp. of Pls.' Mot. for Prelim. Inj. ¶ 115 (May 22, 2015) (Doc. 12). The medicine is prescribed by doctors such as the Physician Plaintiffs, based on their medical training, for treatment of this condition even though such use has not been approved by FDA. Furthermore, Amarin's proposed speech, outlined in the Complaint and Motion for Preliminary Injunction, is carefully qualified, with multiple disclaimers, so as to avoid any risk of misleading the sophisticated and well-trained medical audience Amarin wants to address. The free flow of this information is consistent with the First Amendment and this Circuit's precedent.

III. Controlling First Amendment Principles Preclude Censoring Amarin's Proposed Speech.

A. Holding Amarin Liable Based on the Content of the Speech and the Identity of the Speaker Would Be Presumptively Unconstitutional.

As the Supreme Court reaffirmed in *Sorrell v. IMS Health, Inc.*, 131 S. Ct. 2653 (2011), "[s]peech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment." *Id.* at 2659. The First Amendment does not merely protect Amarin's proposed speech; it affords heightened protection to it. Even after FDA's June 5 letter to Amarin, FDA cannot enforce its off-label promotion regulations against Amarin's effort to share information about Vascepa because to do so would be a content-based and speaker-based restriction on speech disfavored by the government.

FDA's regulations single out Amarin's speech for liability based on its content. A content-based restriction "distinguishes between 'favored speech' and 'disfavored speech on the basis of the ideas or views expressed.'" *Caronia,* 703 F.3d at 165 (quoting *Turner Broad. Sys.,*

Inc. v. FCC, 512 U.S. 622, 643 (1994)). As illustrated by past prosecutions, warning letters, and public statements, the Government targets manufacturers' speech about unapproved uses, even where those uses are medically accepted. *Id.* at 154 ("The government has repeatedly prosecuted—and obtained convictions against—pharmaceutical companies and their representatives for misbranding based on their off-label promotion."); *id.* at 164-65 (holding that "[t]he government's construction of the FDCA's misbranding provisions to prohibit and criminalize the promotion of off-label drug use by pharmaceutical manufacturers" was a content-based restriction on speech); *see also, e.g.*, FDA Warning Letter to Marc Beer, CEO, Aegerion Pharmaceuticals, Inc. (Nov. 8, 2013) (threatening enforcement action based on an executive's statements on a television news program). That is a quintessential content-based restriction on speech.

FDA's regulations also single out manufacturers' speech for liability based on the identity of the speaker. The Government prosecutes manufacturers, *and only manufacturers*, for their truthful and non-misleading speech concerning unapproved uses of their drugs, even if those uses are medically accepted as is the case here. Truthful information that a physician independently hears or reads about an approved or unapproved use (*e.g.*, in a peer-reviewed medical journal, on the Internet, or from another doctor, an insurance company, or a government representative) is not subject to any restriction. But a manufacturer that said exactly the same thing would risk criminal and civil liability under FDA's regulations. The regulations thus "ha[ve] the effect of preventing [manufacturers]—and only [manufacturers]—from communicating with physicians in an effective and informative manner." *Caronia*, 703 F.3d at 165 (quoting *Sorrell*, 131 S. Ct. at 2663).

Laws that impose content- and speaker-based burdens on manufacturers' speech are subject to heightened judicial scrutiny, whether the speech is commercial or non-commercial. All such restrictions are presumptively unconstitutional. *Sorrell*, 131 S. Ct. at 2665; *Caronia*, 703 F.3d at 162-63. "In the ordinary case it is all but dispositive to conclude that a law is content-based and, in practice, viewpoint-discriminatory" because "'[c]ontent-based regulations are presumptively invalid.'" *Sorrell*, 131 S. Ct. at 2667 (quoting *R.A.V. v. St. Paul*, 505 U.S. 377, 382 (1992)). That is particularly the case when the restrictions impose criminal liability for engaging in speech. *Caronia*, 703 F.3d at 163 (citing cases). Because the threat of criminal liability for Amarin's proposed statements about Vascepa is content- and speaker-based, there is no need to judge whether that proposed speech is designed to effect a transaction or is otherwise commercial in nature. The Government cannot overcome the strong presumption that the ban is unconstitutional.

B. Holding Amarin Liable For Its Proposed Speech Would Fail the *Central Hudson* Test.

Restricting Amarin's truthful statements about Vascepa also cannot withstand the intermediate scrutiny applicable to infringements on commercial speech under *Central Hudson Gas & Electric Corp. v. Public Service Commission of N.Y.*, 447 U.S. 557 (1980). The First Amendment permits restrictions on commercial speech only if: (a) the speech "concerns unlawful activity or is misleading"; or (b) the restriction (1) furthers a "substantial" governmental interest, (2) does so "directly," and (3) does so without being "more extensive than is necessary to serve that interest." *Thompson*, 535 U.S. at 367; *accord Cent. Hudson*, 447 U.S. at 565-67.

As discussed above, Amarin's proposed speech does not concern unlawful activity because the unapproved use of Vascepa to treat patients with persistently high triglycerides is

lawful.[2] Nor could the type of speech that Amarin proposes—carefully qualified speech about well-supported research—come close to being misleading.[3] (Indeed, the proposed disclaimers, in our view, go well beyond the level necessary to ensure truthful and non-misleading speech entitled to First Amendment protection.) Therefore, even if the *Central Hudson* framework were applicable, any government restriction of Amarin's proposed speech must directly advance a substantial interest and cannot be more extensive than necessary.

In *Caronia*, the Government asserted that its putative interest in protecting the public health and the integrity of FDA's drug approval process warranted censorship of speech. The Second Circuit declared both interests invalid under both *Sorrell* and *Central Hudson*. As to public health, the Court stated, "As off-label drug use itself is not prohibited, it does not follow that prohibiting the truthful promotion of off-label drug use by a particular class of speakers would directly further the government's goals of preserving the efficacy and integrity of the FDA's drug approval process and reducing patient exposure to unsafe and ineffective drugs." *Caronia*, 703 F.3d at 166.

The same reasoning is especially germane here. Vascepa is compendia-listed for the treatment of persistently high triglycerides and, as a result, doctors will consider it as a

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[2] Nor does Amarin's proposed speech about Vascepa concern unlawful activity under the False Claims Act. Because the unapproved use at issue here is supported by one of the drug compendia specified in Section 1927 of the Social Security Act, the claims are reimbursable. Even assuming, *arguendo*, that the use at issue were not medically accepted, Amarin could not be held liable for its truthful statements about that use unless the speech directly caused the submission of an unlawful claim for payment. *See Ashcroft v. Free Speech Coal.*, 535 U.S. 234, 253 (2002); *Hess v. Indiana*, 414 U.S. 105, 108-09 (1973) (per curiam); *Brandenburg v. Ohio*, 395 U.S. 444, 447-48 (1969) (per curiam); *Rice v. Paladin Enters., Inc.*, 128 F.3d 233, 247 (4th Cir. 1997). In the context of truthful speech, the First Amendment requires the Government to show a direct causal nexus with unlawful activity because, as the Supreme Court articulated, "[t]he mere tendency of speech to encourage unlawful acts is not a sufficient reason for banning it." *Free Speech Coal.*, 535 U.S. at 253.

[3] The Government cannot plausibly claim that any of Amarin's carefully qualified statements about Vascepa are misleading because it has determined the same statements about the same substance are not misleading when made by dietary supplement manufacturers to a lay audience.

therapeutic option and will prescribe it to patients for this indication, regardless of whether FDA permits Amarin to speak with doctors about that use. Consequently, whatever interests FDA may have in precluding such speech, the physicians' need (and the needs of their patients) for truthful and non-misleading information significantly outweighs any hypothetical regulatory concerns that the FDA might have. Even if FDA disapproved of this use of Vascepa—which the Agency has not done—"[t]he fear that people would make bad decisions if given truthful information cannot justify content-based burdens on speech," especially "when the audience, in this case prescribing physicians, consists of sophisticated and experienced consumers." *Sorrell*, 131 S. Ct. at 2670-71 (internal quotation marks omitted). "[P]rohibiting off-label promotion by a pharmaceutical manufacturer while simultaneously allowing off-label use 'paternalistically' interferes with the ability of physicians and patients to receive potentially relevant treatment information; such barriers to information could inhibit, to the public's detriment, informed and intelligent treatment decisions." *Caronia*, 703 F.3d at 166. Physicians are sophisticated and well trained; they need to know what studies show, especially when, as here, patients are being prescribed the drug in a medically accepted manner. In fact, given that doctors such as the Physician Plaintiffs are already prescribing Vascepa for unapproved uses, a public interest in the safe and effective use of drugs dictates that information about such uses flow freely to doctors so that they may use such therapies to treat patients based on the latest truthful, non-misleading information.

Nor can the Government justify restricting Amarin's truthful speech about the unapproved use of Vascepa as necessary to protect the integrity of the drug approval process. First, under the Medicaid Act, the Government is required to subsidize unapproved uses that are medically accepted as set forth in specified compendia—such as the unapproved use of Vascepa

to treat persistently high triglycerides. Although listing in a compendium is not a prerequisite to First Amendment protection, it is, to say the least, anomalous for one part of the Department of Health and Human Services to implement the Medicaid Act that encourages a particular use by making it reimbursable, while another part of the same Department, operating under the FDCA, deems speech about that use a threat to its regulatory regime. In *Caronia*, the Second Circuit rejected the claim that restrictions on promotion of unapproved uses were necessary to preserve the FDA's approval process, reasoning that there were many alternative policies that would more directly advance that interest. 703 F.3d at 167-68 (giving examples of alternative regulatory structures that did not burden manufacturer speech).

Finally, preserving an incentive to pursue supplemental approval for the use of Vascepa in patients with persistently high triglycerides cannot justify a restriction on Amarin's speech. First, the level of disclaimers that Amarin proposes to provide in connection with information concerning Vascepa for this indication provides it with every incentive to seek FDA's approval of this supplemental use. Amarin in fact did pursue that avenue and is continuing to pursue an additional clinical trial that FDA has requested in order to obtain supplemental approval of this indication.

Even if the Government could identify a substantial interest that is directly advanced by restricting Amarin's proposed speech, holding Amarin criminally liable for that speech would clearly qualify as "more extensive than is necessary to serve that interest" because Vascepa is safe and medically accepted and because Amarin specifically proposes using disclaimers to avoid misleading doctors as to the conclusions of its research and whether prescribing the drug can be reimbursed**.** Indeed, these facts present a compelling case under the *Central Hudson* framework, and in our view do not come close to the outer boundaries of First Amendment

protected speech under *Caronia.* In *Caronia*, the Second Circuit made clear that the FDA's ban on off-label promotion was not narrowly drawn to advance the Government's asserted interests. 703 F.3d at 167-68. Among other examples, it reasoned that "if the government is concerned that off-label promotion may mislead physicians" it could develop guidance about what statements tend to mislead doctors or could "develop its warning or disclaimer systems, or develop safety tiers within the off-label market, to distinguish between drugs." *Id.* at 168. Amarin is already seeking to avoid misleading physicians, without any of the guidance that an appropriate, narrowly drawn policy could provide. Imposing criminal liability on Amarin, therefore, would be excessive to say the least.

For the foregoing reasons, imposing liability on Amarin for its proposed speech would fail First Amendment scrutiny under *Central Hudson*.

IV. FDA's Litigation-Driven Regulatory Letter to Amarin Highlights the Burdens on Protected Speech and FDA's Failure to Provide Clear and Binding Guidance

FDA's June 5 regulatory letter to Amarin purports to "recognize[] the value to health care professionals of truthful and non-misleading scientific or medical publications on unapproved new uses." ECF 24, Ex. A at 5 (quoting FDA, *Revised Draft Guidance for Industry, Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices* (Feb. 2014)) ("06/05/15 FDA Letter"). The letter, however, only underscores the serious constitutional problems identified in Plaintiffs' Complaint.

A. FDA's Statements about the Truthful and Non-Misleading Speech It Will Permit Are Vague, Hedged, and Predicated on an Improper Distinction Between Promotional and Scientific Communications

In disavowing concerns with some of the information that Amarin "proposed to communicate," the Agency states that its views "are informed by the unusual combination of circumstances presented here," and it then proceeds to list five that are unique to this case.

"*Under these circumstances,*" FDA states, it does not intend to object to the proposed communications "if made in the manner and to the extent described below." FDA thus creates a one-off discretionary exception, applicable to this case and nowhere else, precisely the type of case-by-case determination regarding the legality of speech that the First Amendment forbids. *See Se. Promotions, Ltd. v. Conrad*, 420 U.S. 546, 553 (1975) ("the danger of censorship and of abridgment of our precious First Amendment freedoms is too great where officials have unbridled discretion over a forum's use"); *Saia v. People of State of New York*, 334 U.S. 558, 562 (1948)(leaving decisions on speech to "uncontrolled discretion. . . sanctions a device for suppression of free communication of ideas"). Moreover, the letter relies exclusively on guidance documents that FDA itself contends are non-binding. Even if they would be binding when finalized, many of the guidance documents cited in FDA's letter remain in "draft" form. PhRMA and others have submitted comments to FDA objecting to many aspects of these draft guidance documents, because, among other things, they continue to censor and burden protected speech based on both its content and the identity of the speaker.

FDA's letter is not the first instance of a discretionary modification of ostensibly nonbinding guidance infringing on First Amendment rights. When manufacturers have challenged FDA's approach to speech about unapproved uses in Court, FDA has made ad hoc statements backing off of certain of those policies as a matter of enforcement discretion and with carefully vague caveats. FDA should not be permitted to avoid judicial scrutiny of its published regulations restricting protected speech on the basis of such non-final and potentially non-binding "guidance" and such revocable assertions of enforcement discretion. *See* U.S. Memo. in Supp. of Mot. to Dismiss or for Summ. J., at 16, *Par Pharm., Inc. v. United States et al.*, No. 1:11-cv-01820 (D.D.C. Jan. 11, 2012) (ECF 14-1) (seeking dismissal of similar First

Amendment lawsuit because "the statements described in the complaint would not by themselves subject Par to prosecution); U.S. Memo. in Supp. of Mot. to Dismiss or for Summ. J. at 18, *Allergan, Inc. v. United States et al.*, No. 1:09-cv-01879 (D.D.C. June 11, 2010) (likewise seeking dismissal of similar First Amendment lawsuit because the FDCA and FDA regulations "leave ample room for Allergan to disseminate truthful, non-promotional information" about an unapproved use).

As in prior instances, FDA's letter to Amarin contains significant caveats that undermine its clarity and limit its value both as a means of narrowing the issues in the case and as a guide to other manufacturers that, like Amarin, want to provide doctors with truthful and non-misleading information about unapproved uses of their medicines. For example, FDA states that it does not "have concerns with *much of the information*" Amarin proposes to communicate and that it would not consider dissemination of "*most of that information* to be false or misleading." 06/05/15 FDA Letter at 1 (emphases added). FDA is not specific in the letter as to what *is* objectionable, beyond proffering an imprecise and improper distinction between scientific and promotional communications. Thus, for example, FDA concedes the value only of "truthful and non-misleading *scientific or medical publications.*" *Id.* at 5 (emphasis added).

FDA relies on this same improper distinction to impose other unconstitutional restrictions on Amarin's truthful and non-misleading speech. Thus, FDA asserts that Amarin is limited to "[d]istributing such information in educational or scientific settings, and not including such information with or attached to promotional or marketing materials." *Id.* at 7.[4] Moreover, FDA allows communication of this truthful information only "by persons with the appropriate

[4] Although FDA in the letter characterizes these burdens as "recommendations," they are no more hortatory than the other guidance documents that FDA asserts are non-binding but that have been the predicates of multiple criminal prosecutions.

background or training to accurately communicate this scientific information"—meaning that pharmaceutical sales representatives or "detailers" generally would be prohibited from speaking. *Id.* Other than providing copies (or perhaps summaries) of medical journal articles and other published scientific or medical texts, moreover, FDA's letter—citing a FDA "draft" guidance document—asserts that manufacturers may provide information about unapproved uses only in response to "unsolicited requests" from healthcare professionals. *Id.* at 5 n.13 (citing FDA, *Draft Guidance for Industry, Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices* (Dec. 2011)).

If one thing is clear from *Sorrell,* it is that the artificial distinction between "promotional" and "scientific" speech by biopharmaceutical companies is not a valid basis for restricting truthful and non-misleading communications. The Court struck down an effort by Vermont to treat speech by biopharmaceutical company detailers as somehow entitled to less respect than other forms of communication and to make it more difficult for detailers to communicate that information. The Supreme Court specifically affirmed the value of medical product detailing, noting that, "The defect in Vermont's law is made clear by the fact that many listeners find detailing instructive." *Sorrell*, 131 S. Ct. at 2671. Nonetheless, FDA continues to make invalid and arbitrary distinctions between Amarin's "scientific" speech and "promotion," and between company detailers and other speakers, central to its litigation-driven letter. Under the FDA's construct, Amarin can engage in certain "scientific" speech, but not "promotion." Indeed, according to FDA's letter, company speakers risk criminal and civil enforcement if a detailer provides a reprint in a potentially "promotional" setting or along with "promotional" materials, or if a medical affairs representative of the company speaks to a doctor about a scientific study without the doctor first making an "unsolicited request." Under the First Amendment, FDA

cannot limit the form of truthful and non-misleading communications, or designate the persons in a company who are allowed to share truthful, non-misleading information. Nor can FDA cure its First Amendment problem by making such pronouncements through made-for-litigation letters that do not have the force of law and that have not been subjected to notice-and-comment rulemaking. *See Christopher v. SmithKline Beecham Corp.*, 132 S. Ct. 2156, 2166 (2012) (an agency does not deserve deference for what amounts to a "convenient litigating position"). The First Amendment requires clear rules regarding any boundaries on speech, not ad hoc, discretionary exceptions.

FDA's letter also imposes unnecessary burdens on truthful and non-misleading speech. FDA demands that Amarin make additional, unnecessary disclosures—duplicative of the extensive disclosures Amarin already proposed—including a disclosure about three studies conducted by *other* manufacturers involving *other* drugs. *See* 06/05/15 FDA Letter at 7. Coupled with the limitations on "promotional" speech, these required statements burden truthful and non-misleading speech at least as much as did Vermont's restrictions on the information detailers could use in *Sorrell.* There, as here, the government sought "to achieve its policy objectives through the indirect means of restraining certain speech by certain speakers—that is, by diminishing detailers' ability to influence prescription decisions. Those who seek to censor or burden free expression often assert that disfavored speech has adverse effects. But the fear that people would make bad decisions if given truthful information cannot justify content-based' burdens on speech." *Sorrell*, 131 S. Ct. at 2670-71 (citation and internal quotation marks omitted).

B. FDA Incorrectly Suggests that Its Regulations and Draft Guidance Documents Do Not Prohibit Speech

Beyond the extensive caveats in FDA's June 5 letter, the letter also previews the Agency's theory that its regulations do not prohibit speech at all, but rather use speech only as "evidence that [a drug] is intended for a use that would render [the drug] an unapproved new drug or misbranded." 06/05/15 FDA Letter at 1; *accord id.* at 5, 5 n.13, 6, 8, 10 (all similar). This theory mirrors the Government's refrain in prior litigation (including *Caronia*) that its interpretations of the FDCA target only *conduct*, not speech. The Government's effort to evade First Amendment scrutiny of FDA's regulations fails.

As an initial matter, the Government cannot credibly contend that its regulations and draft guidance documents prohibit only conduct because it has repeatedly characterized the regulations as criminalizing "off-label *promotion*." U.S. Accountability Office, GAO-08-835, Prescription Drugs: FDA's Oversight of the Promotion of Drugs for Off-Label Uses 1-6, 20 tbl. 2 (2008) (emphasis added) (referring to numerous prosecutions and regulatory actions alleging "off-label promotion"); *see also* U.S. Reply in Supp. of Mot. to Dismiss and for Summ. J. and Resp. to Cross-Mot. for Summ. J. at 6-7, 14, 20, 25, *Allergan, Inc. v. United States*, No. 09-1879 (JDB) (D.D.C. Mar. 29, 2010) (emphasizing distinction between what the government refers to as "promotion" and other speech, and arguing that only promotional speech about an off-label use creates a new intended use). Moreover, the regulations make it a crime to "*advertise[] or represent[]*" an unapproved use without providing information about the unapproved use in the drug's labeling, while at the same time the regulations bar companies from providing that information. 21. C.F.R. § 201.100(c)(1) (emphasis added). An enforcement action against Amarin or other manufacturers under the FDA regulations, therefore, would be based upon speech. The communication, coupled with the Catch-22 failure to meet an impossible requirement, is the *sine qua non* of the offense.

Neither can the Government credibly contend that an enforcement action against Amarin would implicate speech only as evidence of other crimes. Speech can serve as evidence of intent or motive, but only when the criminal act is distinct from the speech. *See Wisconsin v. Mitchell*, 508 U.S. 476 (1993); *Whittaker v. Thompson*, 353 F.3d 947 (D.C. Cir. 2004). The *only* basis for liability under the government's interpretation of the FDCA is the manufacturer's truthful and non-misleading speech itself. The Second Circuit in *Caronia* distinguished *Whittaker v. Thompson*, in which the petitioner's speech was evidence of the petitioner's intent to commit an unlawful act, selling a compound as a "drug" even though FDA never approved it for any purpose. *Caronia*, 703 F.3d at 165 n.10. In that case, the speech was not protected by the First Amendment because it was designed to mislead purchasers about the product's effectiveness in treating disease. *Whittaker*, 353 F.3d at 953; *see also Caronia*, 703 F.3d at 165 n.10. The petitioner's speech, therefore, could be used as evidence of the intention to sell the product for a use that the law sought to prevent. In contrast, Amarin's proposed speech is not misleading and the law does not seek to prevent the use of Vascepa to treat persistently high triglycerides. The Government cannot credibly claim otherwise.

CONCLUSION

Because the law of this Circuit is that FDA's censorship of truthful, non-misleading speech regarding unapproved uses of medicines is unconstitutional, the Government cannot credibly suggest a permissible basis for punishing Amarin based on the speech proposed in the Complaint. In fact, the FDA's purported exercise of enforcement discretion proves the defect in the government's enforcement of the Federal Food, Drug, and Cosmetic Act in general. Any distinction the Government might try to draw between conduct and speech would be so philosophical as to be impermissibly vague. Similarly, the Government's purported and

undefined distinction between companies' "promotion" and "scientific" speech, which has no basis in First Amendment precedent, similarly puts the enforcement decision entirely in the Government's control.

A vague law violates due process both because regulated parties do not know what is required of them and because it leaves room for an enforcer to act in an arbitrary or discriminatory way. *F.C.C. v. Fox Television Stations, Inc.*, 132 S. Ct. 2307 (2012). When speech is involved, those due process requirements must be even more rigorously applied. *Id*; *United States v. Williams*, 553 U.S. 285, 292 (2008); *Reno v. Am. Civil Liberties Union*, 521 U.S. 844, 871-72 (1997). Without clear warning as to when its proposed speech could be used to support an enforcement action, Amarin might have to err on the side of avoiding potential liability and forgo speech even when courts would ultimately validate it. This type of chilling effect is anathema to the First Amendment and controlling precedent. It is also highly detrimental to physicians and to patients, who benefit from having truthful and non-misleading information about medically accepted, unapproved uses available to them. The Court should act to prevent the censorship the Government proposes in this case.

For the foregoing reasons, PhRMA urges the Court to grant Amarin's motion for preliminary injunction.

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Respectfully Submitted,

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