EXHIBIT A

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, v. UNITED STATES FOOD & DRUG ADMINISTRATION; UNITED STATES OF AMERICA; STEPHEN OSTROFF, M.D., Acting Commissioner of Food and Drugs; and SYLVIA MATHEWS BURWELL, Secretary of the United States Department of Health & Human Services, Defendants.	Civil Action No. 1:15-cv-3588 (PAE)

BRIEF OF THE MEDICAL INFORMATION WORKING GROUP AS *AMICUS CURIAE* IN SUPPORT OF PLAINTIFFS

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June 11, 2015

RULE 7.1 CORPORATE DISCLOSURE STATEMENT

Pursuant to Federal Rule of Civil Procedure 7.1, and to enable District Judges and Magistrate Judges of the Court to evaluate possible disqualification or recusal, the undersigned counsel for *amicus curiae*, the Medical Information Working Group ("MIWG"), a private non-governmental entity composed of major manufacturers of prescription drugs and medical devices, certifies that the following members of the MIWG are submitting this brief: Bayer Healthcare Pharmaceuticals, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., Eli Lilly and Company, Genentech, Inc., GlaxoSmithKline LLC, Johnson & Johnson, Novartis Pharmaceuticals Corporation, Novo Nordisk, Inc., Pfizer Inc., and sanofi-aventis U.S. LLC. And the undersigned counsel for *amicus curiae* certifies further that the following are corporate parents, affiliates and/or subsidiaries of such members, which are publicly held:

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STATEMENT OF INTEREST OF *AMICUS CURIAE*

The Medical Information Working Group ("MIWG") is an informal working group of major manufacturers of prescription drugs, biologics, and medical devices.[1] The MIWG was formed in 2006 to address the federal regulatory framework and enforcement climate affecting manufacturer dissemination of information about prescription drugs, biological products, and medical devices, including information about new uses of approved products. In particular, the MIWG has sought to address concerns that the present regulatory framework, due to its unclear rules and harsh penalties, fails to provide adequate notice of the line between permissible and impermissible speech, and chills manufacturer dissemination of valuable scientific information. Consistent with this mission, the MIWG has a strong interest in the issues presented here.

ARGUMENT

This case raises significant issues regarding the regulatory framework that governs manufacturer speech about FDA-approved products. *Amicus* acknowledges the important role that FDA plays in reviewing the safety and efficacy of new drugs and medical devices prior to their marketing authorization. But that role does not justify categorical prohibitions on truthful and non-misleading manufacturer speech or vague regulations that chill such speech under threat of criminal punishment. *Amicus* urges the Court to rule that, as applied to Amarin's proposed speech, FDA's regulations have an unconstitutional chilling effect on truthful, non-misleading speech.

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[1] Neither plaintiffs nor their counsel authored this brief in whole or in part, or made a monetary contribution intended to fund the preparation or submission of this brief. The following members of the MIWG join in the filing of this brief: Bayer Healthcare Pharmaceuticals, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., Eli Lilly and Company, Genentech, Inc., GlaxoSmithKline LLC, Johnson & Johnson, Novartis Pharmaceuticals Corporation, Novo Nordisk, Inc., Pfizer Inc., and sanofi-aventis U.S. LLC.

Off-label use of FDA-approved drugs and devices is legal, common, and often beneficial to patients. Prescribers and other sophisticated participants in the health care system need information about the benefits and risks of medical products as used in clinical practice, including off-label uses. Manufacturers are often the best—and sometimes only—source of this important information. Thus, as the Second Circuit has held, restricting manufacturers' truthful, non-misleading speech about off-label uses prevents physicians from receiving valuable information that benefits patients. *United States v. Caronia*, 703 F.3d 149, 167 (2d Cir. 2012).

The FDA restricts such speech through the highly disfavored mechanism of content- and speaker-based rules. Those regulations are therefore subject to heightened scrutiny. *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653 (2011); *Caronia*, 703 F.3d at 164-65. As Pharmaceutical Research and Manufacturers of America (PhRMA) explains in its *amicus* brief, FDA's regulations do not withstand such heightened scrutiny as applied to Amarin's proposed speech.

The MIWG here highlights particular First Amendment concerns arising from the lack of clarity in the regulatory regime governing manufacturer speech. The need for clarity is particularly acute in light of the potential for imposition of draconian criminal penalties, which exacerbate the chill on speech. Yet the governing regulations are hopelessly vague. The government has, thus far, largely failed to clarify these rules, despite repeated requests. Rather, as with its June 5, 2015, post-Complaint letter to Amarin ("Amarin Letter") [Dkt. No. 24, Ex. A], FDA has adopted a practice of announcing interpretations of the rules through non-binding pronouncements, including in litigation and case-specific enforcement letters. As a result, FDA retains nearly unfettered discretion to make after-the-fact, ad hoc judgments about manufacturer speech, including that particular speech, together with any number of additional circumstantial facts the government deems relevant, reveals an impermissible "intent" by the manufacturer that

its product be used off-label. Because few manufacturers can risk the consequences of being criminally charged, the government is able to obtain sizeable monetary settlements, while actively avoiding judicial review of the speech-restricting standards it employs. The lack of clarity in this regulatory regime has a constitutionally intolerable chilling effect on manufacturers' right to provide truthful and non-misleading information about lawful uses of their products. Rather than obviating this concern, the FDA's post-Complaint Amarin Letter illustrates both the problem with FDA's ad hoc approach to speech restrictions and the need for judicial review to establish the First Amendment limits on FDA's ability to restrict truthful and non-misleading manufacturer speech about lawful uses of medical products.

I. TRUTHFUL AND NON-MISLEADING MANUFACTURER SPEECH ABOUT LAWFUL USES OF FDA-APPROVED DRUGS IS HIGHLY VALUABLE AND CONSTITUTIONALLY PROTECTED.

FDA's broad restrictions on manufacturer speech stifle the dissemination to physicians and payers of valuable information about lawful uses of medical products. As we explain in greater detail below, those restrictions flow from a series of ambiguous regulations that effectively treat a drug as "misbranded" within the meaning of a criminal law if FDA concludes that a manufacturer's speech about the drug is intended to promote uses not set forth in the FDA-approved labeling or fails to meet FDA's "substantial evidence" standard. FDA-approved labeling, however, does not provide all of the information that these constituencies need in deciding whether or how to prescribe a drug or medical device, or to pay for its use. Doctors may wish to depart from the FDA-approved labeling, a so-called "off-label" use. Off-label use of FDA-approved drugs is legal, common, and often beneficial to patients. Truthful and non-misleading manufacturer speech to convey information about such uses serves valuable purposes and is entitled to constitutional protection. Manufacturers also possess information about the comparative effectiveness of treatment options, and their relative economic costs and benefits.

Dissemination of this information can enhance public health and safety, serving the same interests that the FDA itself seeks to promote.

A. Off-label Use Is Lawful, Common, And Often Highly Beneficial To Patients.

As the Second Circuit has made clear, "off-label drug usage is not unlawful." *Caronia*, 703 F.3d at 166. Rather, "physicians can prescribe, and patients can use, drugs for off-label purposes." *Id.*; *see* 21 C.F.R. § 312.2(d) (exempting from FDA regulations "the use in the practice of medicine for an unlabeled indication of a new drug product approved" by FDA); *see also* 21 U.S.C. § 396 (providing that the FDCA does not "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").

Not only is off-label use lawful, it "is an accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medicine." *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 & n.5 (2001) (quoting from an article that "[o]ff-label use is widespread in the medical community and often is essential to giving patients optimal medical care"). In some cases, "the practice of medicine may require a practitioner to use drugs off-label to provide the most appropriate treatment for a patient." American Academy of Pediatrics, Committee on Drugs, *Uses of Drugs Not Described in the Package Insert (Off-Label Uses)*, 110 Pediatrics 181, 182 (2002) ("AAP"). In specialties such as oncology and pediatrics, "patient care could not proceed without off-label prescribing." Rebecca Dresser & Joel Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37(3) J.L. Med. & Ethics 476 (2009) ("*Off-Label Prescribing*"). "An off-label use may provide the best available intervention for a patient" and at times "may be the only treatment option for seriously ill patients." *Id*. at 476, 481.

"The full and ultimate role of a drug is rarely evident at the time of its initial approval and labeling"; often, "[m]any of the most important uses and toxicities emerge" after a drug is on the market. AAP at 182. For many medical treatments, there is no prospect of timely progression from off- to on-label use. Treatments for rare diseases, for example, are likely to remain off-label, because the high costs of the FDA approval process "and the small number of people with these diseases makes it impossible to evaluate products according to ordinary clinical trial criteria." *Off-Label Prescribing* at 481. Or a treatment may already be the standard of care, thus making clinical studies comparing the treatment to other treatments untenable on ethical grounds. Or the drug may have many similar competitors, including possibly generic competitors, such that the costs of additional research cannot be recovered.

For these reasons, "the FDA's drug approval process generally contemplates that approved drugs will be used in off-label ways." *Caronia*, 703 F.3d at 166. The FDA recognizes that "off-label uses or treatment regimens may be important therapeutic options and may even constitute a medically recognized standard of care." FDA, Draft Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices 2 (Dec. 2011) ("Unsolicited Requests Guidance"). The law even requires off-label usage in some circumstances: where off-label use provides the standard of care, a doctor's failure to prescribe a drug off-label could constitute malpractice. *See* Mem. of the Am. Med. Ass'n House of Delegates, Resolution 820, *Off-Label Use of Pharmaceuticals*, Sept. 21, 2005. And the government not only allows, but also subsidizes, off-label use. The Medicare and Medicaid programs are obligated to reimburse for certain off-label uses that are listed in medical compendia. *See* 42 U.S.C. § 1396r-8(k)(6) (Medicaid); 42 U.S.C. § 1395y(a)(1)(A); Medicare Benefit Policy Manual, Ch. 15, §

50.4.2 (Medicare). The legal requirement that the government pay for some off-label uses highlights the importance to physicians and payers of information regarding those uses.

B. Truthful, Non-Misleading Off-Label Speech By Manufacturers Is Valuable And Constitutionally Protected.

An essential role of the First Amendment is protecting the "free flow of information." *Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council*, 425 U.S. 748, 765 (1976). That is especially important "in the fields of medicine and public health, where information can save lives." *Sorrell*, 131 S. Ct. at 2664. Thus, the Supreme Court has recognized that "[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.

Speech about off-label uses is valuable to physicians in many ways. The FDA recognizes the "value to health care professionals of truthful and non-misleading scientific or medical publications on unapproved new uses." FDA, Draft Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices 6 (Feb. 2014) ("Revised Good Reprint Practices"); Amarin Letter at 5. The Second Circuit has endorsed off-label speech: "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." *Caronia*, 703 F.3d at 167. In contrast, "barriers to information about off-label use could inhibit, to the public's detriment, informed and intelligent treatment decisions." *Id.* A product's FDA-approved labeling does not contain all of the information that physicians require concerning off-label uses. Physicians must obtain from other sources this information, including safety data associated with clinical care. As FDA recognizes, "[t]he physician is … responsible for making the final judgment as to which, if any, of the available drugs his patient will receive in the light of the information contained in their labeling and other adequate scientific data available to him." Legal

Status Of Approved Labeling For Prescription Drugs; Prescribing For Uses Unapproved By The Food And Drug Administration, 37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972).

Health insurance companies and other health care financing entities—"payers"—also rely on off-label speech. Payers seek out and rely on a broad range of scientific evidence including meta-analyses and observational studies and other "real world data" (not merely what appears in a drug's FDA-approved labeling) to make decisions about which drugs to include on plan formularies, and with what restrictions. Payers benefit from, and may require, extensive data and other information about off-label uses to make these decisions, which affect millions of patients. Payers use these data to evaluate the relative effectiveness and safety of different medications and to evaluate outcomes associated with them. With access to a robust flow of information, payers can improve patient care while controlling costs through encouraging the use of the least costly, and most effective, treatment options.

Speech about off-label uses is no less valuable just because the speaker is the manufacturer. *See Caronia*, 703 F.3d at 165. To the contrary, as the Supreme Court recognized in *Wyeth v. Levine*, "manufacturers have superior access to information about their drugs," 555 U.S. 555, 578-79 (2009), and so are often the best—and sometimes only—sources of information about off-label uses of medical products, including real-world data. As FDA recognizes, "[s]cientific or medical departments within drug or medical device firms often maintain a large body of information about their products," and this information is generally "robust and current." Unsolicited Requests Guidance at 2, 3. Other speakers "may not provide or have access to the most accurate and up-to-date information about the firm's products." *Id.* at 3. Indeed, FDA requires manufacturers to collect and analyze a great deal of information about their products, including information about off-label uses. For instance, FDA requires manufacturers to review and analyze information about

adverse events associated with their products, including events that involve an off-label use. 21 C.F.R. § 314.80(b)-(c) (2009); *see also* 21 U.S.C. § 321(n) (requiring labeling and advertising to include information about material risks of common or usual uses, including off-label uses). Manufacturers also obtain information about their products by sponsoring various studies, communicating with physicians and consultants, and monitoring publicly available information, including scientific papers. Manufacturers have a strong incentive, as well as the capacity and expertise, to collect and synthesize this information, and are well-positioned to provide the information to physicians "in a truthful, non-misleading, and accurate manner." Unsolicited Requests Guidance at 3.

The value of off-label speech is further demonstrated because other entities—including regulators, payers, academics, and physicians—are free to disseminate and discuss data that do not satisfy FDA's narrow standards, with the goal of enabling doctors to make better-informed choices about the care of their patients, and payers to make more well-informed decisions about coverage and reimbursement. For example, the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices ("ACIP"), which makes recommendations on how to use vaccines to control diseases in the United States, is free to and often does recommend uses of FDA-approved vaccines in a manner (or for a population) that is beyond the four corners of the FDA-approved product labeling. Manufacturers, however, may not freely discuss those ACIP recommendations with doctors or payers because, in FDA's view, that would be a criminal violation of the FDCA. FDA's regulatory regime criminalizes speech solely on the basis of the identity of the speaker, which the First Amendment forbids. *See infra* Part II.A.[2]

[2] FDA permits speech by manufacturers only in narrow circumstances. *See infra* Part II.B.2.

Restrictions on truthful and non-misleading manufacturer speech hurt health care providers and the patients they treat. Several years ago, the Seventh Circuit wondered, "if a given use is lawful, and thus can be written about freely in newspapers or blogs, and discussed among hospitals … doesn't it make a good deal of sense to allow speech by the … manufacturer, which after all will have the best information? Why privilege speech by the uninformed?" *United States v. Caputo*, 517 F.3d 935, 939 (7th Cir. 2008). The Second Circuit made the point more directly: "prohibiting off-label promotion *by a pharmaceutical manufacturer* … interferes with the ability of physicians and patients to receive potentially relevant treatment information." *Caronia*, 703 F.3d at 166 (emphasis added).

C. FDA Also Restricts Valuable and Protected Manufacturer Speech About *On*-Label Uses Of Their Products.

The FDA's restriction of First Amendment-protected manufacturer speech is not limited to off-label uses, but extends to manufacturers' ability to communicate certain truthful, non-misleading information about *on*-label uses. Payers and providers rely heavily on scientific studies that compare the effectiveness of two or more drugs ("comparative effectiveness research" or "CER") in order to select treatment options that are most therapeutically appropriate and cost-effective. *See* Institute of Medicine, Initial Priorities for Comparative Effectiveness Research 29 (2009). Because much of CER is based on meta-analyses, observational studies, and other "real-world" data, it typically does not satisfy FDA's "substantial evidence" standard, and so, under FDA regulations, manufacturers may not disseminate it—even if it concerns on-label uses. *See* 21 C.F.R. §§ 202.1(e)(6)(ii), 314.126.

The fact that some CER does not satisfy FDA's definition of "substantial evidence" does not make it inherently misleading, however. Indeed, the Agency for Healthcare Research & Quality, housed within HHS, and the Patient Centered Outcomes and Research Institute, a

nonprofit entity established by Congress, are specifically charged with conducting and disseminating CER—which may involve both off-and on-label uses. As Congress recognized, CER is highly valuable. And that is so whether it concerns on- or off-label use and whether it is disseminated by manufacturers or by others. The FDA's restrictions on *manufacturers'* ability to disseminate the same type of truthful, non-misleading information that other government agencies are charged with collecting and disseminating—including information about the FDA-approved uses of their drugs—confirms the extent to which FDA restricts constitutionally protected speech using impermissible speaker-based rules.

II. THE FDA'S UNCLEAR REGULATIONS CONCERNING OFF-LABEL SPEECH HAVE AN IMPERMISSIBLE CHILLING EFFECT ON AMARIN'S ABILITY TO PROVIDE TRUTHFUL AND MEDICALLY VALUABLE INFORMATION TO SOPHISTICATED PHYSICIANS.

The FDA's regulatory regime governing off-label speech is subject to heightened scrutiny not only because it restricts truthful and non-misleading speech that is valuable to health care providers and payers, but also because it does so based on the content of the speech and the identity of the speaker. Content-based restrictions are particularly suspect here, because the audience is experienced and sophisticated, and the restrictions are enforced through criminal penalties. In addition to other constitutional deficiencies of such speaker-based restrictions, *see* Br. of *Amicus* PhRMA, FDA's regulatory regime fails to provide fair notice to manufacturers so as to avoid impermissibly chilling valuable speech. The government's regulations are essentially open-ended and thus difficult to apply in particular settings, denying fair notice. In light of its associated draconian penalties, this regime has a significant chilling effect on manufacturers' ability to provide truthful, non-misleading and valuable information to physicians. In this case, that is constitutionally impermissible.

A. Because The Off-Label Speech Restrictions Are Content- And Speaker-Based, And Impose Criminal Penalties, They Must Be Clear And Precise.

Sorrell makes clear that where a law restricts truthful, non-misleading speech on the basis of its content and the identity of the speaker, that law "must be subjected to heightened judicial scrutiny," even for "commercial" speech. 131 S. Ct. at 2659; *see id.* at 2664 (holding that "[c]ommercial speech is no exception" to the heightened judicial scrutiny applicable to speaker- and content-based speech restrictions). Content- and speaker-based restrictions on commercial speech fail this heightened scrutiny "in the ordinary case." *Id.* at 2667.

As the Second Circuit held in *Caronia*, "[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 is content- and speaker-based, and, therefore, subject to heightened scrutiny." 703 F.3d at 164-65. The restrictions are speaker-based because they "target[] one kind of speaker—pharmaceutical manufacturers—while allowing others to speak without restriction." *Id.* at 165. The FDA prohibits manufacturers and distributors from many forms of communication about off-label uses of FDA-approved products, regardless of whether such speech is truthful, non-misleading and scientifically substantiated. By contrast, all other classes of speakers are entirely free to "speak about off-label use without consequence." *Id.* The restrictions are content-based because they "disfavor[] marketing, that is, speech with a particular content." *Sorrell*, 131 S. Ct. at 2663. The restrictions permit certain non-promotional speech about off-label uses, but generally prohibit manufacturers from promoting off-label uses. *See infra* Part II.B.2. In addition, the restrictions are content-based because "speech about the government-approved use of drugs is permitted, while certain speech about the off-label use of drugs—that is, uses not approved by the government—is prohibited." *Caronia*, 703 F.3d at 165.

The First Amendment requires "precision … when a statute regulates the content of speech." *Reno v. ACLU*, 521 U.S. 844, 874 (1997). The "standards of permissible statutory vagueness are strict in the area of free expression. Because First Amendment freedoms need breathing space to survive, government may regulate in the area only with narrow specificity." *Keyishian v. Bd. of Regents of the Univ. of N.Y.*, 385 U.S. 589, 604 (1967). Vagueness in "a content based-regulation of speech" is particularly problematic, and "raises special First Amendment concerns because of its obvious chilling effect on free speech." *Reno*, 521 U.S. at 871-72. Accordingly, "when speech is involved, rigorous adherence … is necessary" to the requirements that government regulations must provide "fair notice of what is prohibited," as well as "precision and guidance … so that those enforcing the law do not act in an arbitrary or discriminatory way." *FCC v. Fox Television Stations, Inc.*, 132 S. Ct. 2307, 2317 (2012).[3]

The need for "narrow specificity" is especially pronounced in the case of off-label speech about FDA-approved drugs. First, restrictions that chill truthful, non-misleading speech are particularly offensive to First Amendment values—and unjustified—where the audience "consists of sophisticated and experienced consumers" such as "prescribing physicians." *Sorrell*, 131 S. Ct. at 2671. *See also Caronia*, 703 F.3d at 166. Second, "problems of vagueness" are "particularly treacherous where, as here, the violation of [a law's] terms carries criminal penalties and fear of incurring these sanctions may deter those who seek to exercise protected First Amendment rights." *Buckley v. Valeo*, 424 U.S. 1, 76-77 (1976); *see Reno*, 521 U.S. at 872 ("The severity of criminal

[3] This brief focuses on the First Amendment's insistence on clarity when the government restricts speech. The First Amendment also imposes other requirements, including that the government cannot restrict more speech than necessary, such as by prohibiting speech on the ground that it is misleading when adequate disclosures could address that concern. Some of those other limits are addressed in the Brief of *Amicus* PhRMA. *See also Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999).

sanctions may well cause speakers to remain silent rather than communicate even arguably unlawful words, ideas, and images.").

As described in Amarin's Complaint, FDA has taken the position that "virtually all manufacturer communication to healthcare professionals about the off-label use of prescription drugs" renders the drug criminally "misbranded" under 21 U.S.C. § 331. Compl. ¶ 141 [Dkt. No. 1]. A person convicted of criminal misbranding faces up to a year of imprisonment for a first offense, and up to three years for subsequent offenses. 21 U.S.C. § 333(a). Companies convicted of misbranding face severe corporate criminal sanctions as well as potential exclusion from participation in the Medicare and Medicaid programs. 42 U.S.C. § 1320a-7; 42 C.F.R. § 1001.901. Exclusion "is effectively a death penalty—it will put the corporation out of business." Barry J. Pollack, *Time to Stop Living Vicariously: A Better Approach to Corporate Criminal Liability*, 46 Am. Crim. L. Rev. 1393, 1403 (2009). These harsh penalties magnify the need for "the precision that the First Amendment requires," *Reno*, 521 U.S. at 874; manufacturers will inevitably err on the side of less communication—to the potential detriment of public health and safety—in order to avoid destructive criminal sanctions.

B. The Off-Label Speech Restrictions Have A Constitutionally Impermissible Lack Of Clarity.

As applied to truthful and non-misleading off-label promotion, the FDA's speech restrictions suffer from a constitutionally impermissible lack of clarity. In *Caronia*, the Second Circuit "decline[d] to adopt the government's construction of the FDCA's misbranding provisions to prohibit manufacturer promotion alone as it would unconstitutionally restrict free speech," and held that "the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug." 703 F.3d at 168-69. But the government has not clarified the reach of its off-

label promotion restrictions following *Caronia*, and instead continues to instruct pharmaceutical manufacturers that off-label promotion may constitute criminal misbranding. *See* Revised Good Reprint Practices 9 (warning that use of published scientific studies to "promote an unapproved use" "might be used as evidence" of misbranding). Indeed, FDA officials have stated that *Caronia* will not "significantly affect" the agency's enforcement practices, and that it will "continu[e] to enforce the misbranding provisions … including through criminal prosecution where appropriate, in cases involving off-label promotion." Jill Wechsler, *Tom Abrams: Caronia Won't Stop Off-Label Enforcement*, PHARMEXEC.com (Jan. 29, 2013).

More broadly, the agency has never made clear the scope of what it considers to be prohibited off-label promotion. Its regulations and guidance documents either fail to provide any definition of key terms or provide only inherently indeterminate "definitions." The FDA's purported "safe harbors" do not clarify the restrictions, and are largely non-binding.

1. The Regulations Governing Off-Label Speech Are Ambiguous.

The FDCA "and its accompanying regulations do not expressly prohibit or criminalize off-label promotion." *Caronia*, 703 F.3d at 160. Rather, the speech restrictions arise from a tangle of statutory provisions, regulations, non-binding guidance documents, and government enforcement practices, none of which gives manufacturers clear notice as to what speech is permitted and what speech is not.

Federal law provides that a drug is misbranded if its "labeling" lacks "adequate directions for use." 21 U.S.C. §§ 331, 352(f)(1). Corresponding regulations declare that prescription drugs cannot satisfy the "adequate directions" requirement, then exempt prescription drugs if the labeling bears "adequate information for its use … under which practitioners … can use the drug safely and for the purposes for which it is intended, including all purposes for which it is advertised or represented." 21 C.F.R. § 201.100(c)(1); *see* 21 C.F.R. § 201.5. Another regulation,

21 C.F.R. § 201.128, defines "intended uses or words of similar import" as referring "to the objective intent of the persons legally responsible for the labeling of drugs," which may be "determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article," including the "advertising matter, or oral or written statements by such persons or their representatives." Accordingly, the government takes the position that it "can offer evidence of a defendant's off-label promotion to prove a drug's intended use and, thus, mislabeling for that intended use." *Caronia*, 703 F.3d at 161.

As *Caronia* explained, these tangled regulations provide little guidance as to what speech is permissible and what speech is not. It "still remains unclear how the government would identify criminal misbranding from communications between drug manufacturers and physicians authorized to prescribe drugs for off-label use." *Id.* at 162 n.9. The phrase "advertised or represented" in 21 C.F.R. § 201.100 is not defined. "Intended uses" is defined by 21 C.F.R. § 201.128, but in language that "fails to clearly mark the boundary between permissible and impermissible speech." *Buckley*, 424 U.S. at 41. The regulation provides that an intended use "is determined by" the manufacturer's "expressions or may be shown by the circumstances surrounding the distribution." 21 C.F.R. § 201.128. It then provides examples of some "expressions" and "circumstances," but sets no limits and provides no standard for determining *which* "expressions," in *which* "circumstances," establish the forbidden "objective intent."

The "circumstances surrounding the distribution" prong of 21 C.F.R. § 201.128 thus renders 21 C.F.R. § 201.100 entirely open-ended. Under the literal terms of 21 C.F.R. § 201.128, the "circumstance" that a manufacturer has "knowledge" that physicians are prescribing its product "for a purpose for which it is neither labeled nor advertised" might establish an FDCA violation. Because off-label prescriptions are common, and manufacturers must monitor how their

products are used, this interpretation makes it nearly impossible for manufacturers to avoid violating the law. *See supra* Part I; 21 C.F.R. § 314.80. At times, the government has seemed to adopt this interpretation.[4] In other cases, the government has taken the position that the regulations do not reach quite so broadly—without, however, clearly identifying how far it believes the regulations do reach.[5] This approach leaves the government with almost untrammeled enforcement discretion. *See Gentile v. State Bar of Nev.*, 501 U.S. 1028, 1051 (1991) ("The prohibition against vague regulations of speech is based in part on the need to eliminate the impermissible risk of discriminatory enforcement").

In virtually any case, the government can argue that, when placed in the context of unspecified additional "circumstances," manufacturer speech reveals an impermissible "objective intent" to promote off-label use. Thus, the regulations "put[] the speaker … wholly at the mercy of the varied understanding of his hearers and consequently of whatever inference may be drawn as to his intent and meaning" and "offer[] no security for free discussion." *Buckley*, 424 U.S. at 43, *quoting Thomas v. Collins*, 323 U.S. 516 (1945). The situation here is even more problematic than that in *Buckley*: manufacturers are wholly at the mercy of the varied understandings *of the government* and of whatever inferences *the government* chooses to draw.

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[4] *See* Gov't Requests to Charge at 18, *United States v. Caronia*, 06-cr-00229-ENV (E.D.N.Y. Sept. 2, 2008), ECF No. 77 (Government's proposed jury instruction, adopted by District Court, that a manufacturer will have violated the Misbranding Provisions if it has "knowledge" that a drug it has introduced into commerce will be used off label by a physician).

[5] Gov't Br. at 8, 28, *Par Pharm. Inc. v. United States*, 11-cv-01820-RWR (D.D.C. Jan. 1, 2012), ECF No. 14-1 ("A manufacturer's knowledge that a drug may be prescribed for an unapproved use does not lead, *by itself*, to a conclusion that the unapproved use is intended," but "[k]nowledge that a drug is being offered and used for unapproved purposes is one of the circumstances that may be taken into account."); *see Ass'n of Am. Physicians & Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204, 207-08 (D.D.C. 2002) ("[E]ven the FDA has repeatedly stated that it may only regulate claimed uses of drugs, not all foreseeable or actual uses").

2. The Purported "Safe Harbors" Do Not Clarify The Regulatory Scheme.

The vagueness of the regulatory scheme is not minimized—and in many respects is exacerbated—by the FDA's purported "safe harbors." For years, manufacturers have sought clarifications of the "intended use" restrictions, without success.[6] Although FDA has begun a process that manufacturers hope will produce much-needed clarity, at present, the only guidance available consists of a single regulation that allows for "the full exchange of scientific information concerning [a] drug," 21 C.F.R. § 312.7 (2009), and several guidance documents.[7] These limited pronouncements do not provide manufacturers adequate means "for determining when [their] remarks pass from the safe harbor … to the forbidden sea." *Gentile*, 501 U.S. at 1049.

First, with the exception of the "scientific exchange" regulation, FDA's pronouncements "do[] not purport to be binding on the enforcement authorities." *Hynes v. Borough of Oradell*, 425 U.S. 610, 622 n.6 (1976). "[T]he due process protection against vague regulations does not leave regulated parties at the mercy of *noblesse oblige*," but rather requires that the limits on the

[6] A review of online records at www.regulations.gov reveals at least 24 advisory-opinion requests seeking guidance about the scope of the restrictions since 2000, yet none has resulted in the issuance of a formal, binding advisory opinion. Moreover, in conversations with requesters, FDA has "indicated that the Food and Drug Administration no longer issue[s] advisory opinions." *See* Letter from Susan H. Hargrove, Smith, Anderson, Blount, Dorsett, Mitchell & Jernigan LLP to Jane A. Axelrad, Assoc. Dir. For Policy, CDER (Sept. 9, 2009); Letter from Jeffrey Shuren, Assoc. Comm'r for Policy and Planning, FDA to Mark J. Scheineson, Alston & Bird LLP (June 2, 2008).

[7] In its Amarin Letter (at 5-6), FDA implies that Amarin failed to give FDA adequate opportunity to clarify its regulatory regime. The MIWG notes that it filed its first Citizen Petition asking for clarification of FDA's speech restrictions four years ago, in 2011, and has made numerous further submissions to FDA, including a second citizen petition in 2013, requesting clarification of and substantive changes to the existing regulatory framework. On June 6, 2014, FDA granted both petitions and announced that it would undertake a "comprehensive review of the regulatory regime governing communications about medical products" as requested by the MIWG. Letter from Leslie Kux, Assistant Commissioner for Policy, FDA to Alan R. Bennett and Joan McPhee, Ropes & Gray LLP, and Coleen Klasmeier and Paul Kalb, Sidley Austin LLP, Docket Nos. FDA-2011-P-0512 and FDA-2013-P-1079 (June 6, 2014). The MIWG appreciates FDA's ongoing efforts to address the issues raised in its submissions. This brief describes the problematic lack of clarity that pervades the regime in its current state.

government's enforcement powers be explicit and binding. *Fox*, 132 S. Ct. at 2318 (internal quotation marks and alterations omitted).

Further, given the government's frequent change of positions, manufacturers can take little if any comfort from non-binding guidance. For example, an FDA guidance document permitted manufacturers to distribute "pivotal study" reprints, but the document has disappeared from the FDA's website and its list of effective guidance documents, rendering its legal status unclear. *See* Advertising and Promotion; Guidances, 61 Fed. Reg. 52,800 (Oct. 8, 1996). And FDA has taken inconsistent positions on whether "scientific exchange" is one of several distinct safe harbors, or is the *only* safe harbor. *Compare, e.g.*, Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64,074, 64,095-96 (Dec. 3, 1997) ("Scientific and Educational Activities") *and* FDA, Guidance for Industry: 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) ("Good Reprint Practices") (suggesting guidance documents describe types of scientific exchange) *with* Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Treatment Use and Sale, 52 Fed. Reg. 19,466, 19,475 (May 22, 1987) (suggesting scientific exchange is a distinct safe harbor).

More fundamentally, no regulation or guidance document purports to explain the "circumstances" prong of the "intended use" regulation, or its application to 21 C.F.R. § 201.100, in a manner that cabins its reach. Instead, FDA's "safe harbors" introduce additional ambiguities. For instance, the safe harbors explicitly exclude manufacturer "promotion" of off-label uses. *See, e.g.*, Good Reprint Practices; Unsolicited Requests Guidance at 2; Scientific and Educational Activities. They leave unclear, however, what constitutes "promotion," a term not drawn from the

statute or the "intended use" regulations, and not defined even in the non-binding guidance documents. As *Buckley* said of the line between "advocacy" and "discussion," any distinction between "promotion" of off-label uses and non-promotional speech about those uses is one that "may often dissolve in practical application." 424 U.S. at 42. For example, the FDA might consider even a manufacturer's warnings about the dangers of off-label use to be "promotion" if the warnings provide specific information about especially dangerous doses or practices, or ways that the danger could be reduced. *See, e.g.*, Compl. ¶ 76, *Allergan v. United States*, No. 1:09-cv-01879 (D.D.C. Oct. 1, 2009), ECF No. 1. The FDA might consider even speech about *on-label* uses to be off-label "promotion" in some circumstances. *See* Gov't Br. at 27, *Par Pharm. Inc. v. United States*, 1:11-cv-01820-RWR (D.D.C. Jan. 1, 2012), ECF No. 14-1. "No speaker, in such circumstances, safely could assume that anything he might say upon the general subject would not be understood" as promotion of an off-label use. *Buckley*, 424 U.S. at 43.

The scope of the safe harbor for industry-supported scientific and educational activities is similarly uncertain: the FDA's guidance document lists a dozen different factors, each broadly phrased, and any of which alone could (although is not "likely to") establish a manufacturer's non-compliance. *See* Scientific and Educational Activities, 62 Fed. Reg. at 64,096-99. Moreover, the document states that the agency may also find non-compliance based on other factors, not listed in the guidance. *Id.* This does little to limit the agency's discretion.

The guidance documents also fail to make clear whether all off-label speech that does not fall within a specific "safe harbor" is prohibited. For instance, it is generally believed that manufacturers may provide "information to formulary committees, managed care organizations, and other third-party payers in order to obtain coverage of and reimbursement for their products." Citizen Pet. of Allergan, Inc. et al. at 10, FDA-2011-P-0512-0001 (July 5, 2011). None of the safe

harbors explicitly covers this practice, however, and the "FDA itself has not publicly stated" its position. *Id.* FDA has thus failed to provide the required "clarity in regulation" that "is essential to the protections provided by the Due Process Clause of the Fifth Amendment." *Fox*, 132 S. Ct. at 2317.

The Amarin Letter continues FDA's problematic approach to speech restrictions. Acknowledging the need for clarification in how FDA's "existing guidance and current thinking applies to [Amarin's] proposed communications," FDA states only that in "the unusual combination of circumstances presented" by Amarin, FDA "does not intend to object to Amarin's proposed communications if made in the manner and to the extent described below." Amarin Letter at 6. In other words, the Letter confirms that FDA's regulations would prohibit Amarin's speech, but that FDA has chosen to permit some of the speech in a limited manner, as an exercise of enforcement discretion on which no other manufacturer may rely. In the Amarin Letter, FDA states that Amarin may provide "truthful and non-misleading summaries of the results of the ANCHOR trial," *id.* at 6, although the FDA's revised draft guidance concerning good reprint practices states that dissemination of studies regarding off-label uses "*should* … [b]e in the form of an unabridged reprint or copy of an article," and "*should not* … [b]e … summarized … to emphasize or promote an unapproved use." Revised Good Reprint Practices 7-9 (emphasis added). FDA does not explain how its specific position permitting Amarin's studies squares with its general position declaring that dissemination of study summaries regarding an off-label use will be treated as evidence of intended use that will render the manufacturer conduct criminal.[8] FDA also declares that dietary supplement manufacturers are able to make qualified health claims only

[8] Nor does FDA square its statement that drug manufacturers can disseminate meta-analyses and historically controlled data (Amarin Letter at 8) with the fact that permission to do so that had been conferred by the Good Reprint Practices guidance in 2009 was eliminated in the 2014 Revised Good Reprint Practices draft guidance.

"through the exercise of FDA's enforcement discretion," which FDA declines to extend to identical claims Amarin seeks to make about Vascepa, because Vascepa is, for other purposes, regulated as a drug. *See* Amarin Letter at 9-10. FDA is, in its view, able to draw such distinctions between different speakers' ability to make identical claims because FDA regards all such speech as permissible only in the exercise of its discretion. The First Amendment does not tolerate a regime in which speech is either categorically prohibited or arguably prohibited by unclear regulations, with authorization to speak granted only by the agency based on case-specific assessments. Such a regime operates as an impermissible prior restraint of speech. *See Neb. Press Ass'n v. Stuart*, 427 U.S. 539, 559 (1976).

III. IN LIGHT OF THE IMPORTANCE OF THE ISSUES THIS CASE RAISES AND THE LACK OF CLARITY IN THE LAW, THERE IS A COMPELLING NEED FOR JUDICIAL REVIEW.

The state of affairs described above—in which an ambiguous regulatory regime is paired with a draconian enforcement regime to chill speech by those most knowledgeable about the lawful and sometimes necessary uses of their products—has persisted far too long. This lack of clarity coupled with threat of dire punishment has allowed the government time and again to avoid judicial review of these speech restrictions. Notwithstanding FDA's Amarin Letter, this Court's review is essential to ensure the proper flow of valuable medical and scientific information, and to lift the significant chilling effect on constitutionally protected speech.

A. The Speech-Chilling Regulatory and Enforcement Regime Urgently Requires Judicial Review.

The speech-chilling regulatory framework has evaded review in significant part due to the government's aggressive enforcement regime. Because of the crushing penalties manufacturers face if convicted and the threat of exclusion from participation in the Federal health care

programs, most enforcement actions result in "conference room settlements."[9] These resolutions chill speech, yet do nothing to clarify the rules. Through these settlements, the government has avoided, and will continue to avoid, judicial review of its suppression of manufacturer speech.[10] Even in affirmative cases brought by manufacturers, the government has consistently resisted judicial review.[11] It would appear that the government intends to rely on its eleventh hour Amarin Letter to evade judicial review here as well. *See* Dkt. No. 21.

Averting judicial review has afforded prosecutors an effective monopoly to determine what speech is permissible. As Judge Lynch has explained, "Our criminal justice system … has gradually transformed from an adversarial into an inquisitorial system, in which guilt and punishment are increasingly decided not in courts, but through a kind of administrative

[9] For example: Press Release, Dep't of Justice, Shire Pharmaceuticals LLC to Pay $56.5 Million to Resolve False Claims Act Allegations Relating to Drug Marketing and Promotion Practices (Sept. 24, 2014), http://www.justice.gov/opa/pr/shire-pharmaceuticals-llc-pay-565-million-resolve-false-claims-act-allegations-relating-drug; Press Release, Dep't of Justice, Endo Pharmaceuticals and Endo Health Solutions to Pay $192.7 Million to Resolve Criminal and Civil Liability Relating to Marketing of Prescription Drug Lipoderm for Unapproved Uses (Feb. 21, 2014), http://www.justice.gov/opa/pr/endo-pharmaceuticals-and-endo-health-solutions-pay-1927-million-resolve-criminal-and-civil; Press Release, Dep't of Justice, Par Pharmaceuticals Pleads Guilty and Agrees to Pay $45 Million to Resolve Civil and Criminal Allegations Related to Off-Label Marketing (Mar. 5, 2013), http://www.justice.gov/opa/pr/par-pharmaceuticals-pleads-guilty-and-agrees-pay-45-million-resolve-civil-and-criminal.

[10] "[B]y negotiating settlements under the FD&C and the False Claims Acts, DOJ has avoided judicial review of its enforcement theories and procedures, fueling the likelihood that its significantly altered approach to unlawful drug promotion will continue unchecked." Vicki W. Girard, *Punishing Pharmaceutical Companies for Unlawful Promotion of Approved Drugs: Why the False Claims Act is the Wrong Rx* 9-10 (2008) (Georgetown Law Faculty Working Papers), *available at* http://scholarship.law.georgetown.edu/fwps papers/74.

[11] *See, e.g.*, Defendants' Br. at 12, *Par Pharm., Inc. v. United States*, No. 11-1820 (D.D.C. Jan. 11, 2012), ECF No. 14; Defendant's Br. at 13, *Allergan, Inc. v. United States*, No. 09-1879 (D.D.C. Dec. 11, 2009), ECF No. 18. The government required dismissal of these civil challenges to FDA's speech restrictions as a prerequisite to resolving criminal investigations.

adjudication, in which prosecutors play the part of magistrates or administrators."[12] Abdicating the field to enforcement agencies through the absence of judicial review is plainly not appropriate where First Amendment rights are implicated.

Courts apply relaxed jurisdictional rules in First Amendment cases to avoid precisely this untenable situation, where restrictions on free expression can be "tested only by those hardy enough to risk criminal prosecution" or civil sanctions. *Dombrowski v. Pfister*, 380 U.S. 479, 486-87 (1965). Where manufacturers must either curtail the "conduct of their affairs" or "risk serious criminal and civil penalties for the unlawful distribution of 'misbranded'" products, then "access to the courts … under the Declaratory Judgment Act must be permitted" absent exceptional circumstances. *Abbott Labs. v. Gardner*, 387 U.S. 136, 153 (1967) (pre-enforcement challenge by pharmaceutical manufacturers). Indeed, "it was the very purpose of the Declaratory Judgment Act to ameliorate" such "dilemma[s]." *Id.* at 152. As such, this Court should address and resolve the dilemmas that Amarin and many others face.

B. Amarin's Complaint and Motion Are Appropriate for Judicial Review.

A pre-enforcement challenge such as that brought by Amarin is appropriate for judicial review where, as here, regulations chill protected First Amendment activity through the threat of criminal or civil penalties. The Second Circuit "assess[es] pre-enforcement First Amendment claims … under somewhat relaxed standing and ripeness rules." *Nat'l Org. for Marriage v. Walsh*, 714 F.3d 682, 689 (2013). That is because, "without the possibility of pre-enforcement challenges, plaintiffs contesting statutes or regulations on First Amendment grounds face an unattractive set of options if they are barred from bringing a facial challenge." *Id.* (internal quotation marks omitted). If courts do not take up pre-enforcement challenges, plaintiffs will be

[12] Gerard E. Lynch, *The Role of Criminal Law in Policing Corporate Misconduct*, 60 Law & Contemp. Probs. 23, 55 (1997).

forced to either "refrain[] from activity they believe the First Amendment protects, or risk civil or criminal penalties for violating the challenged law." *Id.*

In this Circuit, although "[a] plaintiff must allege something more than an abstract, subjective fear that his rights are chilled," "a real and imminent fear of such chilling is enough." *Id*. A plaintiff "need not demonstrate to a certainty that it will be prosecuted," but "only that it has an actual and well-founded fear that the law will be enforced against it." *Id.* at 689 (internal quotation marks omitted). These principles apply "in the civil context as well." *Hedges v. Obama*, 724 F.3d 170, 196-97 (2d Cir. 2013). After all, "[t]he fear of civil penalties can be as inhibiting of speech as can trepidation in the face of threatened criminal prosecution." *Vt. Right to Life Comm., Inc. v. Sorrell*, 221 F.3d 376, 382 (2d Cir. 2000).

Amarin's challenge satisfies these standards. As demonstrated above, the regulatory regime governing off-label speech does more than create a merely "abstract" or "speculative" chilling effect. "The very intricacy" of the off-label speech regime and "the uncertainty as to the scope of its proscriptions make it a highly efficient *in terrorem* mechanism." *Keyishian*, 385 U.S. at 601. That effect is magnified by the threat of criminal penalties. The regulatory regime places manufacturers at risk of criminal and civil sanctions if they cannot correctly guess where the government will draw the line between permissible and impermissible speech. And while most manufacturers dedicate substantial time and resources to ensuring that their business practices are compliant with FDA rules and regulations, they avoid truthful, non-misleading and beneficial speech they fear could be deemed a violation of FDA's ill-defined regulatory regime.

For many years now, the government has pursued an aggressive campaign to enforce its off-label speech regime. *See supra* note 9. Manufacturers have also been subjected to a large number of *qui tam* suits seeking staggering liability based on alleged off-label promotion. *Id.*

FDA's Amarin Letter confirms that it would regard distribution beyond the "manner and extent" it identifies as evidence of intended use, and that FDA would regard inclusion of qualified health claims (the same claims as appear in dietary supplements containing essentially the same active ingredients) in Vascepa's "labeling" (which FDA construes broadly to encompass most communications by manufacturers) as sufficient to render Vascepa misbranded. *See* Amarin Letter at 6, 10. And, in any event, FDA does not determine enforcement policy for the Department of Justice, which is not a party to FDA's Amarin Letter. Accordingly, Amarin's fear of criminal prosecution or civil sanctions is real and well-founded.

* * * * *

The FDA's off-label speech regulations are unconstitutional as applied to Amarin in this case. Judged under heightened scrutiny, the government's speaker- and content-based regulations have a constitutionally intolerable chilling effect on truthful and non-misleading information that Amarin seeks to communicate to an audience of sophisticated and experienced prescribing physicians. The danger of FDA's regulatory regime "is, in large measure, one of self-censorship; a harm that can be realized even without an actual prosecution," making pre-enforcement review plainly appropriate. *Virginia v. Am. Booksellers*, 484 U.S. 381, 393 (1988). In light of the constitutional interests at stake, this Court should hear and uphold Amarin's First Amendment right to make truthful, non-misleading statements to healthcare professionals.

CONCLUSION

For the reasons set forth above, the relief that plaintiff requests should be granted.

Dated: New York, New York
June 11, 2015

Dated: Boston, Massachusetts
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