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., and SYLVIA MATTHEWS BURWELL,

Defendants.

15 Civ. 3588 (PAE)

OPINION & ORDER

PAUL A. ENGELMAYER, District Judge:

In *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012), the Court of Appeals for the Second Circuit vacated a pharmaceutical sales representative's conviction for conspiring to introduce a misbranded drug into interstate commerce, in violation of 21 U.S.C. §§ 331(a) and 333(a)(1). The conviction was based on Caronia's having promoted a drug for "off-label use," that is, a use other than the one approved by the U.S. Food and Drug Administration (the "FDA"). Caronia's conduct to promote the off-label use, however, had consisted solely of truthful and non-misleading speech. The Second Circuit held that, to avoid infringing the First Amendment, the misbranding provisions of the Federal Food, Drug and Cosmetic Act (the "FDCA") must be construed "as not prohibiting and criminalizing the truthful off-label promotion of FDA-approved prescription drugs" where the off-label use itself is lawful. 703 F.3d at 168.

This case grows out of the decision in *Caronia* and involves the same misbranding provisions. Plaintiff Amarin Pharma, Inc. ("Amarin") manufactures a triglyceride-lowering drug, Vascepa. The

FDA has approved Vascepa for one use, but doctors have widely, and lawfully, prescribed it for another. Amarin wishes to make truthful statements to doctors relating to Vascepa's off-label use. The specific statements Amarin seeks to make are derived largely from an FDA-approved study of Vascepa's off-label use, and from writings by the FDA itself on that subject. Amarin therefore contends, and the FDA largely but not wholly concedes, that the statements Amarin seeks to make are truthful and non-misleading. However, the FDA, recognizing that Amarin's purpose in making these statements would be to promote an unapproved use of Vascepa, has threatened to bring misbranding charges against Amarin (and, presumably, its employees) if it does so.

In this action, Amarin claims that the FDA's threat of a misbranding action is chilling it from engaging in constitutionally protected truthful speech. Amarin seeks preliminary relief to ensure its ability to engage in truthful and non-misleading speech free from the threat of a misbranding action. For the reasons that follow, the Court grants such relief.

I. Background[1]

Amarin is a biopharmaceutical company incorporated in Delaware and based in New Jersey. Compl. ¶ 24. It and four medical doctors resident in New York[2] (collectively, "Amarin")

[1] The facts relevant to Amarin's motion for preliminary relief are drawn from the Complaint, Dkt. 1 ("Compl."); plaintiffs' brief in support of that motion, Dkt. 13 ("Amarin Br."); the declarations in support of Dr. Eric M. Rishe, Dkt. 6 ("Rishe Decl."), Dr. Jonathan Herbst, Dkt. 7 ("Herbst Decl."), Dr. Ralph Yung, Dkt. 8 ("Yung Decl."), Dr. Peter M. Gottesfeld, Dkt. 9 ("Gottesfeld Decl."), Aaron Berg, Dkt. 10 ("Berg Decl."), Joel Kurtzberg, Dkt. 11 ("Kurtzberg Decl."), and Steven Ketchum, Dkt. 12 ("Ketchum Decl."); the FDA's brief in opposition, Dkt. 51 ("FDA Br."); the declarations in opposition of Janet Woodcock, Dkt. 52 ("Woodcock Decl."), Ellen London, Dkt. 53, 56 ("London Decl."), and Curtis Rosebraugh, Dkt. 54 ("Rosebraugh Decl."); and the declarations in further support from Ketchum, Dkt. 64 ("Ketchum Reply Decl."), Scott Gottlieb, M.D., Dkt. 65 ("Gottlieb Decl."), and Paul H. Rubin, Dkt. 66 ("Rubin Decl."). References to "Tr." are to the transcript of oral argument, held on July 7, 2015. *See* Dkt. 70.

[2] Dr. Herbst practices internal medicine in Rye Brook. Compl. ¶ 20. Dr. Rishe practices internal medicine, hematology, and oncology in Riverdale. *Id.* ¶ 21. Dr. Gottesfeld practices family

bring this suit against the FDA, two officials with responsibility over the FDA (Dr. Stephen Ostroff and Sylvia Matthews Burwell), and the United States (collectively, the "FDA").[3] The FDA is the federal agency responsible for approving, disapproving, and otherwise regulating food, drugs, medical devices, and biologics under the FDCA. *Id.* ¶ 25.

In this background section, the Court first reviews the statutory and regulatory framework under the FDCA governing the sale and marketing of drugs, the provisions relevant to the off-label promotion of drugs, and the FDA's response to date to the *Caronia* decision addressing the interplay between these provisions and the First Amendment. The Court then reviews the FDA's evaluation of Vascepa and the basis for its decision to not approve it for the off-label use at issue here. The Court then reviews this lawsuit and Amarin's application for preliminary relief.

A. The Statutory and Regulatory Framework

1. Brief History of the FDCA

Before 1938, drug manufacturers could market drugs without premarket approval for safety or effectiveness.[4] In 1938, a year after more than 100 Americans died after ingesting a toxic drug (elixir sulfanilamide), Congress enacted the FDCA.[5]

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medicine in Mt. Kisco and Cortlandt Manor. *Id.* ¶ 22. Dr. Yung practices internal medicine and endocrinology in the Bronx. *Id.* ¶ 23. The Court refers to the four collectively as the "doctor plaintiffs."

[3] Dr. Ostroff is sued in his official capacity as the Acting Commissioner of Food and Drugs. *Id.* ¶ 26. He is the FDA's most senior official, and is directly responsible for administering the FDCA. *Id.* Burwell, to whom Dr. Ostroff reports, is sued in her official capacity as Secretary of the Department of Health and Human Services ("HHS"). *Id.* ¶ 27.

[4] Henry A. Waxman, *A History of Adverse Drug Experiences: Congress Had Ample Evidence to Support Restrictions on the Promotion of Prescription Practices*, 58 Food & Drug L.J. 299, 300 (2003) [hereinafter, "Waxman, *A History*"].

[5] *See* Carol Ballentine, *Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident*, FDA Consumer (June 1981), http://www.fda.gov/AboutFDA/WhatWeDo/History/

As originally enacted, the FDCA required drugs to be approved for safety, but not for effectiveness, before their introduction into the market. *See* Drug Industry Act of 1962, S. Rep. No. 1744, at 37 (1962), *reprinted in* 1962 U.S.C.C.A.N. 2884 (reprinted at London Decl., Ex. Z-4, at 8). As a result, even where the evidence did not support a manufacturer's therapeutic claims, the FDA still approved of drugs for general distribution as long as they were shown to be "safe under conditions proposed for their use in the labeling." *Id.*

This regulatory regime led to a profusion of drug advertising that had "a deliberate intent to mislead." *Id.*; *see also* The Drug Industry Antitrust Act of 1962: Hearings before the Antitrust Subcomm. of the H. Comm. on the Judiciary, 87th Cong. 67 (reprinted at London Decl., Ex. AA-1, at 4) ("[T]he physician is bombarded with seductive advertising which fails to tell the truth, the whole truth, and nothing but the truth. This often leads him into prescribing a new drug without adequate warning or information about its possible side effects and, indeed, without any solid clinical evidence that the drug is effective or is even as safe as the advertisers claim."); Waxman, *A History*, 58 Food & Drug L.J. at 301–02.

In response to rampant false and misleading advertising of drugs, Congress amended the FDCA by enacting the Drug Amendments of 1962. These require manufacturers to demonstrate that their drugs are both safe *and* effective for their intended uses before they are approved for distribution. Pub. L. No. 87-781, 76 Stat. 780 (1962) ("Kefauver-Harris Amendments"); 21 U.S.C. § 355(a), (d).[6] Specifically, the FDCA, as amended, provides that: "No person shall

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ProductRegulation/SulfanilamideDisaster/default.htm.

[6] *See also* Waxman, *A History*, 58 Food & Drug L.J. at 301 ("The hearings showed that the pharmaceutical marketplace was filled with misleading promotional material on which physicians relied, [and] that there was no reliable source of evidence from which physicians could tell effective drugs from ineffective drugs").

introduce or deliver for introduction into interstate commerce any new drug," without the FDA's approval of a "new drug application," which must demonstrate the drug's safety and efficacy through a series of pre-clinical and clinical trials, and must indicate the proposed labeling for the drug. 21 U.S.C. § 355. FDA approval is therefore necessary before a manufacturer can distribute a drug.

2. The Prescription and Use of Approved Drugs for Off-Label Purposes

Significant here, however, the FDA does not regulate doctors. After a drug has been approved by the FDA, a doctor may lawfully prescribe it for both FDA-approved and non-FDA approved ("off-label") uses. *See Caronia*, 703 F.3d at 153 (citing *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001); *Weaver v. Reagen*, 886 F.2d 194, 198 (8th Cir. 1989); John E. Osborn, *Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information*, 10 Yale J. Health Pol'y L. & Ethics 299, 303 (2010) ("Physicians may prescribe FDA-approved drugs . . . for any therapeutic use that is appropriate in their medical judgment.")).

The prescription of FDA-approved drugs for off-label purposes is widespread. The most comprehensive study on off-label prescriptions in the United States, conducted in 2001, found that approximately 21% of prescriptions were for off-label purposes. *See* Randall S. Stafford, *Regulating Off-Label Drug Use: Rethinking the Role of the FDA*, 358 N. Engl. J. Med. 1427, 1427 (2008).[7] In certain fields, off-label prescription is the norm rather than the exception. *See* Euni Lee et al., *Off-label prescribing patterns of antidepressants in children and adolescents*, 21

[7] *See also* Ryan Abbott & Ian Ayres, *Evidence and Extrapolation: Mechanisms for Regulating Off-label Uses of Drugs and Devices*, 64 Duke L.J. 377, 388 (2014) (citing this study); Marc A. Rodwin, *Rooting Out Institutional Corruption to Manage Inappropriate Off-label Drug Use*, 41 J. L. Med. & Ethics 654, 656 (2013) (citing this as the "leading study tracking off-label uses").

Pharmacoepidemiology & Drug Safety 137 (2012) (in 2000-2006 study, more than 90% of antidepressants prescribed to children and adolescents in an outpatient care setting were for off-label purposes); Douglas L. Leslie et al., *Off-label use of antipsychotic medication in the department of Veterans Affairs health system*, 60 Psychiatric Servs. 1175 (2009) (based on review of Veterans Affairs databases, more than 60% of prescriptions of antipsychotic drugs in 2007 were for off-label use); *see also* Ishaq Lat et al., *Off-label medication use in adult Critical care patients*, 26 J. Critical Care 89, 91 (2010) (study of medication orders for 414 patients in 37 intensive care units across nation showed that more than 35% were for an off-label purpose and that 97% of patients received at least one off-label medication).

And the therapeutic—indeed, sometimes life-saving—value of off-label uses of FDA-approved drugs has been widely recognized.

In the area of oncology, for example, doctors commonly prescribe drugs for off-label purposes. For a doctor treating a cancer patient, the option of waiting years for possible FDA approval of a new use for an existing drug will often be untenable, and drugs approved by the FDA to treat one type of cancer have proven effective in combatting others, including by reducing tumors or enhancing the effectiveness of chemotherapy.[8] In 2009, in recognition that certain drugs may be a cancer patient's "last hope," Medicare expanded its coverage of cancer treatment drugs to include drugs not FDA-approved for that purpose. For example, Medicare

[8] Am. Cancer Soc'y, *Off-label Drug Use*, http://www.cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/chemotherapy/off-label-drug-use (last visited Aug. 7, 2015).

today covers Gemzar, a drug that the FDA has approved to treat only four types of cancer, to treat a dozen other cancers, including advanced cervical cancer.[9]

In other areas of medicine, too, there are numerous examples in which drugs have been successfully prescribed to treat conditions other than those for which the FDA approved them.[10]

A doctor's off-label prescription also may involve using a drug for an approved condition but at an unapproved dosage or directed to an unapproved patient population. For example, many drugs that the FDA has approved for use by adults have not been approved for pediatric use, in some instances because of the challenges presented by testing drugs on infants and children. As a result, the labels on these drugs lack instructions as to pediatric doses. Pediatricians, however, commonly prescribe such drugs to children;[11] this off-label usage has

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[9] Reed Abelson & Andrew Pollack, *Medicare Widens Drugs It Accepts for Cancer*, N.Y. Times (Jan. 26, 2009), http://www.nytimes.com/2009/01/27/health/27cancer.html?pagewanted=all.

[10] For example: (1) Viagra was originally approved to treat chest pain caused by heart disease, but was later prescribed off-label to treat erectile dysfunction, before it was approved for that use. James O'Reilly & Amy Dalal, *Off-label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, 12 Annals Health L. 295, 298 (2003). (2) Aspirin also was prescribed off-label to reduce the risk of heart attacks, before the FDA approved that use in 1998. *Id.* (3) Avastin, a drug approved to treat cancer, has been widely prescribed by ophthalmologists to treat age-related macular degeneration, which causes vision loss and blindness. Press Release, National Institutes of Health, *Avastin and Lucentis are equivalent in treating age-related macular degeneration* (Apr. 30, 2012), http://www.nih.gov/news/health/apr2012/nei-30a.htm; *see also* Peter Whoriskey & Dan Keating, *An effective eye drug is available for $50. But many doctors choose a $2,000 alternative*, Wash. Post (Dec. 7, 2013), http://www.washingtonpost.com/business/economy/an-effective-eye-drug-is-available-for-50-but-many-doctors-choose-a-2000-alternative/2013/12/07/1a96628e-55e7-11e3-8304-caf30787c0a9_story.html. And (4) scientists have discovered that patients with moderate to severe eczema can be successfully treated with a rheumatoid arthritis drug. Ziba Kashef, *Yale researchers beat untreatable eczema with arthritis drug*, YaleNews (July 20, 2015), http://news.yale.edu/2015/07/20/yale-researchers-beat-untreatable-eczema-arthritis-drug.

[11] Jeffrey L. Blumer, *Off-Label Uses of Drugs in Children*, 104 Pediatrics 598, 602 (1999). As of 2014, less than half of FDA-approved drugs included specific labeling for children. Am. Academy of Pediatrics, *AAP Makes Recommendations on Use of Off-Label Drugs for Children*

proven effective in treating children for, among other things, severe emotional and behavioral disorders,[12] respiratory and allergic diseases,[13] and pain.[14]

The FDA itself has long recognized the benefits of using prescription drugs for off-label purposes. As early as 1982, the FDA stated that:

> Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such "unapproved" or, more precisely, "unlabeled" uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature.

U.S. Food and Drug Admin., *FDA Drug Bulletin*, 12 FDA Drug Bull. 1, 5 (1982). And in 2009, the FDA acknowledged that: "[O]ff-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care."[15] Court decisions in the area have

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(Feb. 24, 2014), https://www.aap.org/en-us/about-the-aap/aap-press-room/pages/AAP-Makes-Recommendations-On-Use-of-Off-Label-Drugs-for-Children.aspx.

[12] *See, e.g.*, Joyce Nolan Harrison et al., *Antipsychotic Medication Prescribing Trends in Children and Adolescents*, 26 J. Pediatric Health Care 139 (2012).

[13] *See, e.g.*, Diana Silva et al., *Off-label prescribing for allergic diseases in children*, 7 World Allergy Organ. J. 4 (2014).

[14] *See, e.g.*, Christopher Wittich, *Ten Common Questions (and Their Answers) About Off-label Drug Use*, 87 Mayo Clinic Proceedings 982 (2012) ("For example, morphine has never received an FDA indication for pain treatment in children, but it is extensively used for this indication in hospitalized pediatric patients."); *see also* Am. Academy of Pediatrics, *Off-Label Medications Prescribed to Nearly All Pediatric Intensive Care Patients* (Oct. 21, 2012), https://www.aap.org/en-us/about-the-aap/aap-press-room/Pages/Off-Label-Medications-Prescribed-to-Nearly-All-Pediatric-Intensive-Care-Patients.aspx (in intensive care unit of an urban children's hospital, off-label treatments were ordered for 96% of all pediatric patients, and 100% of patients between ages 13–17, making "[t]reatment with off-label medications . . . the rule rather than the exception in the [pediatric intensive care unit].").

[15] U.S. Food and Drug Admin., *Draft Guidance, Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices* (2009), http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm.

similarly recognized this point. *See, e.g.*, *Caronia*, 703 F.3d at 153; *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 56–58 (D.D.C. 1998) [hereinafter "*Friedman*"], *amended*, 36 F. Supp. 2d 16 (D.D.C. 1999), *appeal dismissed, judgment vacated in part sub nom., Wash. Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000).

3. The FDA's Prohibition on the Promotion of Drugs for Off-Label Use

Notwithstanding the potential benefits of off-label use of approved drugs, the FDA has long taken the position that a drug manufacturer who markets or promotes an approved drug for an unapproved use violates the FDCA. This position reflects an application of, rather than an explicit prohibition within, the FDCA; as the Second Circuit observed in *Caronia*: "The FDCA and its accompanying regulations do not expressly prohibit the 'promotion' or 'marketing' of drugs for off-label use." 703 F.3d at 154.

Specifically, the FDA's position is that a manufacturer who markets or promotes an off-label drug risks criminal liability for "misbranding" under 21 U.S.C. § 331(a), which prohibits "[t]he introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded." Misbranding carries a term of up to one year imprisonment and a fine of up to $1,000 per occurrence, *see* 21 U.S.C. § 333(a)(1), but if the defendant either acted with "the intent to defraud or mislead" or is a repeat offender, a term of up to three years imprisonment and a fine of up to $10,000 is authorized, *see id.* § 333(a)(2).

Under the statute, a drug is misbranded if its labeling does not contain "adequate directions for use." *Id.* § 352(f).[16] The FDA has defined "adequate directions for use" as

[16] As summarized in *Caronia:* "A drug is also misbranded if, *inter alia*: its label is false or misleading; the label fails to display required information prominently; its container is

"directions under which the lay[person] can use a drug safely and for the purposes for which it is intended." 21 C.F.R. § 201.5. It has defined "intended use" as "the objective intent of the persons legally responsible for the labeling of drugs"; "intended use" may be demonstrated by "oral or written statements by such persons or their representatives" and "the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised." *Id.* § 201.128.[17]

Among the materials that may serve as proof of a manufacturer's intended use are promotional statements by the company or its representatives. *See id.* § 201.5. "Off-label promotional statements could thus presumably constitute evidence of an intended use of a drug that the FDA has not approved." *Caronia*, 703 F.3d at 155 (citing 21 C.F.R. § 201.5). FDA regulations state that a manufacturer that wishes to market or promote an approved drug for a new use (whether a new condition, dosage, or population) must submit a "supplemental new drug application"; the drug must undergo new clinical trials to demonstrate its safety and effectiveness for the new use. 21 C.F.R. § 314.70; *Friedman*, 13 F. Supp. 2d at 55. Until the FDA has approved the new use, the manufacturer may not promote the drug for that use. 21 C.F.R. § 314.70.

misleading; or it is dangerous to health when used in the dosage, manner, frequency, or duration prescribed, recommended, or suggested on the label." 703 F.3d at 154 n.3 (citing 21 U.S.C. §§ 352(a)–(n))

[17] The FDCA defines labeling to include all written, printed, or graphic material "(1) upon any [drug] or any of its containers or wrappers, or (2) accompanying such [drug]." 21 U.S.C. § 321(k) & (m). In addition to packaging and inserts, "labeling" has "been construed to include nearly every form of drug company promotional activity, including booklets, pamphlets, mailing pieces, bulletins, and all literature that supplements, explains, or is otherwise textually related to the product." *Friedman*, 13 F. Supp. 2d at 55 (citing 21 C.F.R. § 202.1(1)(2) (1997); *Kordel v. United States*, 335 U.S. 345, 350 (1948); *United States v. Vitamin Indus., Inc.*, 130 F. Supp. 755, 765–66 (D. Neb. 1955)).

On the basis of these provisions, in recent years, federal prosecutors, in conjunction with the FDA, have actively pursued criminal misbranding charges against pharmaceutical companies and their sales representatives based on their promotion of approved drugs for non-approved purposes.

For example, in 2012, GlaxoSmithKline LLC ("GSK") pled guilty in the District of Massachusetts to introducing two misbranded drugs into interstate commerce, and paid a $1 billion fine and forfeiture. One misbranding charge was based on GSK's promotion of the drug Paxil for treating depression in patients under age 18; the FDA had not approved Paxil for pediatric use. The other was based on GSK's promotion of the drug Wellbutrin for weight loss, and to treat sexual dysfunction, substance addictions, and attention deficit hyperactivity disorder; the FDA had approved the drug only to treat major depressive disorder.[18] In 2012, Abbott Laboratories Inc. ("Abbott Labs") pled guilty in the Western District of Virginia to misbranding the drug Depakote, and paid a $500 million fine. The FDA had approved Depakote only for epileptic seizures, bipolar mania, and the prevention of migraines, but Abbott Labs had promoted it for other uses, including treating schizophrenia.[19] And in 2010, Allergan Inc. ("Allergan") pled guilty in the Northern District of Georgia to misbranding based on its off-label promotion of the therapeutic version of Botox, and paid a $375 million fine. The FDA had approved Botox to

[18] Press Release, U.S. Dep't of Justice, *GlaxoSmithKline to Plead Guilty and Pay $3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data* (July 2, 2012), http://www.justice.gov/opa/pr/glaxosmithkline-plead-guilty-and-pay-3-billion-resolve-fraud-allegations-and-failure-report.

[19] Press Release, U.S. Dep't of Justice, *Abbott Labs to Pay $1.5 Billion to Resolve Criminal & Civil Investigations of Off-label Promotion of Depakote* (May 7, 2012), http://www.justice.gov/opa/pr/abbott-labs-pay-15-billion-resolve-criminal-civil-investigations-label-promotion-depakote [hereinafter, "Abbott Labs DOJ"].

treat crossed eyes, involuntary eyelid and neck muscle contraction, excessive underarm sweating, and adult upper-limb spasticity, but Allergan had promoted it for headache, pain, spasticity, and juvenile cerebral palsy.[20] *See also Caronia*, 703 F.2d at 154 (listing examples of enforcement action); Kurtzberg Decl., Exs. 1–3 (same).

In instances where a manufacturer's statements promoting a drug's off-label use are untrue or misleading or may promote unsafe usage, the FDA has explained, such misbranding actions further public safety. There are many examples in which prescriptions of an approved drug for off-label use has caused harm. For example, Gabitril, a drug approved to treat partial seizures, was prescribed off-label to treat psychiatric conditions, but caused patients to suffer seizures and status epilepticus.[21] And the off-label use of quinine for nocturnal leg cramps caused adverse reactions, including thrombocytopenia and gastrointestinal bleeding.[22]

More broadly, the FDA has stated, its goal in pursuing misbranding charges against manufacturers based on the off-label promotion of drugs is to encourage use of the FDA's drug review and approval process. Such prosecutions, the FDA has stated, deter manufacturers from

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[20] Press Release, U.S. Dep't of Justice, *Allergan Agrees to Plead Guilty and Pay $600 Million to Resolve Allegations of Off-Label Promotion of Botox* (Sept. 1, 2010), http://www.justice.gov/opa/pr/allergan-agrees-plead-guilty-and-pay-600-million-resolve-allegations-label-promotion-botox [hereinafter, "Allergan DOJ"].

[21] Tewodros Eguale et al., *Drug, Patient, and Physician Characteristics Associated with Off-label Prescribing in Primary Care*, 172 Archives Internal Med. 781 (2012); *see also* Press Release, U.S. Food and Drug Admin., *Information for Healthcare Professionals: Tiagabine hydrochloride (marketed as Gabitril) – Seizures in Patients without Epilepsy* (February 18, 2005), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126114.htm.

[22] Eguale, *supra* note 21; *see also* Press Release, U.S. Food and Drug Admin., *FDA Drug Safety Communication: New risk management plan and patient medication guide for Qualaquin (quinine sulfate)* (July 8, 2010), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm218202.htm.

evading the FDA's review process for additional uses of approved drugs. For example, in announcing the settlement with Allergan regarding Botox, the FDA stated: "The FDA approval process ensures that pharmaceutical companies market their medications for uses that are proven to be safe and effective, and this case demonstrates that companies that fail to comply with these rules face criminal prosecution and stiff penalties."[23] And in describing its settlement with Abbott Labs regarding Depakote, the FDA stated that the settlement reflected the agency's commitment to "hold[ing] pharmaceutical companies accountable for marketing practices that undermine the drug approval process."[24]

In addition to facing criminal exposure for misbranding, a drug manufacturer who promotes a drug for off-label use may face civil suit under the False Claims Act ("FCA"), 31 U.S.C. § 3729 *et seq.*, on the theory that the company, in the course of its off-label promotion, caused false claims to be submitted to government health care programs for non-covered and non–FDA-approved uses.[25] In recent years, the Government has brought FCA claims on this theory, often in conjunction with criminal prosecutions under the FDCA for misbranding.

4. The FDA's Regulations as to Manufacturers' Marketing Materials and Responses to Inquiries Regarding Off-Label Usage

A final set of relevant FDA regulations are those relating to a manufacturer's marketing materials. When a manufacturer applies for approval to market a new drug, it must submit to the

[23] Allergan DOJ.

[24] Abbott Labs DOJ.

[25] Under the FCA, a person who knowingly "causes to be presented a false or fraudulent claim for payment or approval" or who knowingly makes or causes to be made "a false record or statement material to a false or fraudulent claim" to the United States Government must pay, per claim, a civil penalty of between $5,000 to $10,000, and may also be required to pay treble damages. 31 U.S.C. § 3729.

FDA "specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product." 21 C.F.R. § 314.81(B)(3)(i); *id.* § 601.12(f)(4). Otherwise, the FDA generally does not require a manufacturer to seek pre-approval of materials promoting a drug for an FDA-approved purpose.[26]

The FDA does, however, encourage manufacturers to request advisory comments before a drug's launch, with respect to promotional materials aimed at healthcare professionals.[27] Such materials may include sales or visual aids, advertisements in medical journals, and product websites.[28] The FDA's Office of Prescription Drug Promotion (the "OPDP") reviews such materials to ensure, *inter alia*, that they are not false or misleading; it provides written comments on proposed materials, reviews complaints of alleged violations, and initiates enforcement actions as to materials it finds false or misleading.[29] The OPDP also operates a "Bad Ad"

[26] U.S. Food and Drug Admin., *OPDP Frequently Asked Questions (FAQs)*, http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090308.htm (last visited Aug. 7, 2015).

[27] *See* U.S. Food and Drug Admin., *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs Guidance for Industry* (2015), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf [hereinafter, "FDA Promotional Guidance"]; 21 C.F.R. § 202.1(j)(4).

[28] FDA Promotional Guidance, at 8.

[29] U.S. Food and Drug Admin., *The Office of Prescription Drug Promotion (OPDP)*, http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090142.htm (last visited Aug. 7, 2015).

program that receives reports of alleged violations of the FDA's restrictions on promotion, including reports of promotion of a drug for an unapproved use.[30]

The FDA also has issued draft guidance as to how manufacturers should respond to unsolicited requests for off-label information about prescription drugs.[31]

If a person makes a *private* unsolicited request for off-label information, the manufacturer should disseminate information only to that person and tailored to answer only the requester's specific question. The information disseminated must be truthful, non-misleading, accurate, and balanced. The FDA further recommends that responses to questions or requests for information about off-label usage be referred to the manufacturer's medical or scientific representative or department, and that sales and marketing personnel have no input on the content of the manufacturer's response. Manufacturers are required to maintain records of all such requests for information and of the information that was provided in response.[32]

If a person makes a *public* unsolicited request for off-label information (for example, on an Internet forum), the FDA requires that the manufacturer provide only its contact information,

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[30] *See* U.S. Food and Drug Admin., *Truthful Prescription Drug Advertising and Promotion*, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/DrugMarketingAdvertisingandCommunications/ucm209384.htm (last visited Aug. 7, 2015); *see also* U.S. Food and Drug Admin., *Key Points of the Bad Ad Program*, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/DrugMarketingAdvertisingandCommunications/ucm211498.htm (last visited Aug. 7, 2015). If the OPDP determines that a promotion is illegal, it will initiate enforcement by issuing an Untitled Letter, a Warning Letter, or a referral for criminal investigation. *Id.*

[31] *See* U.S. Food and Drug Admin., *Guidance for Industry Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices* (2011), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf.

[32] *Id.* at 7–9.

and not include any off-label information, even if it is truthful and non-misleading. The FDA advises the manufacturer to state that the question raised pertains to an unapproved use and that the individual can contact the manufacturer's medical/scientific representative or medical affairs department with the specific unsolicited request to obtain more information.[33]

5. The Decision in *Caronia* and the FDA's Regulatory Response

Before *Caronia*, only limited First Amendment challenges to the FDA's policies with respect to the off-label promotion of approved drugs had reached the courts, and none had challenged the FDA's application of the misbranding provisions to truthful and non-misleading promotional statements.

Most notable of these First Amendment challenges was the 1998 decision in *Friedman*, *supra*. The plaintiff there, a public interest group, sought to enjoin as facially unconstitutional FDA policies (expressed in guidance documents) that had restricted manufacturers from distributing textbook excerpts and article reprints from medical and scientific journals to the extent they (1) addressed off-label uses of FDA-approved drugs and (2) were truthful and non-misleading. The district court rejected the FDA's argument that these communications proposed an illegal transaction and thus were unprotected. 13 F. Supp. 2d at 62–65; *see Wash. Legal Found. v. Henney*, 202 F.3d 331, 334 (D.C. Cir. 2000). It held that the communications were commercial speech and that the FDA's restrictions were unconstitutional under the test for commercial speech of *Central Hudson Gas and Electric Corp. v. Public Service Communication of New York*, 447 U.S. 557 (1980). Although recognizing that the FDA's policies advanced a substantial government interest in requiring manufacturers to submit supplemental applications

[33] *Id.* at 11.

for new drug uses, 13 F. Supp. 2d at 70–73, the court held the FDA's restrictions on such speech were more extensive than necessary, and thus breached the First Amendment, *id.* at 65–69, 72–74. It enjoined the FDA from prohibiting manufacturers from distributing the reprints and excerpts "regardless of whether such [materials] include[] a significant or exclusive focus" on off-label uses. *Id.* at 74–75. However, while the case was on appeal, the FDA adopted a much narrower construction of its guidance documents. This mooted the controversy and caused the injunction to be lifted.[34]

The Second Circuit's 2012 decision in *Caronia* addressed, for the first time, the interplay between the FDCA's misbranding provisions and the First Amendment. A drug manufacturer's sales representative, Caronia, was caught on tape touting to doctors the drug Xyrem, which the FDA had approved to treat narcoleptic patients, for unapproved uses. Caronia was charged and convicted of conspiracy to misbrand based on his truthful statements regarding those off-label

[34] Specifically, after the injunction had issued, the Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 ("FDAMA") took effect. FDAMA permits a manufacturer to disseminate "written information concerning the safety, effectiveness, or benefit of a use not described in the approved labeling of a drug or device," under certain conditions. *Wash. Legal Found. v. Henney*, 202 F.3d 331, 334 (D.C. Cir. 2000) (citing 21 U.S.C. § 360aaa(a)). The FDA took the position that the district court's application of *Central Hudson* in *Friedman* restricted only the FDA guidance documents at issue and did not bear on FDAMA. *Friedman*, 36 F. Supp. 2d at 18. The district court held, however, that its ruling and injunction applied more broadly than to the specific guidance documents at issue. *Id.* After supplemental briefing on the constitutionality of FDAMA's restrictions on manufacturer promotion of off-label uses, the district court held that those provisions, like the earlier guidance documents, facially violated the First Amendment. *Wash. Legal Found. v. Henney*, 56 F. Supp. 2d 81 (D.D.C. 1999). The FDA appealed the district court's rulings both as to FDAMA and the guidance documents. At argument before the D.C. Circuit, the FDA adopted a much narrower construction of FDAMA and the guidance documents than previously articulated; the new construction, the plaintiff agreed, eliminated its claim of a facial First Amendment violation. The D.C. Circuit accordingly dismissed the FDA's appeal and vacated the district court's decisions to the extent they had declared FDAMA and the FDA's guidance unconstitutional. *Henney*, 202 F.3d at 336–37.

uses. Vacating the conviction, the Second Circuit held that a manufacturer's speech promoting off-label use is constitutionally protected commercial speech, and that the First Amendment places limits on a misbranding prosecution to the extent it is based on the truthful promotion of FDA-approved drugs for off-label use. Applying the principle of constitutional avoidance, the Circuit held that the FDCA's misbranding provisions could not be construed "to criminalize the simple promotion of a drug's off-label use by pharmaceutical manufacturers and their representatives because such a construction—and a conviction obtained under [this] application of the FDCA—would run afoul of the First Amendment." 703 F.3d at 162. Thus, the Circuit held, "[t]he government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug." *Id.* at 169.

Later, the Court reviews *Caronia* in detail, *see infra*, pp. 43–53, because, unlike Amarin, and unlike much secondary commentary,[35] the FDA reads that decision narrowly, and as turning on the particular circumstances of Caronia's trial. The FDA thereby reads *Caronia* to preserve for the Government the ability to bring a misbranding action against a manufacturer or its representative where the conduct at issue consists solely of truthful and non-misleading speech promoting an off-label use of an approved drug. This reading of *Caronia* is reflected in the position the FDA has taken in this case.

[35] Commentators have widely viewed *Caronia* as consequential in the area of commercial speech and as imposing significant limits on prosecutions for misbranding. *See, e.g.*, Peter G. Neiman, Seth B. Orkand, & Peter K. Vigeland, *Revisiting 'Off-Label' Drug Promotion Resolutions in Light of* 'Caronia,' N.Y. L.J. (Feb. 28, 2013); Alison Frankel, *Why U.S. is forgoing appeal of landmark 2nd Circuit off-label ruling*, Reuters (Jan. 24, 2013); John Bentivoglio, *How* Caronia *Could Reshape Government Investigations*, Law360 (Jan. 2, 2013); David Frum, *Drug industry's free speech helps doctors*, CNN (Dec. 10, 2012); Katie Thomas, *Ruling is Victory for Drug Companies in Promoting Medicine for Other Uses*, N.Y. Times (Dec. 3, 2012).

In February 2014, the FDA responded to *Caronia* by issuing updated draft guidance as to the dissemination of scientific or medical journal articles. The FDA authorized manufacturers to distribute such articles relating to unapproved uses of drugs, under certain conditions.[36] When a manufacturer distributes journal articles that include information on off-label uses of its drug, the FDA stated, it will not use the fact of such distribution as evidence of the manufacturer's intent that the drug be used for an unapproved use, provided that the manufacturer makes certain disclosures with the articles. But, the FDA has stated, if a sales representative characterizes an article to suggest that a drug is safe or effective for an unapproved use, the agency may use such speech as evidence that the manufacturer intended to promote that use.[37]

Separately, in June 2014, the FDA agreed, in response to a citizen petition, to conduct a "comprehensive review [of its] regulatory regime governing communications about medical products," with the intent to issue, within a year, new guidance regarding such issues.[38] As of this decision, no such guidance has issued. During this litigation, the FDA told Amarin that "new guidance will be forthcoming,"[39] but at argument on July 7, 2015, the FDA declined to state what the status or timetable is with respect to such guidance. Tr. 73–74.

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[36] *See* U.S. Food and Drug Admin., *Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices* (2012), http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm387652.pdf.

[37] *Id.* at 3.

[38] Citizen Petition Response from Leslie Kux, J.D., Assistant Commissioner for Policy, FDA, to Alan R. Bennett, Ropes & Gray, et al., Docket Nos. FDA-2011-P-0512 and FDA-2013-P-1079, FDA (June 6, 2014) (reprinted at London Decl., Ex. Q).

[39] *See* Dkt. 24, Ex. A, at 5–6 ("Woodcock Letter").

B. History of the FDA's Review of Vascepa

1. Overview

Vascepa was developed by Amarin to improve cardiovascular health. It is composed of pure eicosapentaenoic acid ("EPA"), an omega-3 fatty acid.[40] Amarin has sought FDA approval for two separate uses of Vascepa.

First, on September 25, 2011, Amarin sought, and on July 26, 2012, received, FDA approval to market Vascepa for treating adult patients with triglyceride levels above 500 mg/dL of blood ("severe hypertriglyceridemia," or "very high triglycerides"). Persons with severe hypertriglyceridemia have increased risk of pancreatitis and cardiovascular disease. *See* Ketchum Decl., Ex. 1 ("FDA Approval Letter"), at 1 (approving new drug application for use of Vascepa "as an adjunct to diet to reduce triglyceride . . . levels in adult patients with severe . . . hypertriglyceridemia"); Ketchum Decl., Ex. 2 ("FDA-approved label for Vascepa"); *see also* Woodcock Letter, at 1–2. The FDA approved Vascepa based on a showing that Vascepa was effective in reducing very high triglyceride levels. FDA Approval Letter, at 1.

Second, Amarin has sought approval to market Vascepa for patients with triglyceride levels between 200 and 499 mg/dL of blood and who are already on statin therapy ("persistently high triglycerides"). This second use is the off-label use at issue in this case. It is undisputed that Vascepa is effective in reducing such triglyceride levels, as reflected in an FDA-approved study (the "ANCHOR study") of this point and as confirmed by the FDA in correspondence with Amarin. It is also undisputed that Vascepa is safe, insofar as it is safely used for persons with severe hypertriglyceridemia and, as discussed further below, the FDA has allowed a chemically similar dietary supplement to be sold to the public. The FDA, however, has denied Amarin's

[40] Woodcock Letter, at 1.

application for approval of this second use because recent scientific studies have left it unclear whether reducing the triglyceride levels of persons with persistently high triglycerides reduces cardiovascular risk.

2. Clinical Trials of Vascepa for Patients with Persistently High Triglycerides

The following recaps the relevant history of the FDA's review of Vascepa for the second use—for patients with persistently high triglyceride levels.

While completing the study that led to FDA approval of Vascepa for the treatment of patients with very high triglycerides (the "MARINE" study), Amarin sought to examine the effect of Vascepa in treating persistently high triglyceride levels. It did so pursuant to the FDA's "special protocol assessment," or "SPA," program. An SPA agreement is a written agreement that a manufacturer may enter into with the FDA, which sets out the design and size parameters for clinical trials of a new drug, and the conditions under which the FDA would approve the drug.[41] For the manufacturer, such an agreement minimizes development risk by providing regulatory predictability: Provided that the manufacturer follows the procedure set in the SPA agreement and the drug proves meets the benchmarks for effectiveness set in the agreement, the FDA must approve the drug. The FDA can rescind an SPA agreement only if "a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun."[42]

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[41] U.S. Food and Drug Admin., *Guidance for Industry: Special Protocol Assessment* (2002), at 2, http://www.fda.gov/downloads/Drugs/.../Guidances/ucm080571.pdf [hereinafter, "SPA Guidance"].

[42] *Id.* at 10.

Amarin's SPA agreement with the FDA regarding Vascepa for the second use was entered into on July 6, 2009. London Decl., Ex. B ("ANCHOR SPA Agreement"). The agreement set out the design of a clinical trial (the "ANCHOR study") to test whether Vascepa was effective at lowering triglycerides in patients with persistently high triglyceride levels. ANCHOR SPA Agreement, at 1. The ANCHOR study was also designed to test the numerical effect of Vascepa on other lipid, lipoprotein, and inflammatory parameters relevant to cardiovascular health, such as non-HDL cholesterol. *Id.* Amarin also agreed to undertake a separate clinical study, aimed at testing whether Vascepa was effective in helping prevent major cardiovascular events in high-risk patients, including those with persistently high triglyceride levels. This study was called "REDUCE-IT." The FDA required that Amarin enroll at least 50% of planned patients in the REDUCE-IT study before it would accept for review Amarin's application for approval of Vascepa for patients with persistently high triglycerides under the ANCHOR SPA Agreement.[43] This requirement was designed to ensure that the clinical study aimed at testing Vascepa's effect on cardiovascular risk reduction was well underway before the FDA decided whether to approve the use of Vascepa in treating such patients.

Consistent with this, on August 5, 2011, while the ANCHOR test was ongoing, Amarin entered into another SPA agreement with the FDA, this one keyed to the REDUCE-IT study. *See* London Decl., Ex. E ("REDUCE-IT SPA Agreement"). The REDUCE-IT study is ongoing. It is expected to be completed by the end of 2017, with results to be available in 2018. Ketchum Decl. ¶ 71.

[43] According to Amarin, this enrollment requirement cost the company more than $100 million, and caused a more-than-16-month delay in Amarin's submission of its supplemental new drug application. Compl. ¶ 66.

The ANCHOR study achieved each numeric objective that the SPA Agreement had set: The results showed that Vascepa produced a statistically significant decrease in triglyceride levels in persons with persistently high triglycerides, as well as in other lipid, lipoprotein, and inflammatory biomarkers. *Id.* ¶ 62; Christie M. Ballantyne et al., *Efficacy and Safety of Eicosapentaenoic Acid Ethyl Ester (AMR101) Therapy in Statin-Treated Patients with Persistent High Triglycerides (from the ANCHOR Study)*, 110 Am. J. of Cardiology 984, 985, 987 (2012) (reprinted in Ketchum Decl., Ex. 5).

On February 21, 2013, Amarin submitted a supplemental new drug application to the FDA, based on the ANCHOR trial results and the ANCHOR SPA Agreement.[44] London Decl., Ex. H, at 1 ("Feb. 21, 2013 Amarin SNDA Letter"). Because Amarin had met all requirements for approval set out in the ANCHOR SPA Agreement, Amarin anticipated that the FDA would approve Vascepa for the additional use that Amarin sought, *i.e.*, by patients with persistently high triglycerides. Ketchum Decl. ¶ 79.

However, on October 16, 2013, the FDA convened a public Advisory Committee regarding Vascepa to determine if reductions in triglyceride levels, as demonstrated in the ANCHOR study results, would reduce cardiovascular risk. Ketchum Decl., Ex. 109 ("10/16/13 Tr."); *see also* Ketchum Decl., Ex. 111 ("FDA SPA Rescind Agreement Letter"). The FDA noted that three different clinical trials (the ACCORD-Lipid, AIM-HIGH, and HPS2-THRIVE studies) involving other manufacturers' triglyceride-reducing drugs (which each used either

[44] Amarin and the FDA amended the ANCHOR SPA Agreement in May 2010. The substance of these amendments is not relevant here. References here to the ANCHOR SPA Agreement after May 2010 are to the agreement as amended.

fenofibrates or niacin)[45] had found that the reduction of triglyceride levels in patients with persistently high triglycerides had had no impact on the risk of cardiovascular events. *Id.* at 1. The FDA Advisory Committee concluded that although Amarin had satisfied the terms of the ANCHOR SPA Agreement and that Vascepa had reduced triglyceride levels in patients with persistently high triglycerides, there was "substantial uncertainty" whether reducing triglyceride levels would significantly reduce the risk for cardiovascular events in such patients. *Id.* at 2.

On October 29, 2013, the FDA rescinded the ANCHOR SPA Agreement, finding that a "substantial scientific issue" had arisen as to whether the reduction of triglyceride levels alone established an effective reduction in overall cardiovascular risk in patients with persistently high triglyceride levels. *Id.* Amarin appealed the decision through three successive levels of FDA review. *See* London Decl., Ex. G ("April 22, 2014 FDA Appeal Denied Letter"); London Decl., Ex. K ("Sept. 11, 2014 FDA Appeal Denied Letter").

3. The FDA's April 27, 2015 Complete Response Letter

On April 27, 2015, the FDA issued its Complete Response Letter ("CRL"), a central document here. *See* London Decl., Ex. M. The FDA there acknowledged that the ANCHOR study had been carried out consistent with its specifications. It also acknowledged that Vascepa had significantly reduced triglyceride levels in patients with persistently high such levels, and had met the statistical "endpoints," or goals, set in the ANCHOR study. The FDA noted that the "primary endpoint" of that study had been the percentage change in triglyceride levels during a 12-week period of usage by such statin-treated patients. It recognized that the patients in the

[45] Amarin claims that fenofibrates and niacin are "in different drug classes than Vascepa, work differently in the body, and showed less favorable safety profiles than Vascepa in their clinical trials." Ketchum Decl. ¶ 82.

study who had used Vascepa experienced a 21.5% "treatment difference" over those who had used a placebo (mineral oil), controlling for all other variables. *Id.* at 1.

However, the FDA refused to approve Amarin's proposed new use for Vascepa to lower triglyceride levels among such patients. It explained that the "clinical rationale," or premise, of the ANCHOR study had been that reducing triglyceride levels in that population would reduce the risk of cardiovascular events. But, the FDA stated, the results of the clinical trials involving other drugs that had also reduced triglyceride levels had yielded "insufficient data to support a drug-induced change in serum [triglycerides] as a surrogate for reducing [cardiovascular] risk in this population." *Id.* at 2. These trials "failed to demonstrate any additional benefit" of such drugs, and although some later analyses had suggested that patients with high triglycerides may benefit from using such drugs, "this remains to be confirmed." *Id.* The FDA added: "Given the current level of uncertainty regarding the benefits of drug-induced changes in lipid/lipoprotein parameters on [cardiovascular] risk among statin-treated patients with residually high [triglycerides], you will need to provide evidence that Vascepa reduces the risk of major adverse [cardiovascular] events in patients at high risk for cardiovascular disease . . . . We anticipate that the final results from the REDUCE-IT trial could be submitted to satisfy this deficiency." *Id.* at 2. Accordingly, the FDA stated, before it would approve Vascepa for use in patients with persistently high triglycerides, Amarin would need to supply evidence, such as from the ongoing REDUCE-IT study, that the drug reduces the risk of cardiovascular events. *Id.*

The FDA also refused to approve Amarin's request to include the ANCHOR results in the Vascepa label. It "reserve[d] comment until the application is otherwise adequate." *Id.*

In the penultimate sentence of the CRL, the FDA stated: "This product [Vascepa] may be considered to be misbranded under the [FDCA] if it is marketed with this change before approval of this supplemental application." *Id.* at 4.[46] The CRL did not elaborate on this point.

C. This Litigation

1. The Complaint

On May 7, 2015, 10 days after receiving the CRL, Amarin and the doctor plaintiffs filed the Complaint. Dkt. 1 ("Compl."). It brought an as-applied First Amendment challenge to FDA regulations that prohibit Amarin "from making completely truthful and non-misleading statements about its product to sophisticated healthcare professionals," including the doctor plaintiffs. Compl. ¶ 1.

Specifically, the Complaint alleged that Amarin wishes to make truthful statements to healthcare professionals (hereinafter, "doctors") regarding Vascepa, including that the ANCHOR study demonstrates that Vascepa significantly reduces triglyceride levels in patients with persistently high triglyceride levels. But, it alleged, Amarin is inhibited from doing so by the FDA's threat, articulated in the CRL, to bring a misbranding action based on such off-label promotion.

The Complaint alleged that doctors desire and may act on this information: "[D]octors across America" commonly prescribe drugs to treat "patients at risk for cardiovascular disease and who have persistently high triglyceride levels in their blood (*i.e.*, high despite statin therapy) to lower those patients' triglycerides and/or non-HDL cholesterol." *Id.* ¶ 2. Prescribing such

[46] The same day it issued the CRL, the FDA rescinded its approval for the drugs of the other manufacturers (*i.e.*, those containing fenofibrates and niacin) that it cited as having reduced triglyceride levels in patients with persistently high triglycerides. Ketchum Decl., Exs. 118–19, 122. The manufacturers of those drugs were, like Amarin, thus prohibited from promoting their drugs for that patient population. *Id.*

drugs "is a medically-accepted practice supported by numerous national and international cardiovascular treatment guidelines and position statements"; doctors do so "because, in their medical judgment, drug therapy is the best course of treatment for these patients." *Id.* (footnote citing treatment guidelines and position statements omitted). Moreover, doctors prescribe such drugs "even though there is not yet definitive clinical evidence affirmatively demonstrating that lowering triglyceride levels and/or non-HDL cholesterol levels in such patients ultimately reduces cardiovascular risk." *Id.* ¶ 6. Such doctors, the Complaint alleged, "need truthful and non-misleading information about these drugs to make informed decisions about what is best for their patients," but the "[FDA]'s current regime for regulating the flow of 'off-label' information to doctors about prescription drugs . . . severely restricts medical professionals' access to information from the source most knowledgeable about the drugs: the drug manufacturers—in this case, Amarin." *Id.* ¶ 3.

As to Vascepa specifically, the Complaint stated, the FDA does not dispute that an FDA-approved "double-blind, placebo-controlled trial"—the ANCHOR study—had "demonstrat[ed] that Vascepa reduces triglyceride levels and has other favorable effects in adult patients with persistently high triglycerides." *Id.* ¶ 7. But, it alleged, because the FDA had refused to approve Vascepa for use in treating this patient population, "Amarin now finds itself in a bind":

> Using pharmaceuticals like Vascepa in the treatment of patients with persistently high triglycerides is commonplace in medical practice.[47] However, because FDA has refused to approve Vascepa for patients with persistently high triglycerides, Amarin may not communicate truthful and non-misleading information about Vascepa to healthcare professionals such as the Doctor Plaintiffs without fear of criminal prosecution and civil liability. That is because FDA regulations forbid promotion of drugs for unapproved or "off-label" uses, even if such promotion is

[47] Amarin has stated that, in the year ending in March 2014, more than 50% of Vascepa prescriptions were for patients with persistently high triglycerides. Ketchum Decl., Ex. 25.

> entirely truthful and presented in a non-misleading manner. . . . FDA's treatment of Vascepa therefore operates to keep doctors, such as the Doctor Plaintiffs, and consequently their patients, in the dark about all of the options for drug therapy they are legally empowered to prescribe to treat persistently high triglyceride levels."

Id. ¶¶ 8–9.

Separately, the Complaint alleged, the FDA's restrictions on off-label promotion of Vascepa harm Amarin because the FDA had—until recently—"permitted manufacturers of other triglyceride-lowering drugs, such as fenofibrates, niacin, and another omega-3 fatty acid-based drug, to market their drugs for treatment of persistently high triglycerides." *Id.* ¶ 9. Amarin, however, is prohibited from communicating to doctors information about Vascepa, a "treatment alternative." *Id.* Further, the Complaint alleged, the FDA's ban on off-label promotion of Vascepa prevented it from making the same "qualified health claim" that the FDA, for more than a decade, has allowed manufacturers of dietary supplements containing a chemically identical omega-3 fatty acid to make to consumers: "Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary artery disease." *Id.* ¶ 11. This, the Complaint alleged, has led doctors "to advise their patients to take omega-3 dietary supplements instead of pharmaceuticals like Vascepa." *Id.* ¶ 116.

The Complaint therefore sought relief recognizing that the "FDA's prohibitions on 'off-label' promotion, as applied to truthful and non-misleading speech Amarin wishes to make," are unconstitutional under the First Amendment, and that Amarin may engage in truthful and non-misleading speech to doctors about Vascepa free from the risk of criminal prosecution even if such speech constitutes off-label promotion. *Id.* ¶ 14. Such a holding, the Complaint stated, "falls squarely within Second Circuit precedent." *Id.* (citing *Caronia*).

The Complaint sought protection for Amarin's speech both at a general and a statement-specific level. As to the former, Amarin sought relief confirming that, free from the threat of a

misbranding action, it may engage in truthful and non-misleading speech with doctors intended to promote Vascepa for off-label use, and that its right to engage in such speech includes the right to initiate discussions on that subject and to engage in a dialogue with doctors about it. *See, e.g.*, Compl. ¶¶ 17, 19. As to the latter, Amarin sought a ruling permitting it to make to doctors, free from the threat of such an action, specific "carefully-circumscribed, truthful, and scientifically-accurate statements," *id.* ¶ 15, each drawn from either the ANCHOR study, the CRL letter, or other FDA-approved language. The three specific statements for which Amarin sought such comfort were[48]:

- *Statement #1*: "Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease."

- *Statement #2*: "The ANCHOR study demonstrates that Vascepa lowers triglyceride levels in patients with high triglyceride levels not controlled by diet and statin therapy."

- *Statement #3*: "In the ANCHOR study, Vascepa 4g/day significantly reduced TG [triglycerides], non-HDL-C [non-high density lipoprotein cholesterol or non-"good cholesterol"], Apo B [Apolipoprotein B], VLDL-C [very-low-density lipoprotein cholesterol], TC [total cholesterol] and HDL-C [high density lipoprotein cholesterol or "good cholesterol"] levels from baseline relative to placebo in patients with high (≥200 mg/dL and <500 mg/dL) triglyceride levels not controlled by diet and statin therapy. The reduction in TG [triglycerides] observed with Vascepa was not associated with elevations in LDL-C [low-density lipoprotein cholesterol or "bad cholesterol"] relative to placebo."

Id. ¶ 124.

The Complaint also sought a ruling that Amarin, free of the threat of a misbranding action, may provide doctors with:

[48] The Court has numbered these statements to assist the reader in following the discussion that follows. The Court has similarly also done so for the disclosures that Amarin and the FDA have proposed be made along with Amarin's communications. *See infra*, at pp. 30, 32–33.

- 13 specifically identified peer-reviewed scientific publications relating to the potential effect of EPA on the reduction of the risk of coronary heart disease, *see id.*, Ex. A (listing these publications), and

- A written summary of the ANCHOR study, including a chart reporting efficacy data from that study, *see id.*, Ex. B (containing this summary).

Id. ¶ 124. The Court has appended Amarin's Exhibits A and B to this decision.

Finally, to assure that its statements were not misleading, Amarin proposed to contemporaneously make the following five disclosures to doctors:

- *Amarin Disclosure #1*: "FDA has not approved Vascepa to reduce the risk of coronary heart disease."

- *Amarin Disclosure #2*: "FDA has not approved Vascepa for the treatment of statin-treated patients with mixed dyslipidemia and high (≥ 200 mg/dL and < 500 mg/dL) triglyceride levels."

- *Amarin Disclosure #3*: "The effect of Vascepa on the risk of cardiovascular mortality and morbidity has not been determined."

- *Amarin Disclosure #4*: "A cardiovascular outcomes study of Vascepa designed to evaluate the efficacy of Vascepa in reducing cardiovascular mortality and morbidity in a high risk patient population on statin therapy is currently underway."; and

- *Amarin Disclosure #5*: "Vascepa may not be eligible for reimbursement under government healthcare programs, such as Medicare or Medicaid, to reduce the risk of coronary heart disease or for treatment of statin-treated patients with mixed dyslipidemia and high (≥ 200 mg/dL and < 500 mg/dL) triglyceride levels. We encourage you to check that for yourself."

Id. Without such relief, the Complaint alleged, Amarin and its employees have a "real" fear of criminal prosecution if they engage in truthful off-label promotion of Vascepa, including because the Government has announced its intent "'to pursue aggressively' alleged incidents of 'off-label' promotion." *Id.* ¶¶ 164–66 (reviewing prosecutions, enforcement actions, and FDA statements regarding off-label promotion).

2. Amarin's Motion for Preliminary Relief

On May 22, 2015, Amarin moved for preliminary relief, tracking that sought in the Complaint. It sought an injunction that would prohibit the FDA from bringing a misbranding action against Amarin for its truthful and non-misleading statements to doctors regarding Vascepa, including the statements set out in the Complaint. *See* Dkt. 5 (motion); Dkt. 13 (supporting brief) ("Amarin Br."). Amarin later confirmed that, as an alternative to an injunction blocking enforcement action, effective relief could take the form of a declaration to the effect that the communications it intended were protected against a misbranding action. Tr. 14–15.

Amarin moved primarily under the First Amendment, but alternatively, under the due process clause, on the ground that the FDA's regulations as to misbranding were vague and did not "fairly notify Amarin of what off-label promotion is permitted and what is forbidden." Amarin Br. 3–4. Amarin separately sought protection from civil claims under the FCA, on the premise that the Government might seek to hold Amarin liable if doctors submitted false claims securing reimbursement in connection with Vascepa prescriptions.

3. The FDA's Response—the Woodcock Letter

Before filing the Complaint, Amarin had not previewed to the FDA the communications about Vascepa that it sought to make. In a June 5, 2015 letter by Dr. Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, the FDA set out its position. *See* Dkt. 24, Ex. A ("Woodcock Letter"). The Woodcock Letter narrowed the parties' dispute as to some of Amarin's proposed communications, including by noting that some "fall within the scope" of existing FDA guidance allowing manufacturers to disseminate to doctors "truthful and non-misleading scientific or medical publications on unapproved new uses." *Id.* at 5. The Woodcock Letter further attempted to moot the dispute altogether by proposing defined conditions under

which Amarin could communicate certain of the information in question to doctors, and under which the FDA would then agree not to bring a misbranding action. *Id.* at 1. The Woodcock Letter added that the FDA was "engaged in a comprehensive review of its regulations and guidance documents regarding manufacturers' dissemination of information regarding their medical products, and new guidance will be forthcoming." *Id.* at 5–6.

The Woodcock Letter set out the conditions on which the FDA would acquiesce to certain statements Amarin proposed to make. *See id.* at 6 (if Amarin made its statements "in the manner and to the extent described," FDA would not "object to Amarin's proposed communications."). The letter clustered these statements as follows:

a. *Distribution of results of the ANCHOR study*: As to Amarin's desire to give doctors the ANCHOR study's results, the FDA stated, it would not object to Amarin's giving truthful and non-misleading summaries. The FDA stated that it "would not necessarily have agreed to include [the summary Amarin attached to its Complaint as Exhibit B] in its entirety in FDA-approved labeling if the indication had been approved." *Id.* But, the FDA stated, it would not consider that summary false or misleading, or as evidence of intended off-label promotion, "as long as the distribution of Exhibit B is accompanied with" five specified disclosures "and is disseminated in the manner summarized below." *Id.*

Two of the five disclosures upon which the FDA insisted were Amarin's Disclosures #1 and #3. The other three the FDA sought were:

- *FDA Disclosure #1*: "Any potential financial or affiliation biases between the firm and those who conducted the ANCHOR study."

- *FDA Disclosure #2*: "Vascepa is not approved for the treatment of statin-treated patients with mixed dyslipidemia and high (> 200 mg/dL and < 500 mg/dL) triglyceride levels. FDA declined to approve this indication because the available evidence does not establish that reducing triglycerides

with a drug reduces the risk of cardiovascular events among patients already treated with statins."; and

- *FDA Disclosure #3*: "Recent cardiovascular outcome trials (ACCORD-Lipid, AIM-HIGH, and HPS2-THRIVE) each failed to demonstrate incremental cardiovascular benefit of adding a second lipid-altering drug (fenofibrate or formulations of niacin), despite reducing triglyceride levels, among statin-treated patients with well-controlled low-density lipoprotein-cholesterol."

Id. at 7. FDA Disclosure #2 thus expanded upon Amarin Disclosure #3; FDA Disclosures #1 and #3 were new.[49] The FDA also asked that, "[t]o further protect against misleading the audience," Amarin provide copies of the current FDA-approved labeling and, when distributing a summary of the ANCHOR study, a reprint of a particular journal article. *Id.* And it asked that Amarin distribute "such information in educational or scientific settings, *and not including such information with or attached to promotional or marketing materials*," and "by persons with the appropriate background or training to accurately communicate this scientific information." *Id.* (emphasis added).

Finally, to the extent Amarin chose to provide a summary different from its Exhibit B, the FDA stated that would not find it false or misleading on the conditions that:

> the summary remains factual, does not omit material information, and does not otherwise introduce bias. In particular, the communication could be misleading if it implied or suggested that the ANCHOR study supports the conclusion that lowering triglyceride levels lowers the risk of [cardiovascular disease] in patients already treated with statins or that available evidence establishes that there is a clinical benefit in lowering [triglyceride] levels for patients with high [triglyceride] levels. We also believe that to avoid being misleading any summary would show not only the differences between Vascepa and the mineral oil placebo, but also the changes from baseline to endpoint in each of the treatment groups, as you have done in Exhibit B.

[49] As to Amarin's Disclosures #4 and #5, the FDA stated that it would not object to them, provided they remained truthful and non-misleading. Woodcock Letter, at 7 n.15.

Id. at 6–7.

b. *Distribution of additional reprints*: Amarin, the FDA noted, sought to distribute 13 scientific publications regarding "the potential effect of EPA on the reduction of the risk of coronary heart disease." *Id.* at 8 (citing Compl., Ex. A). The FDA stated that such publications were covered by its existing guidance, and that it would not object to their distribution as long as they were accompanied with the same disclosures and were disseminated in the same manner as the ANCHOR study summary. *Id.*

c. *Coronary heart disease claim*: In its Statement #1, Amarin sought to make, to doctors, the same claim regarding coronary heart disease that the FDA has permitted food and dietary supplement manufacturers to make directly to consumers on the labels of chemically similar omega-3 fatty acids. Woodcock Letter, at 8. The FDA, however, objected to Amarin's making that statement in connection with Vascepa. Doing so "would be potentially harmful to the public health, and [the] FDA would consider such conduct to be *potentially misleading* or potential evidence of intended use." *Id.* at 10 (emphasis added). The coronary heart disease claim, the FDA stated, could cause a physician to prescribe Vascepa in lieu of promoting healthy dietary and lifestyle changes or prescribing statin therapy. *Id.* However, the FDA stated, if Amarin repackaged Vascepa as a dietary supplement, the FDA would not object to including the coronary heart disease claim, on certain conditions. *Id.* The FDA distinguished the context of dietary supplements because a lesser showing is required for health claims on supplement labeling products than on drug labeling. *Id.* at 9. The higher standard for drug labeling, the FDA stated, furthers the public interest, by:

> (1) creating incentives to develop robust scientific data regarding the safety and efficacy of a drug for a particular use; (2) requiring review of those data before the marketing of the product for that use to prevent harm to patients, and to ensure that healthcare providers have a sound basis for making treatment decisions before the

> use is widespread; (3) providing for the review of safety and efficacy data by an independent body to ensure that claims are appropriate supported; (4) requiring the development of labeling that provides information necessary for the safe and effective use of the product; and (5) preventing firms from misleadingly marketing their products.

Id. at 9–10.

4. The FDA's Opposition to Preliminary Relief

On June 23, 2015, the FDA filed its brief opposing preliminary relief. Dkt. 51 ("FDA Br."). It first argued that, if that Amarin accepted the conditions that the FDA had set out in the Woodcock Letter, the controversy would be moot. So long as Amarin took "the reasonable steps outlined in the Letter" regarding the substance and manner of distribution of the ANCHOR summary study and associated reprints, the FDA stated, these would not be bases for an enforcement action. *Id.* at 15. And if Amarin also agreed not to make the coronary heart disease claim, the FDA stated, there would no longer be a "credible threat of prosecution." *Id.* at 16–17.

If Amarin did not modify the statements it proposed to make to doctors, however, the FDA opposed granting preliminary relief. Amarin's plan to make proactive statements to doctors regarding an off-label use of Vascepa, the FDA stated, was, a "frontal assault . . . on the framework for new drug approval that Congress created in 1962." *Id.* at 1. Amarin was seeking "to distribute its drug Vascepa under circumstances which could establish that Amarin intends an unapproved new use for Vascepa, *i.e.*, a use for which FDA has not determined the drug is safe and effective." *Id.* And, the FDA argued, were it to bring a misbranding claim against Amarin based on its promotional statements, this would not "prohibit speech." *Id.* at 2. *Caronia*, the FDA explained, did not block the FDA from using speech as evidence of a manufacturer's intent in a prosecution for misbranding. *Id.* at 3.

5. Amarin's Reply

On June 30, 2015, Amarin replied. Dkt. 67 ("Amarin Reply Br."). Amarin declined the FDA's proposal to moot the controversy. Although it agreed to some disclosures urged by the FDA, Amarin declined to adopt others, or to accept the FDA's limits on the manner by which Amarin distributed summaries and reprints and communicated with doctors. *See* Ketchum Reply Decl. ¶¶ 12–13. Amarin asserted the right to "engage in a full and truthful dialogue with healthcare professionals" aimed at promoting the off-label use of Vascepa. Amarin Reply Br. at 2 (citing Compl. ¶ 93). The FDA's threat to bring a misbranding prosecution based on its truthful and non-misleading statements to doctors, Amarin stated, was an attempt to "refight old, lost battles." *Id.* at 3.

As to specific statements regarding Vascepa, Amarin accepted FDA Disclosure #1, but resisted FDA Disclosures #2 and #3 because these "convey a one-sided and misleading view of the evidence." Ketchum Reply Decl. ¶ 13. If the Court determined that additional disclosures along these lines were necessary, Amarin argued, their text should be modified as follows (the underlined text denotes Amarin's proposed additions):

- *FDA Disclosure #2*: Numerous national and international treatment guidelines and position statements recommend drug therapy as an adjunct to healthy dietary and lifestyle changes and statin therapy for patients at risk for cardiovascular disease and who have persistently high triglyceride levels in their blood (i.e., high despite statin therapy) to lower those patients' triglycerides and/or non-HDL cholesterol. Vascepa is not FDA-approved for the treatment of statin-treated patients with mixed dyslipidemia and high ($\geq$ 200 mg/dL and $<$ 500 mg/dL) triglyceride levels due to current uncertainty regarding the benefit of drug-induced changes in lipid/lipoprotein parameters beyond statin-lowered low-density lipoprotein cholesterol on cardiovascular risk among statin-treated patients with residually high triglycerides. No prospective study has been conducted to test and support what, if any, benefit exists.

- *FDA Disclosure #3*: Recent cardiovascular outcomes trials (ACCORD-Lipid, AIM-HIGH, and HPS2-THRIVE), while not designed to test the

> effect of lowering triglyceride levels in patients with high triglyceride levels after statin therapy, each failed to demonstrate incremental cardiovascular benefit of adding a second lipid-altering drug (fenofibrate or formulations of niacin), despite raising high-density lipoprotein cholesterol and reducing triglyceride levels, among statin-treated patients with well-controlled low-density lipoproteincholesterol.

Id. ¶¶ 22, 25.

Finally, as to the coronary heart disease claim drawn from the dietary supplement labeling, Amarin argued that it should be permitted to use the same text. It argued that, if any change were held necessary to make the claim non-misleading, it consist of adding a sentence (underlined below):

> "Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease. Vascepa should not be taken in place of a healthy diet and lifestyle or statin therapy."

Id. ¶ 31.

6. Argument

On July 7, 2015, the Court heard lengthy argument on Amarin's application for preliminary relief. *See* Dkt. 70 ("Tr."). The argument highlighted the parties' disagreement as to the FDA's latitude, after *Caronia*, to bring misbranding actions based on truthful statements promoting the off-label use of FDA-approved drugs. Argument also focused on the specific statements Amarin has proposed to make to doctors about Vascepa. The Court draws upon these arguments as relevant in the ensuing discussion.

II. Discussion

A. Overview

Amarin argues that the FDA's threat to bring misbranding charges against it if it makes truthful statements promoting the off-label use of Vascepa is chilling it from engaging in, and preventing doctors from receiving, constitutionally protected speech. Amarin argues that under

Caronia, a misbranding action cannot be brought against a manufacturer for conduct that consists solely of truthful and non-misleading speech. Amarin argues that either a preliminary injunction against enforcement action, or declaratory relief recognizing its First Amendment rights, is necessary to eliminate that chill.

In considering Amarin's application, the Court is guided by familiar standards. Amarin must establish that (1) it is likely to succeed on the merits, (2) it is likely to suffer irreparable harm absent preliminary relief, (3) the balance of equities tips in its favor, and (4) preliminary relief is in the public interest. *Winter v. Nat. Res. Def. Council, Inc.*, 555 U.S. 7, 20 (2008). And, because Amarin seeks to alter the status quo, it must show a substantial likelihood of success on the merits. *See N.Y. Progress & Prot. PAC v. Walsh*, 733 F.3d 483, 486 (2d Cir. 2013) (citation omitted).

The parties' dispute centers on the first factor—the likelihood of success on the merits. The merits issue here—whether a misbranding action can be brought against Amarin for the speech it proposes, or whether the FDA's threat of such an action burdens protected speech—raises general and specific questions. At a general level, the parties disagree whether, under *Caronia*, a misbranding action can be brought against a manufacturer whose conduct consists solely of truthful and non-misleading speech to promote off-label use of an approved drug, and whether *Caronia* protects a manufacturer's proactive promotional speech. At a specific level, although the parties have narrowed their differences, they disagree about whether certain statements Amarin proposes to make are, in fact, truthful and non-misleading so as to be constitutionally protected.

The Court addresses the likelihood of success on the merits after first considering, and rejecting, the FDA's threshold argument that this case does not present a case or controversy. After considering the merits, the Court addresses the remaining preliminary relief factors.

B. Case or Controversy

At the threshold, a court "must be sure that there is a justiciable case or controversy under Article III." *Holder v. Humanitarian Law Project*, 561 U.S. 1, 15 (2010). The plaintiff must show that "the 'conflicting contentions of the parties . . . present a real, substantial controversy between parties having adverse legal interests, a dispute definite and concrete, not hypothetical or abstract.'" *Babbitt v. United Farm Workers Nat'l Union*, 442 U.S. 289, 298 (1979) (citation omitted). "One aspect of this limitation is the requirement that the plaintiff have standing to sue," *Hedges v. Obama*, 724 F.3d 170, 188 (2d Cir. 2013), which requires a claim that:

> "1) the plaintiff '[has] suffered an injury in fact—an invasion of a legally protected interest which is (a) concrete and particularized and (b) actual or imminent, not conjectural or hypothetical,' (2) the injury be 'fairly traceable to the challenged action of the defendant,' and (3) it 'be likely, as opposed to merely speculative, that the injury will be redressed by a favorable decision.'"

Id. (quoting *Rothstein v. UBS AG*, 708 F.3d 82, 91 (2d Cir. 2013)).

In the context of a pre-enforcement challenge on constitutional grounds, a plaintiff "must demonstrate a genuine threat that the alleged unconstitutional law is about to be enforced against him." *Brache v. Westchester Cty.*, 658 F.2d 47, 51 (2d Cir. 1981); *see also Babbitt*, 442 U.S. at 298 (challenge proper when "plaintiff has alleged an intention to engage in a course of conduct arguably affected with a constitutional interest, but proscribed by a statute, and there exists a credible threat of prosecution thereunder"). In First Amendment cases, such challenges are assessed "under somewhat relaxed standing and ripeness rules." *Nat'l Org. for Marriage, Inc. v. Walsh*, 714 F.3d 682, 689 (2d Cir. 2013). A plaintiff must still allege "something more than an

abstract, subjective fear that his rights are chilled," but "a real and imminent fear of such chilling is enough." *Id.* Standing thus has been found where no enforcement threat had been directed to the plaintiff, and the only bases to perceive a "credible threat" of enforcement action were the statute's terms and enforcement history. *See, e.g.*, *Virginia v. Am. Booksellers Ass'n*, 484 U.S. 383, 386–393 (1988) (booksellers had standing to challenge new state statute despite lack of specific threat of prosecution); *Holder*, 561 U.S. at 9–16 (plaintiffs had standing to challenge Antiterrorism and Effective Death Penalty Act based on prior prosecutions under act); *see also Susan B. Anthony List v. Driehaus*, 134 S. Ct. 2334, 2342–43 (2014) (collecting cases).

Amarin clearly has standing to challenge the FDA's threat to bring a misbranding action against it if it promotes Vascepa for an off-label use. "[S]tanding is to be determined as of the commencement of suit." *Fenstermaker v. Obama*, 354 F. App'x 452, 455 n.1 (2d Cir. 2009) (summary order) (quoting *Lujan v. Defenders of Wildlife*, 504 U.S. 555, 571 n.5 (1992)); *see also Comer*, 37 F.3d at 791. Here, 10 days before Amarin filed suit, the FDA had expressly threatened in the CRL to bring a misbranding action against it for promoting Vascepa off-label, *i.e.*, if Amarin marketed Vascepa for persons with persistently high triglycerides without approval of that use. CRL, at 4. Particularly given the recent history of misbranding prosecutions against manufacturers based on the same legal theory, this threat gave Amarin a solid and real basis to fear such enforcement action. *See Walsh*, 714 F.3d at 689; *see also* Compl. ¶¶ 145–154 (alleging that FDA's threat to bring misbranding charges will, absent relief, chill Amarin from engaging in protected speech with doctors about off-label use of Vascepa); *id.* ¶¶ 163–64 (recounting history of prosecutions of off-label promotion, and FDA's public statement of intent to continue "to pursue aggressively" off-label promotion).

The FDA argues that the Woodcock Letter largely mooted this controversy, in that the FDA stated there that it did not object to Amarin's dissemination of certain information and would not base an enforcement action on such dissemination. FDA Br. 15–16. But although the Woodcock Letter removed some of Amarin's proposed communications to doctors as potential subjects of enforcement action, it left others in play.

Specifically, the FDA preserved the threat to bring misbranding charges against Amarin for its truthful speech regarding Vascepa in three sets of circumstances. The first is if Amarin distributed summaries and reprints of the ANCHOR study in a manner or format other than that specified by the FDA. Amarin, however, resists these limitations.[50] The second is if Amarin articulated, in connection with Vascepa, the coronary heart disease claim approved for use on chemically similar dietary supplements. Amarin, however, asserts the right to make this statement.[51] Third, and most sweeping, the FDA reserved the right to bring a misbranding action against Amarin if it made proactive truthful statements, or engaged in a dialogue, with doctors regarding the off-label use of Vascepa, because such communications bespeak an intent to

[50] The FDA states that it would not object to providing "truthful and non-misleading summaries of the results of the ANCHOR trial" and reprints if Amarin accompanied these materials with the disclosures the FDA asks be made. *See* Woodcock Letter, at 6 (FDA will not treat distribution as evidence of intended use "[*a*]*s long as* the distribution . . . is accompanied with the disclosures") (emphasis added). Amarin, however, stands on its claim of a right to promote Vascepa for off-label use without including all of the FDA's disclosures. *See* Ketchum Reply Decl. ¶¶ 12–13; Tr. 19–20. The FDA also states that it would refrain from enforcement action if such materials were distributed in "educational or scientific settings," unaccompanied by "promotional or marketing material," and made by "persons with the appropriate background or training to accurately communicate this scientific information." Woodcock Letter, at 7. Amarin has declined to accept these conditions, too. *See, e.g.*, Amarin Reply Br. 5; Compl. ¶¶ 17, 167.

[51] The FDA states that it "would potentially consider [Amarin's] inclusion of the [coronary heart disease] claim . . . in connection with [Amarin's] distribution of Vascepa as misleading," unless Amarin repackages re-labels Vascepa as a dietary supplement. Woodcock Letter, at 10. Amarin has declined to do so. *See, e.g.*, Amarin Reply Br. 10–12.

promote off-label use. Amarin, however, asserts the First Amendment right under *Caronia* to engage in such truthful speech and for the purpose of promoting such use.[52]

In sum, because Amarin did not accept the conditions set in the Woodcock Letter, that letter did not vitiate the CRL's threat of a misbranding action against Amarin or moot this controversy. *See Doe v. U.S. Civil Serv. Comm'n*, 483 F. Supp. 539, 555 (S.D.N.Y. 1980) (rejecting defendants' claim of mootness "because their proposed settlement offer does not remove all 'live issues' present in the case"); *Doe v. Harris*, 696 F.2d 109, 114 (D.C. Cir. 1982) (similar). Fairly read, the Woodcock Letter sharpened for Amarin the circumstances under which the FDA reserved the right to bring a misbranding action. It thereby narrowed the range of communications with respect to which Amarin is exposed to the risk of such an action. But it did not eliminate that risk, by any means. Because Amarin faces a non-extinguished threat of a misbranding prosecution for speech it proposes to undertake as to Vascepa, there remains a live case or controversy.[53]

[52] The FDA states that it will not object to Amarin's truthful statements regarding Vascepa communications *if made in the manner and to the extent specified* [in the Letter]," Woodcock Letter, at 6 (emphasis added). And at argument, the FDA confirmed that it reserves its right to bring enforcement action based solely on truthful and non-misleading speech where the context indicates an intent to promote an unapproved use. *See, e.g.*, Tr. 50–51, 83. These statements do not afford Amarin protection for truthful "proactive" statements or the truthful "dialogue" it seeks to undertake with doctors related to the off-label use of Vascepa. *See* Compl. ¶ 126; Tr. 18.

[53] To the extent Amarin separately seeks preliminary relief in connection with potential claims under the False Claims Act, however, the Court does not find a ripe controversy. The CRL did not mention the FCA. And in the Complaint, neither Amarin nor the doctor plaintiffs express an intention to be party to any practice that has been the subject of prior FCA actions. It is, at this time, wholly conjectural that (1) a doctor who prescribed Vascepa for an off-label use would falsely claim, in seeking medical reimbursement, to have done so for an approved use, or (2) the FDA would seek to hold Amarin accountable for such conduct by a doctor.

C. Amarin's Motion for Preliminary Relief

1. Likelihood of Success on the Merits

Amarin makes two arguments—one broad, one narrow—why the FDA's threat to bring a misbranding action against it for truthful statements promoting the off-label use of Vascepa impermissibly burdens its First Amendment rights, such that its lawsuit seeking relief from this threat is substantially likely to prevail on the merits.

First, Amarin contends, the FDA is wrong to assert the authority to bring a misbranding action against a manufacturer based solely on truthful and non-misleading statements promoting an off-label use. In fact, Amarin argues, under *Caronia*, a misbranding action based on such statements simply cannot be brought. It follows, Amarin argues, that the FDA may not threaten to bring such an action against a manufacturer whose truthful promotional statements are made in a format other than that preferred by the agency.

Second, more narrowly, Amarin contends, the specific statements it proposes to make about Vascepa are truthful and non-misleading, so as to be protected under *Caronia*. These statements, Amarin notes, all derive from the FDA-approved ANCHOR study or writings by (or approved by) the FDA. Amarin argues that the FDA is wrongly disputing that these statements are truthful and non-misleading.

The Court addresses these issues in turn.

a. The scope of First Amendment protection for a manufacturer's truthful and non-misleading promotional statements under *Caronia*

In the CRL, the FDA first raised the prospect of a misbranding action against Amarin. But the CRL was unspecific as to the conduct on which the FDA might base such an action. The FDA stated only that that it might consider Vascepa misbranded if "it is marketed" for use by persons with persistently high triglycerides before the FDA had approved such use. From this,

Amarin inferred that the FDA was threatening to bring a misbranding action based solely on truthful and non-misleading speech in which Amarin might engage that promoted this off-label use, *e.g.*, statements reporting the results of the ANCHOR study.

In opposing preliminary relief, the FDA has now confirmed that Amarin's inference was correct. The FDA's brief, and its responses to the Court's questions at argument, clarify that the FDA is reserving the right to bring a misbranding action against Amarin where the only conduct on which that action would be based are truthful and non-misleading statements promoting this off-label use. In particular, the FDA took the position that, in such an action, it could establish the intent (*mens rea*) and act (*actus reus*) elements of misbranding as follows:

(1) *Intent requirement*: The FDA may use Amarin's statements regarding Vascepa's effect on persistently high triglycerides as objective evidence of Amarin's intent to promote Vascepa for that off-label purpose, *see* FDA Br. 13–14 & n.5, 18, 20–22, 26 n.15, 29; Tr. 50–52, 55–56, 58–59, 65; and

(2) *Act requirement*: The FDA may bring a misbranding action where Amarin's only acts constituting promotion of Vascepa for an off-label use are its truthful and non-misleading statements about that use, provided that these acts support an inference that Amarin intended to promote that off-label use, *see* FDA Br. 13–14; Tr. 51–54, 57, 61–65, 80, 83.[54]

It is the FDA's position on the act requirement that raises First Amendment issues under *Caronia*. At argument, the Court questioned the FDA whether its position as to that requirement is consistent with *Caronia*; the Court stated that it, like Amarin, had read *Caronia* otherwise. The FDA responded that it views *Caronia* as a fact-bound decision that turned on the particular jury instructions and government jury addresses given in Caronia's trial. The FDA stated that it does not read *Caronia* to preclude a misbranding action where the acts to promote off-label use

[54] The FDA's brief separately notes that it may bring a misbranding action based on *misleading* speech regarding an unapproved use of an approved drug. *See, e.g.*, FDA Br. 3, 8, 14, 18 & n.11, 23–24, 32. The FDA's authority to do so, however, is not disputed—or at issue here.

consist solely of truthful and non-misleading speech, provided that the evidence also shows that the drug had been introduced into interstate commerce and that the FDA had not approved it as safe and effective for the off-label use. Tr. 51–54.

The following exchange was indicative:

> THE COURT: [W]e clearly have a very substantial difference of opinion how to read *Caronia*. The government's position is that it can [] found a misbrand[ing] case solely based on the transmission of truthful nonmisleading statements. Although given the [FDA's] regulatory guidance, those statements really need to be initiated by the manufacturer, not made in response to questions from the doctor. Is that correct?
>
> FDA COUNSEL: That's essentially correct, your Honor. And *Caronia* was, again, very careful to make that point in emphasizing repeatedly that it was the government's theory of the prosecution of the case that represented the First Amendment problem and assume[d] without deciding that speech can be used as evidence[.]

Tr. 54–55. Reinforcing the point, the FDA at argument likened misbranding actions based on the promotion of off-label use to other areas of law in which criminal liability can, consistent with the First Amendment, be based on speech alone. Tr. 57. Other crimes where "the speech is the act," the FDA stated, include jury tampering, insider trading, and blackmail. *Id.*; *see also* Tr. 83 ("There are cases in which it's just speech as is often the case when speech is an element of the crime").

In light of the parties' conflicting readings of *Caronia* and the FDA's position that it may bring a misbranding action against a manufacturer based solely on truthful and non-misleading speech evincing the intent to promote an off-label use, the Court has closely reviewed *Caronia*. The Court's considered and firm view is that, under *Caronia*, the FDA may *not* bring such an action based on truthful promotional speech alone, consistent with the First Amendment. A fair reading of that decision refutes the FDA's view that the Second Circuit's ruling was limited to the facts of Caronia's particular case. To be sure, the Circuit closely reviewed the record of

Caronia's trial—in particular, the jury instructions and the government's closing argument. But the Circuit did so to isolate the acts upon which Caronia's conviction had rested—specifically to determine whether Caronia's speech had "served merely as 'evidence of intent'" or whether Caronia had been "prosecuted for his speech." 703 F.3d at 160. The Circuit found the latter, holding that the record revealed that "the government did prosecute Caronia for his speech." *Id.* at 162. As the Circuit put the point: "[T]he proscribed conduct for which Caronia was prosecuted was precisely his speech in aid of pharmaceutical marketing." *Id.*[55] This finding, in turn, led the Circuit to analyze, more broadly, the constitutionality of a misbranding prosecution based solely on truthful promotional speech.

The issue, the Second Circuit stated, was whether, consistent with the First Amendment, a misbranding prosecution can be based on such speech—"the simple promotion of a drug's off-label use." *Id.* at 162. The Circuit held that it cannot. And, noting that the FDCA's misbranding provisions do not expressly prohibit off-label usage, the Circuit, rather than facially invalidating these provisions as Caronia had requested, invoked "the principle of constitutional avoidance" and construed these provisions not to reach such speech. *Id*. at 160.[56] The Circuit's holding to this effect was explicit: "To the extent there is any ambiguity as to whether off-label promotion is tantamount to illegal misbranding, we construe the FDCA narrowly to avoid a seriously constitutional question." *Id.* at 162. It therefore vacated Caronia's conviction.

[55] The truthfulness of Caronia's promotional statements was undisputed at his trial. *See id.* at 165 n.10

[56] Caronia had sought facial invalidation of the misbranding provisions. *See* Brief for Appellant in *Caronia*, Nos. 09-5006-cr, 10-750-cr, 2010 WL 6351495 (2d Cir. Apr. 15, 2010). In vacating his conviction, the Second Circuit noted that its ruling, based on construing those provisions to not reach his conduct, was "for narrower reasons than he urges." *Caronia*, 703 F.3d at 160.

The Second Circuit's thoroughgoing First Amendment analysis in *Caronia*, which led it to construe the FDCA's misbranding provisions so as not to reach truthful speech promoting off-label use, further defeats the FDA's attempt to marginalize the holding in that case as fact-bound. The Circuit cast the issue as whether a misbranding prosecution that "identified [a defendant's] speech alone as the proscribed conduct" is constitutionally permissible. *Id.* And the Circuit's ensuing analysis underscored the categorical, rather than case-specific, nature of its holding that it is not.

The Second Circuit first noted that "'[s]peech in aid of pharmaceutical marketing . . . is a form of expression protected by the . . . First Amendment,'" *id.* at 163 (quoting *Sorrell v. IMS Health, Inc.*, 131 S. Ct. 2653, 2659 (2011)). It then applied to such speech truthfully promoting off-label drug use the four-prong test of *Central Hudson*, used to determine a restriction upon commercial speech violates the First Amendment. 703 F.3d at 164–69.

As to the first *Central Hudson* prong, the Second Circuit stated, promoting off-label drug use concerns "lawful activity" (off-label drug use) and "the promotion of off-label drug use is not in and of itself false or misleading." *Id.* at 165–66. As to the second prong, the Circuit stated, the Government's asserted interests—"preserving the effectiveness and integrity of the FDCA's drug approval process" and "reducing patient exposure to unsafe and ineffective drugs"—are substantial. *Id.* at 166. As to the third prong, which requires that a regulation directly and to a material degree advance the interest asserted, *id.* at 164, the Circuit found it not met. Construing the FDCA to prohibit truthful off-label promotion, the Circuit held, does not directly advance the asserted government interests—because off-label use of approved drugs is lawful, because the FDA's drug approval process itself contemplates such off-label use, and because "prohibiting the truthful promotion of off-label drug usage by a particular class of speakers" would not directly

enhance "the FDA's approval process [or] reduc[e] patient exposure to unsafe and ineffective drugs." *Id.* at 166. On the contrary, penalizing truthful statements promoting an off-label use "'paternalistically' interferes with the ability of physicians and patients to receive potentially relevant treatment information." *Id.* (quoting *Va. Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc.*, 425 U.S. 748, 770 (1976)). Finally, as to the fourth *Central Hudson* prong, which requires that a regulation to be narrowly drawn to further the governmental interests served, the Circuit held that construing the FDCA to ban categorically "off-label promotion by pharmaceutical manufacturers is more extensive than necessary" to achieve the Government's interests. *Id.* at 167. Rather, "[n]umerous, less speech-restrictive alternatives are available, as are non-criminal penalties." *Id.* Accordingly, the Circuit held, "[t]he government has not established a 'reasonable fit' among its interests in drug safety and public health, the lawfulness of off-label use, and its construction of the FDCA to prohibit off-label promotion." *Id.* at 168.

This Court therefore rejects the FDA's reading of *Caronia* as a mere artifact of that case's particular facts and circumstances. By its explicit terms and its clearly-articulated reasoning, *Caronia* simply cannot be read as the proverbial "ticket good for one day only." *See Smith v. Allwright*, 321 U.S. 649, 669 (1944) (Roberts, J., dissenting). On the contrary, the Second Circuit, at the close of its *Caronia* analysis, presented its holding as a definitive one of statutory construction:

> *[W]e decline to adopt the government's construction of the FDCA's misbranding provisions to prohibit manufacturer promotion alone as it would unconstitutionally restrict free speech. We construe the misbranding provisions of the FDCA as not prohibiting and criminalizing the truthful off-label promotion of FDA-approved prescription drugs*. Our conclusion is limited to FDA-approved drugs for which off-label use is not prohibited, and we do not hold, of course, that the FDA cannot regulate the marketing of prescription drugs. We conclude simply 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 (emphasis added).

Therefore, insofar as Amarin seeks preliminary relief recognizing its First Amendment right to be free from a misbranding action based on truthful speech promoting the off-label use of an FDA-approved drug, Amarin has established a substantial likelihood of success on the merits on this point. Under *Caronia*, misbranding is *unlike* the crimes of jury tampering, blackmail, and insider trading to which the FDA has analogized, in which "the speech is the act." Tr. 83. Where the speech at issue consists of truthful and non-misleading speech promoting the off-label use of an FDA-approved drug, such speech, under *Caronia*, *cannot* be the act upon which an action for misbranding is based.

The FDA makes three counterarguments. None is persuasive.

First, the FDA argues that that protecting truthful speech aimed at promoting off-label drug use is "a frontal assault . . . on the framework for new drug approval that Congress created in 1962," FDA Br. 1, because allowing a manufacturer to promote such use "has to the potential to eviscerate [the] FDA drug approval regime." Tr. 41. The short answer is that the FDCA's drug-approval framework predates modern First Amendment law respecting commercial speech. The Supreme Court held in *Central Hudson* (1980) that the First Amendment gives qualified protection to commercial speech and in *Sorrell* (2011) that pharmaceutical marketing qualifies as such speech. It follows that the provisions of a 1962 statute that implicate such speech, such as the FDCA's misbranding provisions, today must be considered, and to the extent ambiguous construed, in light of contemporary First Amendment law, under which truthful and non-misleading commercial speech is constitutionally protected, subject to the *Central Hudson* framework.

The Second Circuit's decision in *Caronia* reflected a careful *Central Hudson* analysis. And the Circuit, in *Caronia*, identified alternative, and less speech-restrictive, means for the FDA to achieve its objectives. The FDA's quarrel is, therefore, ultimately, with *Caronia*. Notably, however, despite a vigorous dissent to the effect that the panel majority had "call[ed] into question the very foundations of our century-old system of drug regulation," *see* 703 F.3d at 169 (Livingston, J., dissenting), the Government neither sought rehearing nor petitioned for certiorari in *Caronia*.[57]

Second, the FDA, consistent with its guidance, urges the Court to limit the holding in *Caronia* to protect only certain types of truthful and non-misleading statements by manufacturers regarding off-label use. The FDA looks askance, for example, at statements made proactively to a doctor as opposed to those responding to a doctor's query; and at statements made to a doctor by a sales or marketing employee, as opposed to those by a scientist or physician. *See, e.g.*, FDA Br. 17; Tr. 53–55, 62–65. As the FDA explains, the types of statements that it disfavors are, by nature, more likely to reflect a manufacturer's intent to promote off-label use of a drug as opposed to being mere responses to requests for information.

But *Caronia* did not turn on the intent element of misbranding. It turned on the *actus reus* requirement. And *Caronia*'s holding was that the FDCA's misbranding provisions cannot constitutionally criminalize, and therefore do not reach, the act of truthful and non-misleading speech promoting off-label use. The Circuit did not limit that holding to a subset of truthful

[57] In its brief, the FDA (FDA Br. 38–41), tracking Judge Livingston's dissent, takes issue with the panel majority's discussion of alternative, less-speech-restrictive means by which the FDA could achieve its objectives. But the proper forum for that critique was a petition for rehearing or certiorari in *Caronia.* This Court cannot override the Second Circuit's definitive construction of the misbranding statute. *See Polestar Maritime Ltd. v. Nanjing Ocean Shipping Co. Ltd.*, 631 F. Supp. 2d 304, 305 (S.D.N.Y. 2009) (citing *World Wrestling Entm't, Inc. v. Jakks Pacific, Inc.*, 425 F. Supp. 2d 484, 499 (S.D.N.Y. 2006)).

promotional speech, such as statements responding to doctors' queries or statements by non-sales personnel. *Caronia* instead construed the misbranding provisions not to reach *any* "truthful off-label promotion of FDA-approved prescription drugs." 703 F.3d at 168–69. And the reasons the Circuit gave in *Caronia* for that holding apply across-the-board to *all* truthful and non-misleading promotional speech. Indeed, the speech on which the *Caronia* prosecution itself was based involved the very types of statements promoting off-label use that the FDA most disfavors: proactive oral statements to a doctor by a manufacturer's sales representative. *See id.* at 155–56.

Third, the FDA notes that *Caronia* does not prohibit the Government from relying on truthful and non-misleading statements to establish, in a misbranding action, that the defendant intended to promote off-label use. *See, e.g.*, FDA Br. 3, 23, 26 & n.15; Tr. 52–54. But the proposition that speech can be admissible in evidence to prove intent or motive in a criminal case[58] is beside the point here. Amarin's lawsuit is directed instead to the act requirement—the situation in which a misbranding action takes aim at truthful, non-misleading speech. And *Caronia* construed the misbranding statute, categorically, not to reach a manufacturer or its representative under those circumstances. That construction applies no matter how obvious it was that the speaker's motivation was to promote such off-label use. Promoting such use, in fact, was transparently Caronia's intent.[59]

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[58] The *Caronia* majority assumed *arguendo* that the Government can offer evidence of a defendant's off-label promotion to establish the element of intent, 703 F.3d at 161, and the dissent squarely so stated, *id.* at 171–77 (Livingston, J., dissenting); *see also id.* at 171 ("'The First Amendment . . . does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent'") (quoting *Wisconsin v. Mitchell*, 508 U.S. 476, 489 (1993)).

[59] Caronia's speech was also in violation of company policy. His company, Orphan Medical, Inc., had a policy that barred him, as a specialty sales representative, from speaking to doctors about off-label uses, and directed him to deflect any questions about off-label use to physicians

The Government is of course correct that truthful speech can serve as evidence of intent. To illustrate, consider a misbranding prosecution of a manufacturer based on promotional actions other than truthful speech. The manufacturer's statements promoting off-label use might be admissible there, to shed light on the intent behind these actions or to present the scheme in full context. At argument, the Court posed a hypothetical in which a manufacturer paid doctors money or bought them resort vacations—allegedly to reward them for prescribing a drug for off-label use. Amarin's counsel agreed that the manufacturer's truthful statements promoting off-label use could well be admissible to prove that its intent in paying the doctors had been to promote off-label (as opposed to, say, on-label) use. Tr. 11. *Caronia* does not limit the Government's ability to use promotional speech to establish intent in a misbranding action with a proper *actus reus*.

And, contrary to the FDA's concern, *Caronia* leaves room for prosecuting off-label marketing as misbranding. Two limits to *Caronia*'s holding are worth highlighting. First, the First Amendment does not protect false or misleading commercial speech. *Caronia*'s construction of the misbranding provisions so to exclude truthful promotion speech affords no protection to a manufacturer that uses false or misleading communications to promote an off-label use. Second, the First Amendment protects expression, not conduct. A manufacturer that engages in non-communicative activities to promote off-label use cannot use the First Amendment as a shield. *Caronia* holds protected, and outside the reach of the FDCA's misbranding provisions, off-label promotion only where it wholly consists of truthful and non-misleading speech.

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employed by Orphan. Caronia, whose salary was based on individual sales, nevertheless twice promoted Xyrem to doctors for unapproved uses. *Id.* at 156–57.

A final observation: Although the FDA cannot require a manufacturer to choreograph its truthful promotional speech to conform to the agency's specifications, there is practical wisdom to much of the FDA's guidance, including that a manufacturer vet and script in advance its statements about a drug's off-label use. A manufacturer that leaves its sales force at liberty to converse unscripted with doctors about off-label use of an approved drug invites a misbranding action if false or misleading (*e.g.*, one-sided or incomplete) representations result. *Caronia* leaves the FDA free to act against such lapses. A manufacturer may also conclude that it is prudent to consult with the FDA before promoting off-label use. Reasonable minds may differ over whether a given statement is misleading in context; and developments in science or medicine may make a once-benign statement misleading. Prior consultation with the FDA may prove a helpful prophylactic, and may avert misbranding charges where the FDA and the manufacturer would take different views of a statement. In the end, however, if the speech at issue is found truthful and non-misleading, under *Caronia*, it may not serve as the basis for a misbranding action.[60]

b. Specific communications relating to Vascepa which Amarin seeks to make

The Court turns next to the specific communications relating to Vascepa which Amarin seeks to make to doctors. As noted, Amarin proposes:

- *To disseminate reprints of 13 peer-reviewed scientific publications*. According to Amarin, each relates to the effect of EPA on the reduction of the risk of coronary heart disease. *See* Compl., Ex. A.

- *To disseminate a statement and chart summarizing the ANCHOR study*. These set out the parameters of the ANCHOR study and the statistical effect shown in that study of Vascepa on triglyceride levels. *See* Compl., Ex. B.

[60] In light of the Court's holding, reinforcing *Caronia*'s construction of the misbranding statute, there is no occasion to address Amarin's alternative ground for relief, to the effect that the misbranding statute is unconstitutionally vague and thus violates due process.

- *To disseminate three textual statements and five textual disclosures*. These are Statements #1 through #3, and Disclosures #1 through #5, addressed above.

The Court evaluates these categories in turn.

At the outset, the Court notes that Vascepa's unusual and extensive regulatory history makes it realistic to determine, at this early stage, the truthfulness of Amarin's proposed statements regarding its off-label use.[61] Here, the FDA has already reviewed the off-label use at issue. It approved the ANCHOR study, which tested Vascepa's effectiveness in reducing triglyceride levels among patients with persistently high triglycerides. And it has confirmed in writing, including in the CRL, that Vascepa has proven effective in doing so. Amarin has thus been able to base its proposed communications about Vascepa almost entirely on statements by the FDA itself.

i. Reprints

With respect to the reprints of the 13 peer-reviewed scientific publications that address the effect of EPA (Vascepa's main component) on coronary heart disease, the FDA does not claim that these, viewed separately or together, are false or misleading. The FDA instead has described these as "the types of publications covered by the [FDA's] existing guidance" governing reprints of scientific publications. *See* Woodcock Letter, at 8. The FDA did caution Amarin not to accompany these reprints with misleading language, *i.e.*, not to characterize an article as definitive or representative where this was not so, or to falsely imply that a study described in a reprint involved Vascepa. *Id.* But Amarin's proposed statements do not do so.

[61] At argument, Amarin and the FDA agreed that the Court can resolve, without discovery, whether the statements at issue are truthful and non-misleading. *See* Tr. 71, 84.

The Court therefore holds, and the FDA does not dispute, that Amarin's dissemination of these reprints, under the circumstances proposed, would be neither false nor misleading.[62]

ii. Summary of the ANCHOR Study

The FDA does not claim that the summary of the ANCHOR study that Amarin appended to its Complaint as Exhibit B is false or misleading. The FDA has noted that summaries or excerpts of a study can be misleading if they omit material information or introduce bias. *See* Woodcock Letter, at 6. But, the FDA stated, Exhibit B "does not raise those types of concerns." *Id.*; *see also* FDA Br. 15.

The Court agrees. Exhibit B is an anodyne—and studiously neutral—overview of the ANCHOR study. It (1) defines—demographically, medically, and numerically—the patient and placebo groups, and (2) reports, statistically, by means of a chart, the outcomes of the 12-week study, including the extent to which Vascepa reduced triglyceride and other lipid parameters in the patient group relative to the placebo group. The Court therefore holds, and the FDA does not dispute, that Amarin's dissemination of this summary is neither false nor misleading.[63]

iii. Agreed-Upon Statements and Disclosures

In neither the Woodcock Letter nor its submissions in this litigation did the FDA object to Statement #2 and Statement #3 that Amarin proposes in its Complaint to make relating to the off-label use of Vascepa. To recap, these are:

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[62] The Woodcock Letter took the position that dissemination of the reprints should be accompanied by the five disclosures set out in that letter. *Id.* at 8. However, as reviewed below, Amarin has agreed to most of these disclosures, and the Court here has approved the others, with modest modifications.

[63] As with the reprints, *see supra*, n.62, the Woodcock Letter took the position that dissemination of the Exhibit B summary should be accompanied with the five disclosures proposed by the FDA, Woodcock Letter, at 6.

- *Statement #2*: "The ANCHOR study demonstrates that Vascepa lowers triglyceride levels in patients with high (≥200 mg/dL and <500 mg/dL) triglyceride levels not controlled by diet and statin therapy."

- *Statement #3*: "In the ANCHOR study, Vascepa 4g/day significantly reduced TG [triglycerides], non-HDL-C [non-high density lipoprotein cholesterol or non-"good cholesterol"], Apo B [Apolipoprotein B], VLDL-C [very-low-density lipoprotein cholesterol], TC [total cholesterol] and HDL-C [high density lipoprotein cholesterol or "good cholesterol"] levels from baseline relative to placebo in patients with high (≥200 mg/dL and <500 mg/dL) triglyceride levels not controlled by diet and statin therapy. The reduction in TG [triglycerides] observed with Vascepa was not associated with elevations in LDL-C [low-density lipoprotein cholesterol or "bad cholesterol"] relative to placebo."

The Court agrees that these statements are truthful and non-misleading. The Court understands that Amarin would accompany these statements by distributing the full text of Exhibit B.

The FDA also agreed to the substance of four of the five disclosures (#1, #3, # 4, and #5) that Amarin proposed in its Complaint to give alongside its statements. To recap, these are:

- *Amarin Disclosure #1*: "FDA has not approved Vascepa to reduce the risk of coronary heart disease."

- *Amarin Disclosure #3*: "The effect of Vascepa on the risk of cardiovascular mortality and morbidity has not been determined."

- *Amarin Disclosure #4*: "A cardiovascular outcomes study of Vascepa designed to evaluate the efficacy of Vascepa in reducing cardiovascular mortality and morbidity in a high risk patient population on statin therapy is currently underway"; and

- *Amarin Disclosure #5*: "Vascepa may not be eligible for reimbursement under government healthcare programs (Medicare/Medicaid) to reduce the risk of coronary heart disease or for treatment of statin-treated patients with mixed dyslipidemia and high (≥200 mg/dL and <500 mg/dL) triglyceride levels. We encourage you to check that for yourself."

See Woodcock Letter, at 7 & n.15.[64] The Court agrees that these statements are, based on current information, truthful and non-misleading.

In addition, Amarin agreed to one of the three disclosures that the FDA proposed be given (in addition to Amarin's disclosures). This would be of:

- *FDA Disclosure #1*: "Any potential financial or affiliation biases between the firm and those who conducted the ANCHOR study."

See Ketchum Reply Decl. ¶ 12.

iv. Contested Disclosures

The parties disagree, however, as to two disclosures. The parties' positions as to each were sharpened over the course of briefing and argument.

(a) Amarin's proposed Disclosure #2

Amarin's proposed Disclosure #2 initially read:

- *Amarin Disclosure #2*: "FDA has not approved Vascepa for the treatment of statin-treated patients with mixed dyslipidemia and high (≥200 mg/dL and <500 mg/dL) triglyceride levels."

Compl. ¶ 124.

In the Woodcock Letter, the FDA took the position that this disclosure should be revised, to explain *why* the FDA had not approved Vascepa for this off-label purpose:

- *FDA Disclosure #2*: "Vascepa is not approved for the treatment of statin-treated patients with mixed dyslipidemia and high (> 200 mg/dL and < 500 mg/dL) triglyceride levels. FDA declined to approve this indication because the available evidence does not establish that reducing triglycerides with a drug reduces the risk of cardiovascular events among patients already treated with statins."

See Woodcock Letter, at 7.

[64] As to the Amarin's Disclosure #1, the FDA proposed, and Amarin has agreed, to reword the disclosure to use the passive voice: to wit, to state: "Vascepa is not approved to reduce the risk of coronary heart disease." Woodcock Letter, at 7; Ketchum Reply Decl. ¶ 12.

Amarin, in its reply, proposed to revise its Disclosure #2 to add an introductory sentence and to revise the disclosure:

- *Amarin's Revised Disclosure #2*: "Numerous national and international treatment guidelines and position statements recommend drug therapy as an adjunct to healthy dietary and lifestyle changes and statin therapy for patients at risk for cardiovascular disease and who have persistently high triglyceride levels in their blood (i.e., high despite statin therapy) to lower those patients' triglycerides and/or non-HDL cholesterol. Vascepa is not FDA-approved for the treatment of statin-treated patients with mixed dyslipidemia and high (≥ 200 mg/dL and < 500 mg/dL) triglyceride levels due to current uncertainty regarding the benefit of drug-induced changes in lipid/lipoprotein parameters beyond statin-lowered low-density lipoprotein cholesterol on cardiovascular risk among statin-treated patients with residually high triglycerides. No prospective study has been conducted to test and support what, if any, benefit exists."

Ketchum Reply Decl. ¶ 22 (underlined text denotes Amarin's proposed additions). Amarin explained that its revision of the back end of the disclosure was necessary to capture accurately the FDA's basis for not approving Vascepa for the off-label use. The FDA's text, Amarin stated, had inaccurately implied that "the available evidence" had affirmatively established that reducing triglycerides with a drug does not reduce cardiovascular risk in the relevant population, whereas in fact, that proposition is unresolved (and is being assessed in the REDUCE-IT study). *Id.* ¶ 16. Amarin explained that its revision of the front of this disclosure was needed because the FDA's text "ma[de] no mention of the potential benefit for patients with persistently high triglycerides and low good cholesterol." *Id.* ¶ 19 (citing CRL, at 2).

At this early stage, the Court's judgment, based on its review of the parties' submissions, is that each party's proposal is less than optimal, but that a revised Disclosure #2, drawing upon both parties' final positions, achieves a truthful and non-misleading result.

As for the back end of the disclosure, the Court agrees with the FDA that an explanation for the FDA's decision not to approve Vascepa for off-label use is warranted, to give doctors a

context in which to understand the agency's decision. Unexplained, the FDA's decision would be, potentially, a mystery. It might foster any number of unhelpful misconceptions. However, the Court agrees with Amarin that the FDA's proposed explanation has the potential to mislead, insofar as it implies that drug-induced triglyceride level reductions among patients with persistently high triglycerides have been affirmatively shown *not* to reduce the risk of cardiovascular events. In fact, as the parties agree, the studies to date on that point are simply not conclusive. Amarin's proposal to explain that there is "current uncertainty" regarding the cardiovascular benefits of such reductions is a fair and neutral statement of the present state of scientific knowledge and of the basis for the FDA's decision not to approve Vascepa to treat patients with persistently high triglycerides. The Court will, however, direct that the word "benefit" in Amarin's proposed text be replaced by the phrase "benefit, if any," so as to eliminate any risk that a doctor would assume that some benefit has been found.

As for the front end of the disclosure, for several reasons, the Court declines—at this stage—to give Amarin comfort with respect to the sentence it seeks synopsizing "[n]umerous national and international treatment guidelines and position statements." First, including this sentence adds a tenor of advocacy to the disclosure, which otherwise is neutral in tone. Second, the FDA, at argument, disputed—and the Court has not had occasion to resolve—whether that sentence is factually accurate. *See* Tr. 75–76 (arguing that this sentence was "based on outdated science"). Third, the sentence, which Amarin did not initially include Disclosure #2, is unnecessary to make the overall disclosure truthful and non-misleading. The addition of a sentence explaining the basis for the FDA's decision does not make it necessary to characterize worldwide treatment guidelines. The overall disclosure is fair and balanced without this sentence.

The Court, accordingly, holds that the following disclosure, drawing upon both parties' drafts, is, at present, truthful and non-misleading.

- "Vascepa is not FDA-approved for the treatment of statin-treated patients with mixed dyslipidemia and high (≥ 200 mg/dL and < 500 mg/dL) triglyceride levels due to current uncertainty regarding the benefit, if any, of drug-induced changes in lipid/lipoprotein parameters beyond statin-lowered low-density lipoprotein cholesterol on cardiovascular risk among statin-treated patients with residually high triglycerides. No prospective study has been conducted to test and support what, if any, benefit exists."

The parties are, of course, at liberty to pursue further refinements to this disclosure as this litigation moves forward.

(b) The FDA's proposed Disclosure #3

The FDA's proposed Disclosure #3 initially read:

- *FDA Disclosure #3*: "Recent cardiovascular outcome trials (ACCORD-Lipid, AIM-HIGH, and HPS2-THRIVE) each failed to demonstrate incremental cardiovascular benefit of adding a second lipid-altering drug (fenofibrate or formulations of niacin), despite reducing triglyceride levels, among statin-treated patients with well-controlled low-density lipoprotein-cholesterol."

Woodcock Letter, at 7. In its reply, Amarin opposed this disclosure as unnecessary. *See* Ketchum Reply Decl. ¶ 25. However, Amarin urged that, if any disclosure along these lines was held necessary, the FDA's proposed disclosure be modified as follows.

- *FDA Disclosure #3*: "Recent cardiovascular outcomes trials (ACCORD-Lipid, AIM-HIGH, and HPS2-THRIVE), while not designed to test the effect of lowering triglyceride levels in patients with high triglyceride levels after statin therapy, each failed to demonstrate incremental cardiovascular benefit of adding a second lipid-altering drug (fenofibrate or formulations of niacin), despite raising high-density lipoprotein cholesterol and reducing triglyceride levels, among statin-treated patients with well-controlled low-density lipoprotein-cholesterol."

Id. (the underlined text denotes Amarin's proposed additions).

This disclosure presents a close question. It is not clear that a disclosure along the lines proposed by the FDA is necessary to make Amarin's overall communications about Vascepa non-misleading. After all, doctors will already have been informed that the basis of the FDA's decision not to approve Vascepa for patients with persistently high triglycerides was the current uncertainty that reducing such triglycerides will yield a cardiovascular benefit. On the other hand, the disclosure drafted by the FDA is undisputedly accurate. And it gives doctors relevant information: The outcomes trials referred to in the FDA's disclosure are the very studies on which the FDA relied in not approving Vascepa's off-label use. The modifications Amarin urges are also factually accurate and add useful context.[65]

At this stage, the Court's judgment is to err on the side of caution, meaning in favor of giving doctors more, not less, information. Because the FDA's disclosure, as modified by Amarin, is factually accurate and non-misleading, that disclosure will usefully guard against any misapprehension. The relief the Court grants—declaring that Amarin's package of proposed communications about Vascepa, as modified herein, is truthful and non-misleading, and therefore under *Caronia* cannot form the *actus reus* of a misbranding action—presupposes that Amarin will make this disclosure.

The parties are, of course, at liberty to revisit this disclosure, too, as this litigation moves forward.

[65] At argument, the FDA did not dispute that Amarin's additions are accurate. The FDA did argue that these clauses were misleading because the outcomes trials to which the disclosure refers did fail to demonstrate cardiovascular benefit. Tr. 78–79. But the FDA's disclosure, even as revised, still unmistakably says just that.

v. Amarin's Proposed Statement #1

In the Complaint, Amarin proposed to make the following statement (the "coronary heart disease claim") to doctors in connection with Vascepa:

> *Statement # 1*: "Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease."

Compl. ¶ 124. Amarin noted that dietary supplement manufacturers are permitted to make this claim, verbatim, to consumers, on the packaging of dietary supplements that are chemically identical to Vascepa. Amarin Br. 8, 19–20.

In the Woodcock Letter, the FDA objected to Amarin's making this statement. Woodcock Letter, at 8–10. It explained that, although there is not "significant scientific agreement" on this point, the coronary heart disease claim is accurate and "supported by credible evidence," and therefore the FDA has permitted this claim to be made in connection with dietary supplements. *See id.* at 9. But, the FDA stated, the lower standard governing health statements on dietary supplements should not be extended to claims for drugs, "which require substantial evidence of effectiveness to support approval for each approved use." *Id.* (citing 21 U.S.C. § 355). And allowing claims "with such a low level of scientific weight could undermine the important public health interests served by the premarket approval requirements for drugs under the FDCA." *Id.* Accordingly, the FDA stated, allowing Amarin to make this statement in connection with Vascepa "would be potentially harmful to the public health, and [the] FDA would consider such conduct to be *potentially misleading*." *Id.* at 10 (emphasis added). The FDA also feared that this claim might lead a doctor to prescribe Vascepa instead of promoting healthy dietary and lifestyle changes or prescribing statin therapy. *Id.*

Before this Court, the FDA argues that use of the coronary heart disease claim in connection with Vascepa would be "potentially misleading," for three reasons. First, it "does not

advise physicians to prescribe Vascepa as an adjunct in combination with statins"; a doctor could wrongly view Vascepa as a substitute for statin therapy. FDA Br. 32–33; Woodcock Decl. ¶ 37. Second, the claim may prompt doctors not to independently review the underlying medical research. FDA Br. 33. Third, the claim could lead doctors wrongly to conclude that the "[s]upportive but not conclusive research" includes the ANCHOR study itself. *Id.* In sum, the claim could "mislead physicians and cause them to conclude that Vascepa itself will provide a reduction in risk of coronary heart disease by lowering triglyceride levels in patients already on statin therapy who have or are at risk for cardiovascular disease." *Id.*; *see also* Woodcock Decl. ¶ 37.

In response, Amarin notes that the coronary heart disease claim is factually accurate, and acquiesced by the FDA in consumer-directed dietary supplement labeling. And, it argues, that claim, couched in nuanced language, would not mislead doctors. Ketchum Reply Decl. ¶ 29. A doctor could not read the statement to mean that "there is substantial evidence to support Vascepa's use to reduce the risk of coronary heart disease," as the claim states only that there is "*supportive but not conclusive research*" that consuming EPA and DHA-omega-3 fatty acids "*may* reduce the risk of coronary heart disease." *Id.* (emphasis in original). And the true statement that "supportive but not conclusive research" reveals possible coronary benefits to consuming EPA and DHA-omega-3 fatty acids may be "clinically relevant to [doctors'] decisions about how to best treat their patients." *Id.* ¶ 30. Finally, to meet the FDA's concern that the claim might lead doctors to forego other useful treatment, Amarin proposes that a sentence be added to that claim as a safeguard:

> Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease. Vascepa should not be taken in place of a healthy diet and lifestyle or statin therapy.

Id. ¶ 31 (the underlined text denotes Amarin's proposed additions).

The Court's assessment, with Amarin, is that the coronary heart disease claim—given its qualified phrasing and its acceptance elsewhere by the FDA, and with the sentence added by Amarin—is presently truthful and non-misleading. Therefore, Amarin may today make that claim, too, without exposing itself to liability for misbranding.

As to its truthfulness, the coronary heart disease claim is undisputedly an accurate account of the current state of scientific research. The FDA acknowledged so at argument, Tr. 49, and for this reason, it has permitted the same statement to be made directly to consumers. While the FDA notes that a higher standard for FDA approval governs health claims for drugs than for dietary supplements, the coronary heart disease claim does not refer to FDA approval or any regulatory standard. That claim is a representation of fact, and a textured one at that, as to the present state of scientific research as to a discrete proposition.

As to whether the claim is misleading if made in connection with Vascepa, the FDA has not so argued. It argues only that the claim is "potentially misleading," and whether it ever became misleading would "depend on [future] circumstances." Tr. 61.[66] But Amarin's lawsuit involves the present. The coronary heart disease claim, in the context of the overall statements Amarin will make, and with the sentence added by Amarin, is not today misleading.

As to the FDA's concern that a doctor might errantly conclude "that there is currently sufficient evidence to support a conclusion that drug-induced decreases in triglyceride levels lead to a reduction in the risk of cardiovascular events in patients on statin therapy," FDA Br. 23,

[66] Asked at argument whether the claim, with the sentence Amarin added, would be misleading, the FDA responded: "It's not that it's misleading, your Honor. The [FDA] has characterized it to be potentially misleading. It would depend on the circumstances that it was disseminated, whether it actually became misleading." Tr. 61.

Amarin's Statement #1 does not say that. And the disclosures that will accompany it refute that. They report that there is current uncertainty whether decreases in triglyceride levels reduce the risk of cardiovascular events, and, indeed, explain that that is why the FDA has not approved Vascepa to treat patients with persistently high triglycerides. Doctors can grasp that point. *See Friedman*, 13 F. Supp. 2d at 67 ("Whether speech is 'inherently misleading' depends on . . . the 'possibilities for deception,' . . . whether 'experience has proved that in fact that such advertising is subject to abuse,' . . . and 'the ability of the intended audience to evaluate the claims made.'") (internal citations omitted).

Nor is a doctor apt to confuse the reference to "[s]upportive but not conclusive research" in Statement #1 with the ANCHOR study. Statement #1 does not refer to that study. And the ANCHOR study is described in detail in Amarin's statements and disclosures. These make clear that the ANCHOR study did not address, let alone reach conclusions about, the impact on coronary heart disease.

Finally, the FDA's concern that future events may one day make the coronary heart disease claim misleading cannot justify treating this presently true and non-misleading statement as if it were unprotected speech. "[A] governmental body seeking to sustain a restriction on commercial speech must demonstrate that the harms it recites are real and that its restriction will in fact alleviate them to a material degree"; "[t]his burden is not satisfied by mere speculation or conjecture." *Edenfield v. Fane*, 507 U.S. 761, 770–71 (1993). The FDA cannot use the "rote invocation of the words 'potentially misleading'" to discharge its burden. *Ibanez v. Fla. Dep't of Business & Prof. Reg., Bd. of Accountancy*, 512 U.S. 136, 146 (1994). Of course, the FDA is at liberty to reassess the factual accuracy of this claim as circumstances change. If and when the FDA repudiates it, the Court would expect Amarin to respond accordingly.

The Court, therefore, holds that the coronary heart disease claim is presently truthful and non-misleading. Amarin may include that claim among its statements to doctors, without incurring liability for misbranding.

vi. Concluding Observation: Changed Circumstances

The Court has held that Amarin's proposed communications, as modified herein, are presently truthful and non-misleading. But the dynamic nature of science and medicine is that knowledge is ever-advancing. A statement that is fair and balanced today may become incomplete or otherwise misleading in the future as new studies are done and new data is acquired. The Court's approval today of these communications is based on the present record. Amarin bears the responsibility, going forward, of assuring that its communications to doctors regarding off-label use of Vascepa remain truthful and non-misleading.

2. Other Preliminary Relief Factors

The Court next addresses irreparable harm. "Where infringement of free speech is claimed, irreparable harm may normally be presumed." *Am. Freedom Def. Initiative v. Metro. Transp. Auth.*, 880 F. Supp. 2d 456, 465–66 (S.D.N.Y. 2012) (citation omitted); *see also N.Y. Magazine v. Metro. Transp. Auth.*, 136 F.3d 123, 127 (2d Cir. 1998) ("The loss of First Amendment freedoms, for even minimal periods of time, unquestionable constitutes irreparable injury.") (internal quotation marks and citation omitted). And here, Amarin has established irreparable harm. Without relief, it has shown, its First Amendment rights will be chilled by the threat of a misbranding action. Amarin thus has "articulate[d] a 'specific present objective harm or a threat of a specific future harm' [so as] to establish a cognizable claim based on the chilling of first amendment rights." *Am. Postal Workers Union, AFL-CIO v. U.S. Postal Serv.*, 766 F.2d 715, 722 (2d Cir. 1985) (quoting *Laird v. Tatum*, 408 U.S. 1, 14 (1972)).

The remaining preliminary relief factors—the balance of equities and the public interest—here are intertwined. The Court "must balance the competing claims of injury and must consider the effect on each party of the granting or withholding of the requested relief," 555 U.S. at 24 (quoting *Amoco Prod. Co. v. Gambell*, 480 U.S. 531, 542 (1987)) (internal quotation marks omitted), and "pay particular regard for the public consequences in employing the extraordinary remedy" of preliminary relief, *id.* (quoting *Weinberger v. Romero-Barcelo*, 456 U.S. 305, 312 (1982)).

Here, the equities, including the public interest, strongly favor granting Amarin relief. Doing so would eliminate the chill on Amarin's First Amendment rights. This serves the public interest, because "securing First Amendment rights is in the public interest," *Walsh*, 733 F.3d at 488, and "the Government does not have an interest" in the unconstitutional enforcement of a law, *id.* (quoting *Am. Civil Liberties Union v. Ashcroft*, 322 F.3d 240, 247 (3d Cir. 2003)).

On the other side of the equation, the FDA fears that sanctioning Amarin's off-label promotion "would set a course toward undermining the drug approval process that Congress enacted in 1962 to cure serious public health problems that resulted from abuses under the prior regime." FDA Br. 49. But the Court's recognition that Amarin may engage in truthful and non-misleading speech about the off-label use of Vascepa merely applies, to one drug, the construction of the misbranding statute adopted in *Caronia*. Had the FDA believed that *Caronia* gravely undermined the drug approval process, it should have sought review of that decision.

Finally, there is no basis to fear that promoting Vascepa for this off-label purpose would endanger the public health. Vascepa is a fish oil product. And it is already widely prescribed to treat patients with persistently high triglycerides. The FDA has acknowledged that it has no

evidence that Vascepa is harmful—indeed, it volunteered that it would not object to Vascepa's being marketed as a dietary supplement. Tr. 46, 70–71.

The balance of equities and the public interest both thus overwhelmingly favor granting relief.

CONCLUSION

For the foregoing reasons, the Court grants Amarin's application for preliminary relief. Specifically the Court declares that:

(1) Amarin may engage in truthful and non-misleading speech promoting the off-label use of Vascepa, *i.e.*, to treat patients with persistently high triglycerides, and under *Caronia*, such speech may not form the basis of a prosecution for misbranding; and

(2) Based on the information presently known, the combination of statements and disclosures that Amarin proposes to make to doctors relating to the use of Vascepa to treat persons with persistently high triglycerides, as such communications have been modified herein, is truthful and non-misleading.

The Clerk of Court is respectfully directed to terminate the motion pending at docket number 5.

An order will follow shortly as to next steps in this litigation.

SO ORDERED.

Paul A. Engelmayer

Paul A. Engelmayer
United States District Judge

Dated: August 7, 2015
New York, New York

EXHIBIT A

Representative Sample of Peer Reviewed Scientific Publications Relevant to the Potential Effect of EPA on the Reduction of the Risk of Coronary Heart Disease

Bays H, Ballantyne C, Braeckman R, et al. Icosapent ethyl, a pure ethyl ester of eicosapentaenoic acid: effects on circulating markers of inflammation from the MARINE and ANCHOR studies. *Am J Cardiovasc Drugs*. 2013;13:37-46.

Doi M, Nosaka K, Miyoshi T, et al. Early eicosapentaenoic acid treatment after percutaneous coronary intervention reduces acute inflammatory responses and ventricular arrhythmias in patients with acute myocardial infarction: a randomized, controlled study. *Int J Cardiol.* 2014:176(3):577-582.

Harris W. Are n-3 fatty acids still cardioprotective? *Curr Opin Clin Nutr Metab Care.* 2013;16(2):141-149.

Matsuzaki M, Yokoyama M, Saito Y, et al. Incremental effects of eicosapentaenoic acid on cardiovascular events in statin-treated patients with coronary artery disease. *Circ J.* 2009;73:1283-1290.

Mozaffarian D, Lemaitre RN, King IB, et al. Plasma phospholipid long-chain omega-3 fatty acids and total and cause-specific mortality in older adults: the cardiovascular health study. *Ann Intern Med.* 2013;158(7):515-525.

Mozaffarian D, Wu JHY. Omega-3 Fatty Acids and Cardiovascular Disease. *J Am Coll Cardiol.* 2011;58(20):2047-2067.

Saito Y, Yokoyama M, Origasa H, et al. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). *Atherosclerosis*. 2008;200:135-140.

Takaki A, Umemoto S, Ono K, et al. Add-on therapy of EPA reduces oxidative stress and inhibits the progression of aortic stiffness in patients with coronary artery disease and statin therapy: a randomized controlled study. *J Atheroscler Thromb.* 2011;18:857-866.

Thies F, Garry JMC, Yaqoob P, et al. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomized controlled trial. *Lancet.* 2003;361:477-485.

Ueeda M, Doumei T, Takaya Y, et al. Serum n-3 polyunsaturated fatty acid levels correlate with the extent of coronary plaques and calcifications in patients with acute myocardial infarction. *Circ J.* 2008;72:1836-1843.

Vecka M, Dusejovska M, Stankova B, et al. N-3 polyunsaturated fatty acids in the treatment of atherogenic dyslipidemia. *Neuroendocrinol Lett.* 2012;33(Suppl. 2):87-92.

Wu JHY, Mozaffarian D. Omega-3 fatty acids, atherosclerosis progression and cardiovascular outcomes in recent trials: new pieces in a complex puzzle. *Heart.* 2014;100(7):530-533.

Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet.* 2007;369:1090-1098.

EXHIBIT B

Co-administration Therapy with Statins for Additional Lipid Management in Mixed Dyslipidemia

The effects of VASCEPA as add-on therapy to treatment with statins were evaluated in a randomized, placebo-controlled, double-blind, parallel-group study of 453 adult patients (226 on VASCEPA and 227 on placebo) with persistent high triglyceride levels (≥200 mg/dL and <500 mg/dL) despite statin therapy. All patients were receiving statin therapy (atorvastatin, rosuvastatin, or simvastatin) and were treated to LDL-C goal prior to randomization. Patients were randomized to either VASCEPA or placebo and treated for 12 weeks with statin co-therapy. The same statin at the same dose was continued throughout the study. The median baseline TG and LDL-C levels in these patients were 259 mg/dL and 83 mg/dL, respectively. The randomized population in this study was mostly Caucasian (96%) and male (61%). The mean age was 61 years and the mean body mass index was 35 kg/m^2. Seventy-three percent (73%) of patients had diabetes at baseline.

The changes in the major lipoprotein lipid parameters for the groups receiving VASCEPA plus statin or placebo plus statin are shown in the following table:

Response to the Addition of VASCEPA to Ongoing Statin Therapy in Patients with High Triglyceride Levels (≥200 mg/dL and <500 mg/dL)

	Vascepa 4 g/day + Statin N=226		Placebo + Statin N=227		Difference (95% Confidence	
Parameter	Baseline	% Change	Baseline	% Change	Interval)	p-value
TG (mg/dL)	265	-18	259	6	-22 (-27, -16)	<0.0001
LDL-C (mg/dL)	82	2	84	9	-6 (-11, -2)	<0.01
Non-HDL-C (mg/dL)	128	-5	128	10	-14 (-17, -10)	<0.0001
Apo B (mg/dL)	93	-2	91	7	-9 (-12, -6)	<0.0001
VLDL-C (mg/dL)	44	-12	42	15	-24 (-32, -17)	<0.0001
TC (mg/dL)	167	-3	168	9	-12 (-15, -9)	<0.0001
HDL-C (mg/dL)	37	-1	39	5	-5 (-7, -2)	<0.01

% Change= Median Percent Change from Baseline
Difference= Median of [VASCEPA % Change – Placebo % Change] (Hodges-Lehmann Estimate)
p-values from Wilcoxon rank-sum test

VASCEPA significantly reduced TG, non-HDL-C, Apo B, VLDL-C, TC and HDL-C levels from baseline relative to placebo. The reduction in TG observed with VASCEPA was not associated with elevations in LDL-C relative to placebo.

The effect of VASCEPA on cardiovascular mortality and morbidity in patients with mixed dyslipidemia has not been determined.