UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

AMARIN PHARMA, INC., DR. JONATHAN HERBST, DR. ERIC RISHE, DR. PETER GOTTESFELD, and DR. RALPH YOUNG, Plaintiffs, v. UNITED STATES FOOD & DRUG ADMINISTRATION, UNITED STATES OF AMERICA, STEPHEN OSTROFF, M.D., in his official capacity as Acting Commissioner of Food and Drugs, and SYLVIA MATHEWS BURWELL, in her official capacity as Secretary of the Department of Health & Human Services, Defendants.	15 Civ. 3588 (PAE) ECF Case

MEMORANDUM OF LAW IN OPPOSITION TO PLAINTIFFS' MOTION FOR PRELIMINARY INJUNCTION

PREET BHARARA
United States Attorney for the
Southern District of New York
Attorney for Defendants
86 Chambers Street, 3rd Floor
New York, New York 10007
Tel.: (212) 637-2737
Fax: (212) 637-2702
Email: ellen.london@usdoj.gov

ELLEN LONDON
Assistant United States Attorney

BENJAMIN C. MIZER
Principal Deputy Assistant Attorney General
Civil Division

JONATHAN F. OLIN
Deputy Assistant Attorney General

SCOTT R. MCINTOSH
Civil Appellate Section

MICHAEL S. BLUME
Director
Consumer Protection Branch

ANDREW E. CLARK
Assistant Director

KERALA T. COWART
Trial Attorney

— Of Counsel —

TABLE OF CONTENTS

PAGE

I. Preliminary Statement 1

II. Regulatory History of Vascepa 4

III. Statutory and Regulatory Background 9

IV. Most of Plaintiffs' Challenges Fail to Present a Case or Controversy 15

V. Plaintiffs Are Not Entitled to a Preliminary Injunction Because They Are Not Likely to Succeed on the Merits 17

A. Amarin's Proposed Speech Is Not Unconstitutionally Infringed 18

1. The First Amendment Allows the Government to Rely on Amarin's Dissemination of the Communications at Issue as Evidence of Intended Use 18

2. The First Amendment Allows the Government to Prohibit Any False or Misleading Statement About Vascepa 23

3. The Challenged FDCA Provisions Meet First Amendment Standards for Regulation of Commercial Speech As Applied To Amarin 23

a) The Requirement That Drugs Be Safe and Effective for Each of Their Intended Uses Directly Advances Substantial Public Health Interests 26

b) The FDCA as Applied to Vascepa Is Narrowly Drawn and Not More Excessive Than Necessary; Any Alternative Would Be Ineffective or Impractical 34

i) Plaintiffs' Proposed Reliance on Disclaimers by Drug Manufacturers Would Be Ineffective 36

ii) Other Alternatives Including All Identified in *Caronia* Likewise Would Be Ineffective and Unfeasible and Are Not Even Proposed by Plaintiffs 37

B. Applying the FDCA to Amarin's Proposed Communications Does Not Violate Plaintiffs' Rights Under the Fifth Amendment 40

C. The Government's Interpretation of the False Claims Act Raises No First Amendment Concerns 45

VI. Plaintiffs Will Not Suffer Irreparable Injury Absent a Preliminary Injunction, the Equities Tip in the Government's Favor, and a Preliminary Injunction Is Not in the Public Interest 48

VII. Conclusion 49

TABLE OF AUTHORITIES

CASES **PAGE**

Action on Smoking & Health v. Harris,
655 F.2d 236 (D.C. Cir. 1980).....21

Advance Pharma., Inc. v. United States,
391 F.3d 377 (2d Cir. 2004).....44

Am. Library Ass'n v. Barr,
956 F.2d 1178 (D.C. Cir. 1992).....16

Bd. of Trustees v. Fox,
492 U.S. 469 (1989).....25, 37

Bruesewitz v. Wyeth LLC,
562 U.S. 223 (2011).....41

Cacchillo v. Insmed, Inc.,
638 F.3d 401 (2d Cir. 2011).....18

Cargill, Inc. v. Charles Kowsky Resources, Inc.,
949 F.2d 51 (2d Cir. 1991).....46

Central Hudson Gas & Electric v. Public Service Commission,
447 U.S. 557 (1980).....3, 23, 24, 27

Clear Channel Outdoor, Inc. v. City of New York,
594 F.3d 94 (2d Cir. 2010).....24

In re Dow Jones & Co.,
842 F.2d 603 (2d Cir. 1988).....17

Edison Pharm. Co. v. FDA,
600 F.2d 831 (D.C. Cir. 1979).....11

FCC v. Fox Television Stations, Inc.,
132 S. Ct. 2307 (2012).....45

Frank v. United States,
78 F.3d 815 (2d Cir. 1996), vacated, 521 U.S. 1114, aff'd on reh'g, 129 F.3d 273 (2d. Cir. 1997).....43, 46

Giboney v. Empire Storage & Ice Co.,
336 U.S. 490 (1949)..... 47-48

Greater New Orleans Broad. Ass'n, Inc. v. United States,
527 U.S. 173 (1999).....25, 31

Kordel v. United States,
335 U.S. 345 (1948).....13, 17

Lehman XS Trust, Series 2006-GP2 v. Greenpoint Mortgage Funding, Inc.,
No. 12 CIV. 7935 ALC, 2014 WL 265784 (S.D.N.Y. Jan. 23, 2014).....15

Marcavage v. City of New York,
689 F.3d 98 (2d Cir. 2012).....25

Marchi v. Bd. of Coop. Educ. Servs. of Albany,
173 F.3d 469 (2d Cir. 1999).....44

Maynard v. Cartwright,
486 U.S. 356 (1988).....44, 46

Munaf v. Geren,
553 U.S. 674 (2008).....18

National Nutritional Foods Ass'n v. Mathews,
557 F.2d 325 (2d Cir. 1977)..... 13-14, 21

Nutritional Health Alliance v. Shalala,
144 F.3d 220 (2d Cir. 1998).....21

Pearson v. Shalala,
164 F.3d 650 (D.C. Cir. 1999).....34, 38

Rafferty v. Judicial Council for the Dist. of Columbia,
131 F.3d 219 (D.C. Cir. 1997).....16, 43

Salinger v. Colting,
607 F.3d 68 (2d Cir. 2010).....18

Sassaman v Gamache,
566 F.3d 307 (2d Cir. 2009).....22

Sorrell v. IMS Health Inc.,
131 S. Ct. 2653 (2011).....24, 31

Susan B. Anthony List v. Driehaus,
134 S. Ct. 2334 (2014).....15

Thompson v. W. States Med. Ctr.,
535 U.S. 357 (2002).....27, 31

Toy Manufacturers of America, Inc. v. Consumer Product Safety Commission,
630 F.2d 70 (2d Cir. 1980).....45

United States ex rel. Frank Solis v. Millennium Pharmaceuticals, Inc.,
09 Civ. 3010 (E.D. Cal. 2014).....47

United States ex rel. Matthew Cestra v. Cephalon, Inc.,
10 Civ. 6457 (S.D.N.Y. 2013).....47

United States ex rel. Nevyas v. Allergan, Inc.,
No. 09-432, 2015 WL 3429381 (E.D. Pa. May 26, 2015).....47

United States ex rel. Pervez v. Beth Israel Medical Ctr.,
736 F. Supp. 2d 804 (S.D.N.Y. 2010).....46

United States v. Article of Drug Designated B-Complex Cholinos Capsules,
362 F.2d 923 (3d Cir. 1966).....22

United States v. Caputo,
517 F.3d 935 (7th Cir. 2008).....23

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

United States v. Cole,
No. 3:13-CV-01606-SI, 2015 WL 471594 (D. Or. Feb. 5, 2015).....22

United States v. Edge Broadcasting Co.,
509 U.S. 418 (1993).....25

United States v. Harkonen,
510 F. App'x 633 (9th Cir. 2013).....23

United States v. Lane Laboratories-USA, Inc.,
324 F. Supp. 2d 547 (D.N.J. 2004).....22

United States v. Lee,
916 F.2d 814 (2d Cir. 1990).....22

United States v. Livdahl,
459 F. Supp. 2d 1255 (S.D. Fla. 2005) 22

United States v. Millpax, Inc.,
313 F.2d 152 (7th Cir. 1963) 21

United States v. Nadi,
996 F.2d 548 (2d Cir. 1993) 45

United States v. Pierce,
No. 13-3687-CR, 2015 WL 2166141 (2d Cir. May 11, 2015) 22

United States v. Sisti,
91 F.3d 305 (2d Cir. 1996) 22

United States v. Spy Factory,
951 F. Supp. 450 (S.D.N.Y. 1997) 45

United States v. Storage Spaces Designated Numbers "8" and "49,"
777 F.2d 1363 (9th Cir. 1985) 21

United States v. Strauss,
999 F.2d 692 (2d Cir. 1993) 45-46

United States v. Sun & Sand Imports, Ltd.,
725 F.2d 184 (2d Cir. 1984) 44

United States v. Urbuteit,
335 U.S. 355 (1948) 13

USV Pharm. Corp. v. Weinberger,
412 U.S. 655 (1973) 28, 39

VIP of Berlin, LLC v. Town of Berlin,
593 F.3d 179 (2d Cir. 2010) 44

Village of Hoffman Estates v. Flipside, Hoffman Estates, Inc.,
455 U.S. 489 (1982) 42

Virginia v. Am. Booksellers Ass'n, Inc.,
484 U.S. 383 (1988) 15-16

Ward v. Rock Against Racism,
491 U.S. 781 (1989) 25

Wash. Legal Foundation v. Henney,
202 F.3d 331 (D.C. Cir. 2000).....10, 20

Wash. Legal Foundation v. Henney,
128 F. Supp. 2d 11 (D.D.C. 2000).....15

Weinberger v. Hynson, Westcott & Dunning, Inc.,
412 U.S. 609 (1973).....10, 11, 12, 19

Whitaker v. Thompson,
353 F.3d 947 (D.C. Cir. 2004).....21-22

Winter v. NRDC,
555 U.S. 7 (2008).....17, 18

Wisconsin v. Mitchell,
508 U.S. 476 (1993).....21, 23, 47

STATUTES

21 U.S.C. § 301 *et seq*.....34

21 U.S.C. § 321(ff).....34

21 U.S.C. § 321(g).....13

21 U.S.C. § 321(g)(1).....10

21 U.S.C. § 321(g)(1)(B)-(C).....10, 12, 13, 34

21 U.S.C. § 321(m).....13

21 U.S.C. § 321(n).....14

21 U.S.C. § 321(p).....10, 13, 36

21 U.S.C. § 331(a).....13, 14, 20

21 U.S.C. § 331(b).....13, 14

21 U.S.C. § 331(c).....13, 14

21 U.S.C. § 331(d).....10, 13

21 U.S.C. § 331(g).....13, 14

21 U.S.C. § 331(k) 13, 14

21 U.S.C. § 352(a) 14

21 U.S.C. § 352(f) 13

21 U.S.C. § 352(f)(1) 13, 29, 36

21 U.S.C. § 352(n) 14, 16

21 U.S.C. § 353(b)(1)(A) 13

21 U.S.C. § 355(a) ..... *passim*

21 U.S.C. § 355(b) 10, 29

21 U.S.C. § 355(d) ..... *passim*

21 U.S.C. §§ 355(d)(1) & (5) 10

21 U.S.C. § 355(e) 10, 19, 34-35

21 U.S.C. § 371 43

31 U.S.C. §§ 3729-3733 46

31 U.S.C. § 3729(a)(1)(A) 46, 47

31 U.S.C. § 3729(a)(1)(B) 46, 47

RULES AND REGULATIONS

21 C.F.R. § 10.115 43

21 C.F.R. § 201.100(c)(1) 13, 29

21 C.F.R. § 201.100(c)(2) 13

21 C.F.R. § 201.100(d) 13

21 C.F.R. § 201.115 13

21 C.F.R. § 201.128 14

21 C.F.R. § 201.5 ..... 13, 29

21 C.F.R. § 201.56 13

21 C.F.R. § 201.57 13

21 C.F.R. § 201.80 13

21 C.F.R. § 202.1(e)(4)(i)(a) 17

21 C.F.R. § 202.1(e)(6) 14

21 C.F.R. § 202.1(j)(4) 8

21 C.F.R. § 202.1(l)(2) 16

21 C.F.R. § 314.126 10

21 C.F.R. § 314.50(d)(5) 11

LEGISLATIVE HISTORY

Administered Prices: Drugs: Report of the Senate Committee on the Judiciary, S. Res. 52, S. Rep. No. 448, 87th Cong. (1961) 28, 30

Dietary Supplement Health and Education Act of 1994, Pub. L. 103-417, 108 Stat. 4325, Sec. 2 Findings 34

Drug Industry Antitrust Act of 1962: Hearings before the Antitrust Subcomm. of the H. Comm. on the Judiciary, 87th Cong. (1962) 11, 12, 28, 30

Drug Industry Act of 1962, S. Rep. No. 1744 (1962), reprinted in 1962 U.S.C.C.A.N. 2884 ..... *passim*

Kafauver-Harris Amendments, Pub. L. No. 87-781, 76 Stat. 780 (1962) 12

OTHER

Aaron S. Kesselheim, Michelle M. Mello, *Prospects for Regulation of Off-Label Drug Promotion in an Era of Expanding Commercial Speech Protection*, 92 N.C. L. Rev. 1539 (2014) 39

Henry A. Waxman, *A History of Adverse Drug Experiences*, 58 Food & Drug L.J. 299 (2003) 11

Michelle M. Mello et al., *"Health Courts" and Accountability for Patient Safety*, 84 Milbank Q. 459, 472 (2006) 41

Simonsen, Skipper & Skipper, *Price Sensitivity of Demand for Prescription Drugs*, Economics Working Paper 2010-3, School of Economics and Management, Aarhus University (Jan. 15, 2010) 40-41

Defendants United States Food & Drug Administration ("FDA"), the United States of America, Stephen Ostroff, M.D., in his official capacity as Acting Commissioner of Food and Drugs, and Sylvia Mathews Burwell, in her official capacity as Secretary of the Department of Health & Human Services ("HHS") (together, the "Government"), by and through their attorney, Preet Bharara, United States Attorney for the Southern District of New York, respectfully submit this memorandum of law in opposition to the motion for preliminary injunction filed by the corporation Amarin Pharma, Inc. ("Amarin"), and individuals Drs. Herbst, Riche, Gottesfeld, and Young ("Doctor Plaintiffs"), collectively "Plaintiffs."

I. Preliminary Statement

This suit is a frontal assault by Plaintiffs on the framework for new drug approval that Congress created in 1962. The specific relief requested in this as-applied constitutional challenge is narrow: Plaintiffs seek a court order that would allow Amarin 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 that the drug is safe and effective. But Plaintiffs' legal arguments strike at the very heart of the new drug approval process, and a court decision in Plaintiffs' favor has the potential to establish precedent that would return the country to the pre-1962 era when companies were not required to prove that their drugs were safe and effective for each of their intended uses.

Contrary to Plaintiffs' contentions, FDA's application of the Federal Food, Drug, and Cosmetic Act ("FDCA") to Amarin's proposed communications—which strikes a balance between enforcing the critical drug approval regime and allowing for flexibility in medical treatment—does not violate either the First or Fifth Amendments and is necessary to protect the public health. Amarin currently has FDA approval to distribute Vascepa for use as an adjunct to

diet to reduce triglyceride levels in adult patients with "very high triglyceride levels." Amarin does not have approval, however, to distribute Vascepa for use by patients with "high" (as opposed to "very high") triglyceride levels who either have or are at risk of coronary heart disease and are already being treated with statins. FDA declined to approve Amarin's supplemental new drug application ("sNDA") for that indication because the sNDA relied on the results of a clinical trial, the "ANCHOR trial," that measured changes in triglyceride levels, and FDA has concluded that there is insufficient scientific evidence that measuring triglyceride levels is an appropriate substitute for measuring cardiovascular outcomes in patients with high triglyceride levels who are already being treated with a statin. Amarin may be able to obtain approval of this additional indication, however, if its ongoing clinical trial measuring cardiovascular outcomes, known as the "REDUCE-IT trial," demonstrates that such an indication is warranted.

Rather than wait to develop substantial scientific evidence to support this additional indication, Amarin seeks a court order allowing it to distribute Vascepa now, under circumstances which suggest that Amarin intends for Vascepa to be used to reduce the risk of coronary heart disease. Yet Congress determined over fifty years ago that drug manufacturers must be required to show—based on substantial scientific evidence—that a drug is both safe and effective for all its intended uses before it can be distributed. That statutory requirement, as set forth in the FDCA and its regulations, protects the public health without burdening the free flow of scientific information, because—first and foremost—it does not prohibit speech. To the extent the FDCA bears on marketing, it does not reach all, or even virtually all, truthful and non-misleading speech by manufacturers regarding unapproved uses of their drugs. In addition, numerous guidance documents clarify how FDA further narrows its application of the statutory

scheme. Amarin elected not to request FDA's views on the marketing at issue in this case, and instead brought this as-applied challenge. Had Amarin asked for FDA's views on its proposed communications prior to filing suit, it would have learned that FDA does not object to most of Amarin's proposed communications. In fact, following the filing of Amarin's Complaint, FDA sent a detailed letter to Amarin on June 5, 2015 (the "June 5 Letter") to clarify how its laws and policies apply to the communications proposed in the Complaint. That letter significantly narrows this dispute.

The only issue remaining before the Court is whether FDA may in the future rely on Amarin's dissemination of certain information—information that FDA has concluded is potentially misleading—as evidence that Amarin intends a new unapproved use for Vascepa, rendering the distribution of Amarin for that use unlawful under the FDCA. Well-established Supreme Court and other precedent demonstrates that such dissemination may be relied upon as evidence of a manufacturer's new intended use of the drug in a prosecution for introducing a misbranded drug or an unapproved new drug into interstate commerce. *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012), does not suggest otherwise.

Alternatively, if the Court were to apply the commercial speech framework of *Central Hudson Gas & Electric v. Public Service Commission*, 447 U.S. 557 (1980), which it should not, FDA's carefully tailored approach must be upheld. Allowing companies such as Amarin to distribute drugs for intended uses that have not been approved by FDA as safe and effective undermines the Congressionally mandated pre-market drug approval process. That process unquestionably advances substantial public health interests, including motivating robust scientific research, providing independent rigorous review of scientific data, requiring review of such data before marketing, ensuring that labeling provides adequate instructions for use, and

monitoring companies' marketing practices—all designed to promote the public health and prevent harm. FDA's approach to requiring that drugs be safe and effective for each of their intended uses is narrowly tailored to directly advance those interests. Thus, Amarin's First Amendment as-applied challenge to the FDCA fails.

Amarin's additional claims likewise fail. Particularly in light of the June 5 Letter, Amarin cannot credibly assert that it is being deprived of due process by reason of an asserted insufficiency of notice of what conduct could lead to a prosecution, nor because the laws and policies in place, as applied to Amarin, purportedly are unconstitutionally vague. Amarin's argument regarding the False Claims Act ("FCA") also fails because Amarin's own representation of the facts would not appear to give rise to liability if no false or otherwise fraudulent claims for payment are made to the Government. Moreover, as noted above, the First Amendment would not be implicated in any potential FCA action because the speech at issue would be used as evidence in support of an element of the FCA, such as scienter or causation, and would not alone be the basis for liability.

Lastly, Amarin is not entitled to a preliminary injunction because the harms to the Government and the public from allowing Amarin to circumvent the drug approval process far outweigh any interim harm Amarin claims it will suffer from not being able to disseminate the small amount of information about Vascepa's unapproved use that FDA found objectionable in its June 5 Letter.

II. Regulatory History of Vascepa[1]

FDA approved Amarin's lipid-altering drug,[2] Vascepa, which is a purified ester of the omega-3 fatty acid eicosapentaenoic acid ("EPA") derived from fish oil, in 2012, for a use relating to reducing the risk of pancreatitis from high triglycerides. June 5 Letter at 1-2; Rosebraugh Decl. ¶ 7. Since then, Amarin has been attempting to obtain approval of Vascepa for a second use that relates to the reduction of the risk of cardiovascular events. June 5 Letter at 2.

To pursue approval for this second use, Amarin conducted the ANCHOR trial, a clinical trial that measured the effects of Vascepa on triglyceride levels in patients who were already taking a statin to lower cholesterol and to reduce the risk of cardiovascular disease. *Id.* The ANCHOR trial was not designed to directly measure cardiovascular outcomes such as heart attacks or strokes. *Id.* In an agreement with Amarin, FDA accepted, based on prevailing scientific understanding at the time, measuring triglyceride levels as a substitute for measuring cardiovascular outcomes in statin-treated patients who have or are at risk for cardiovascular disease—the population for whom Amarin seeks the drug's approval. *Id.*; London Decl., Exs. B & C; Rosebraugh Decl. ¶ 7. At the same time FDA advised Amarin that the results of certain then-ongoing clinical trials would provide important information about whether the reduction of triglyceride levels reduces the risk of cardiovascular events in patients already taking a statin. June 5 Letter at 2; London Decl., Ex. D at 8.

---

[1] A brief summary of the facts is provided herein, and a detailed account is set forth in the June 5 Letter. *See* Dkt. 24, and attached as Exhibit A to the Declaration of Ellen London dated June 23, 2015 ("London Decl."). That letter accurately summarizes relevant aspects of FDA's consideration of Vascepa. *See* Declaration of Dr. Curtis Rosebraugh dated June 22, 2015 ("Rosebraugh Decl.") ¶ 2.

[2] Vascepa is a drug that lowers triglycerides (a type of lipid). *See generally* Rosebraugh Decl.

Prior to FDA's review of the ANCHOR trial, new scientific data from three clinical trials involving other lipid-altering drugs became available. June 5 Letter at 3; London Decl. Ex. G at 7-8; Rosebraugh Decl. ¶¶ 8-9, 13-14, 16-17. These trials were designed to directly measure the effect on cardiovascular outcomes, rather than merely on triglyceride levels, of adding a second lipid-altering drug to statin therapy. June 5 Letter at 3; Rosebraugh Decl. ¶¶ 8, 13, 16. These trials failed to show any additional cardiovascular benefit from taking the other lipid-altering drugs for patients already being treated with a statin. June 5 Letter at 3; Rosebraugh Decl. ¶¶ 9, 14, 17. Accordingly, FDA's current judgment, based on all available scientific data, is that there is insufficient scientific evidence that measuring triglyceride levels is an appropriate substitute for measuring cardiovascular outcomes in patients with high triglyceride levels who are already being treated with a statin. June 5 Letter at 3; Rosebraugh Decl. ¶ 21.

Based on the new scientific data, FDA rescinded its agreement regarding the ANCHOR trial. Rosebraugh Decl. ¶ 20; London Decl., Ex. J at 2. This decision was upheld on administrative appeal on two bases: "(1) no adequate and well-controlled trial has demonstrated a cardiovascular benefit resulting from drug-induced lowering of triglyceride levels in statin-treated patients, and (2) three recent clinical trials failed to show additional cardiovascular benefit of adding a non-statin drug to statin therapy, even though each drug had lowered triglyceride levels significantly in statin-treated patients." Rosebraugh Decl. ¶ 20; *see also* June 5 Letter at 4; London Decl. Exs. G, K, & L. FDA also informed Amarin that FDA would not approve Amarin's sNDA for the use of Vascepa related to the reduction of cardiovascular risk given the lack of evidence that Vascepa reduces that risk. June 5 Letter at 4; London Decl. Ex. M at 2.

FDA also took steps to ensure that the information in the labeling of other lipid-altering drugs was appropriate in light of the totality of the scientific data. *See* Rosebraugh Decl. ¶¶ 10-12, 15, 22-24, for a detailed account of FDA's actions with respect to lipid-altering drugs. In addition to addressing the labeling of other lipid-altering drugs, FDA has actively been seeking to ensure that the information available regarding the impact, if any, of drugs that lower triglycerides on cardiovascular disease is accurate and up to date. *Id.* ¶¶ 28-33.

In response to FDA's concerns about the acceptability of relying on triglyceride levels as a substitute for measuring cardiovascular outcomes, Amarin is now conducting a second clinical trial, the REDUCE-IT trial. June 5 Letter at 2; London Decl., Exs. E & F. Unlike the ANCHOR trial, the REDUCE-IT trial is designed to directly determine Vascepa's effect on cardiovascular outcomes. June 5 Letter at 2-3; Rosebraugh Decl. ¶¶ 19, 21. Amarin has stated that results are expected to be available in 2018. June 5 Letter at 5; Rosebraugh Decl. ¶ 21. If the REDUCE-IT trial generates the necessary evidence to show that Vascepa is both safe and effective for an indication related to reducing cardiovascular outcomes, then FDA would approve an sNDA for that indication, assuming all other approval criteria are met. June 5 Letter at 4-5; Rosebraugh Decl. ¶ 21.

After it failed to obtain FDA approval for its sNDA based on the ANCHOR trial, Amarin filed the instant Complaint seeking an order allowing it to market Vascepa by disseminating the following: summaries of the ANCHOR trial to show that Vascepa lowers triglyceride levels in statin-treated patients, journal articles regarding Vascepa and similar products, and a qualified health claim on certain dietary supplements and foods stating that supportive but not conclusive research shows that the active ingredient in Vascepa and another omega-3 fatty acid called docosahexaenoic acid ("DHA") may reduce the risk of cardiovascular disease (hereinafter "the

heart disease claim"). Compl. ¶ 124. Amarin did not ask for FDA's views regarding these proposed communications before filing the Complaint, although FDA, when requested, regularly provides its views on pharmaceutical companies' proposed marketing statements. *See, e.g.*, 21 C.F.R. § 202.1(j)(4) (describing process for requesting FDA's views in writing regarding proposed advertisements); Declaration of Dr. Janet Woodcock dated June 23, 2015 ("Woodcock Decl.") ¶ 29.

Nonetheless, FDA provided Amarin its views about the proposed communications. FDA's June 5 Letter informed Amarin that FDA "would not consider the dissemination of most of that information to be false or misleading, and we do not intend to rely on it as evidence that Vascepa is intended for a use that would render Vascepa an unapproved new drug or misbranded." June 5 Letter at 1. For example, the letter made clear that FDA would not object to Amarin's distribution of truthful summaries of the ANCHOR trial and reprints of journal articles if it takes certain reasonable steps outlined in the Letter (many of which steps were proposed by Amarin) designed to help prevent the communication from becoming misleading. *Id.* at 6-8. However, FDA expressed concerns about Amarin's use of the heart disease claim. *Id.* at 8. In FDA's view, disseminating this claim—as opposed to reprints and appropriate summaries with appropriate disclosures—is potentially misleading and potentially evidence that Amarin intends Vascepa to be used to reduce the risk of coronary heart disease, a use for which Vascepa has not been approved by FDA as safe and effective. *Id.* at 10.

The heart disease claim is different from the other proposed communications because that claim characterizes the strength of the scientific research and draws conclusions from that research; in other words, the heart disease claim is closer to an opinion piece than a reprint regarding trial results, and thus more likely to induce reliance than the mere presentation of

scientific data, which requires independent judgment to assess. Woodcock Decl. ¶ 41. The express statement that EPA may reduce the risk of coronary heart disease encourages physicians to prescribe Vascepa for that unapproved use in a way that the proposed summary of the ANCHOR results and the reprints do not. *Id.* Allowing Amarin to use the heart disease claim in conjunction with dissemination of the ANCHOR trial results "would only worsen any misconception about the relationship between triglyceride-lowering drugs and cardiovascular disease risk." *Id.* ¶ 37. "Granting Amarin such license would effectively undo FDA's past and continuing efforts to ensure that physicians have the most accurate and up-to-date scientific information" on this issue. *Id.* Based on current evidence, however, the heart disease claim could be made about a dietary supplement, because of the lower standard of scientific evidence accepted for such claims. *Id.* ¶ 30-33; June 5 Letter at 10.

With regard to the reprints and summaries of the ANCHOR results that Amarin seeks to disseminate, the reasonable steps described in the June 5 letter aim to ensure an accurate and balanced presentation of the information and to prevent the dissemination of potentially misleading information about the quantity and quality of the scientific evidence and its applicability to Vascepa. Woodcock Decl. ¶¶ 38-40. To the extent Amarin chooses to disseminate the reprints and summaries about unapproved uses in a manner not described in the June 5 letter, FDA may consider that dissemination as evidence of intended use.

Because of the June 5 Letter, only the following proposed communications (hereinafter "the communications at issue") remain in dispute: the heart disease claim and journal reprints and summaries of the ANCHOR trial results (the latter two only if disseminated in a manner that exceeds the scope of the June 5 Letter).

III. Statutory and Regulatory Background

The linchpin of drug regulation under the FDCA is the requirement that all "new drugs" obtain approval from FDA before they may be distributed in interstate commerce. 21 U.S.C. §§ 331(d), 355(a). Whether an article is considered a "drug" under the FDCA depends upon its intended use: the term "drug" includes any article "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals," and any article other than food "intended to affect the structure or any function of the body of man or other animals." 21 U.S.C. § 321(g)(1)(B)-(C). A "new drug" is any drug that is "not generally recognized, among [qualified] experts . . . as safe and effective for use under the conditions prescribed, recommended, or suggested" in its labeling. 21 U.S.C. § 321(p).

In the wake of public health tragedies, Congress enacted the new drug approval requirements of the FDCA, under which a sponsor must submit a new drug application ("NDA") to FDA demonstrating that its drug is safe and effective for each of its intended uses before the drug may be distributed in interstate commerce for that use. 21 U.S.C. §§ 331(d), 355(a), 321(g)(1) & (p); *see also Wash. Legal Found. v. Henney*, 202 F.3d 331, 332 (D.C. Cir. 2000). Sponsors must collect or generate scientific data on the safety and efficacy of a drug for each intended use and demonstrate to FDA that this data meets the statutory standards. 21 U.S.C. § 355(d)(1) & (5); 21 C.F.R. § 314.126. FDA also reviews and approves the required labeling to help ensure that it conveys accurate and important information for safe and effective use. *See* 21 U.S.C. § 355(b). FDA reviews the manufacturer's data regarding the effectiveness of new drugs under the substantial evidence standard. *See* 21 U.S.C. §§ 355(d), (e); *Weinberger v. Hynson, Westcott & Dunning*, 412 U.S. 609, 613-14 (1973). This "rigorous" standard requires well-controlled scientific data and cannot be satisfied by impressions or beliefs of physicians, reports

lacking in details, or personal testimonials. *Hynson*, 412 U.S. at 630; *see also id.* at 618-19; *Edison Pharm. Co. v. FDA*, 600 F.2d 831, 842-43 (D.C. Cir. 1979); 21 C.F.R. § 314.50(d)(5) (describing the requirements for clinical data). FDA review of the scientific bases for a manufacturer's claims is one of the cornerstones of evidence-based medicine in the United States.

Before 1962, drug manufacturers ordinarily were not required to demonstrate that drugs were effective for each of their intended uses, and drugs were rarely tested to establish effectiveness. Instead, manufacturers marketed drugs for uses regardless of whether there was evidence of efficacy, or even known ineffectiveness; marketed drugs with serious side effects to treat minor conditions even when risks outweighed the benefits; and marketed drugs that were ineffective for serious conditions, even where other effective treatments were available. *See* DRUG INDUSTRY ACT OF 1962, S. REP. NO. 1744, at 36-37 (1962), *reprinted in* 1962 U.S.C.C.A.N. 2884 (London Decl. Ex. Z); *The Drug Industry Antitrust Act of 1962: Hearings before the Antitrust Subcomm. of the H. Comm. on the Judiciary*, 87th Cong. 171-74 (1962) [hereinafter *Drug Industry Antitrust Act Hearings*] (London Decl. Ex. AA); *see generally* Henry A. Waxman, *A History of Adverse Drug Experiences: Congress Had Ample Evidence to Support Restrictions on the Promotion of Prescription Drugs*, 58 Food & Drug L.J. 299, 300-306 (2003). Although manufacturers making false or misleading claims could be subject to enforcement actions after product distribution, such *ex post* remedies failed to deter unsubstantiated and misleading claims and protect the public health. *See* S. REP. No. 1744, at 37 (London Decl. Ex. Z); *Drug Industry Antitrust Act Hearings*, at 67, 171, 173 (London Decl. Ex. AA). As the Secretary of Health, Education, and Welfare told Congress, "[i]t is intolerable to permit the marketing of worthless products under the rules of a cat-and-mouse-game where a manufacturer

can fool the public until [FDA] finally catches up with him." *Drug Industry Antitrust Act Hearings*, at 171 (London Decl. Ex. AA).

Congress sought to end these abuses by enacting the Drug Amendments of 1962. *See* Pub. L. No. 87-781, 76 Stat. 780 (1962) ("Kefauver-Harris Amendments"); *see generally Hynson*, 412 U.S. 609, 618-19 (1973) (FDA's new drug review process is based on "well-established principles of scientific investigation" and represents "an abrupt departure" from the regime that existed before the amendments). These amendments require manufacturers to demonstrate scientifically that their products are effective, as well as safe, for their intended uses before they can be distributed. 21 U.S.C. §§ 355(a), (d); *see also id.* § 321(p). Congress determined that FDA should conduct premarket review for *each* use of the drug, including new uses of approved drugs, to stop drug companies from promoting drugs for uses that had not been shown to be effective (as well as other abuses). *See* S. Rep. No. 1744 at 36-37 (London Decl. Ex. Z). This requirement guards against marketing of an approved drug for an unapproved use without complying with FDA's premarket approval processes, because such marketing would undermine the public health protections afforded by premarket review. *See* Woodcock Decl. ¶ 5.

To the extent Amarin elects to disseminate the communications at issue, such dissemination could, depending on the context at the time, establish a violation of law in at least four ways:

First, Amarin's dissemination of the communications at issue may be considered evidence of intended use that may help establish that Amarin unlawfully distributed an unapproved new drug in interstate commerce. As explained above, the definition of a drug depends on its intended uses, 21 U.S.C. § 321(g)(1)(B)-(C), and a "new drug" is one that is "not generally recognized, among [qualified] experts . . . as safe and effective for use under the

conditions prescribed, recommended, or suggested in the labeling thereof" 21 U.S.C. § 321(p). If the claim is made in "labeling"[3] and establishes a new intended use, Vascepa would be considered an unapproved new drug with respect to that intended use, and distribution of Vascepa for that unapproved new use would therefore be prohibited. 21 U.S.C. §§ 331(d), 355(a), 321(g), (m) & (p).

Second, evidence of a new intended use may also establish a violation of the FDCA's misbranding provisions. A drug is misbranded if, *inter alia*, it lacks adequate directions for all intended uses,[4] and the interstate distribution of misbranded products is illegal. *See* 21 U.S.C. §§ 331(a), (b), (c), (g) & (k). For this violation, the intended use of a drug is "derived or inferred from labeling, promotional material, advertising, and 'any other relevant source.'" *Nat'l*

[3] "Labeling," under § 321(m), includes "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. § 321(m). The Supreme Court has construed this definition to include materials that supplement, explain, or are otherwise textually related to the article. *See Kordel v. United States*, 335 U.S. 345, 349-50 (1948); *United States v. Urbuteit*, 335 U.S. 355, 357 (1948).

[4] A drug's labeling must include "adequate directions for use," 21 U.S.C. § 352(f)(1). Adequate directions for use are "directions under which the layman can use a drug safely and for the purposes for which it is intended." 21 C.F.R. § 201.5. Because prescription drugs, by definition, are "not safe for use except under the supervision of a practitioner licensed by law to administer such drug," 21 U.S.C. § 353(b)(1)(A), the labeling of a prescription drug cannot provide adequate directions for its safe use by laymen. However, the statute also grants authority, which FDA has exercised, to promulgate regulations that establish exemptions from the requirement of adequate directions for use. *See* 21 U.S.C. § 352(f). Among the terms that must be met to satisfy these regulatory exemptions, a prescription drug must have labeling that provides adequate information for its safe and effective use by practitioners for all the purposes for which it is intended, including all purposes for which it is advertised or represented. *See* 21 C.F.R. §§ 201.100(c)(1), 201.100(d), 201.56, 201.57, and 201.80. For new drugs, this labeling also must be approved in an NDA. 21 C.F.R. §§ 201.100(c)(2), 201.100(d), and 201.115.

Nutritional Foods Ass'n v. Mathews, 557 F.2d 325 (2d Cir. 1977); *see also* 21 C.F.R. § 201.128 (regarding bases to determine drug's intended use).[5]

Third, to the extent any of Amarin's communications, when taken in context, are misleading, they could constitute "false or misleading" labeling, rendering Vascepa misbranded, 21 U.S.C. § 352(a), and its distribution in interstate commerce prohibited, 21 U.S.C. §§ 331(a), (b), (c), (g) & (k). Additionally, fourth, to the extent any of Amarin's communications about Vascepa constitute advertising that is "false, lacking in fair balance, or otherwise misleading," Vascepa would be misbranded, *see* 21 C.F.R. § 202.1(e)(6); 21 U.S.C. § 352(n); *see also* 21 U.S.C. § 321(n), and its interstate distribution would be prohibited. 21 U.S.C. §§ 331(a), (b), (c), (g) & (k).

The FDCA's reach does not extend to all communications by drug manufacturers about uses that have not been approved. The dissemination of information about an unapproved use would not, by itself, cause a violation of the FDCA when such information is neither false nor misleading and is not relevant, or sufficient, to infer a new intended use.

In addition to these statutory limitations on FDA's authority, FDA has developed policies regarding when to exercise enforcement discretion, and does not initiate enforcement action under some circumstances even when speech is relevant to establishing intended use. FDA has issued guidance documents describing some of these circumstances, under which FDA would not consider manufacturer communications about unapproved uses of approved products to be

[5] Evidence of a manufacturer's subjective intent to distribute a drug for an unapproved new use is not required to establish a violation of the FDCA. Rather, FDA's regulations provide that intended use "refer[s] to the objective intent of the persons legally responsible for the labeling of drugs." 21 C.F.R. § 201.128; *see also Nat'l Nutritional Foods Ass'n v. Mathews*, 557 F.2d 325, 334 (2d Cir. 1977).

misleading or evidence of intended use. *See* Woodcock Decl. ¶¶ 25-27; London Decl. Exs. N, O, P.[6] Of course, these guidance documents could not possibly capture all circumstances in which FDA would not take enforcement action, and companies are free to ask FDA to provide its views on specific, proposed communications. *See* Woodcock Decl. ¶ 29. Although Amarin did not elect to avail itself of this opportunity prior to filing the present lawsuit, FDA's June 5 Letter aims to clarify the application of the legal framework and FDA policy to Amarin's proposed speech.

IV. Most of Plaintiffs' Challenges Fail to Present a Case or Controversy

In a pre-enforcement First Amendment challenge, the Article III case or controversy requirement is not met unless Plaintiffs can establish a credible threat of prosecution. *See Susan B. Anthony List v. Driehaus*, 134 S. Ct. 2334, 2342 (2014); *Virginia v. Am. Booksellers Ass'n, Inc.*, 484 U.S. 383, 393 (1988). The June 5 Letter makes clear that FDA does not object to Amarin's distribution of summaries and reprints of the ANCHOR trial and journal article reprints, if Amarin takes the reasonable steps outlined in the Letter and ensures that such dissemination is truthful and non-misleading. June 5 Letter at 10. Assuming Amarin takes those steps, then for all but one of the communications proposed in the Complaint, FDA would not rely on such communications in an enforcement action against Amarin. Woodcock Decl. ¶ 30.

---

[6] *Amicus* Washington Legal Foundation ("WLF") asserts, relying on a district court order issued in 1999, that FDA is currently enjoined from relying on its Reprints Guidance regarding the dissemination of medical texts and journal reprints containing information about unapproved uses. WLF Br. at 21-22. As an initial matter, this Court should not consider issues raised by *amici* that were not raised by Plaintiffs. *See Lehman XS Trust, Series 2006-GP2 v. Greenpoint Mortgage Funding, Inc.*, No. 12 CIV. 7935 ALC, 2014 WL 265784, at *2 (S.D.N.Y. Jan. 23, 2014) ("An amicus cannot initiate, create, extend, or enlarge issues.") (quotation omitted). Regardless, WLF's position is incorrect. *See Washington Legal Found. v. Henney*, 128 F. Supp. 2d 11, 15 (D.D.C. 2000) ("[T]he injunction has been wholly vacated by the Court of Appeals.").

Amarin thus cannot show a credible threat of prosecution for the dissemination of information to which the June 5 Letter does not object. To show a credible threat of prosecution, there must be "an actual and well-founded fear" that the challenged statute or regulation will be enforced against the plaintiff in the manner anticipated. *Am. Booksellers Ass'n*, 484 U.S. at 393. Courts dismiss pre-enforcement First Amendment cases for lack of justiciability where the prosecuting authority has represented that it would not enforce the law against the plaintiff in the manner alleged.[7] *See Am. Library Ass'n v. Barr*, 956 F.2d 1178, 1196 (D.C. Cir. 1992) (no standing when government represented it would not invoke challenged provisions against plaintiffs); *Rafferty v. Judicial Council for the Dist. of Columbia*, 131 F.3d 219, 221 (D.C. Cir. 1997) (given council commitments resolving plaintiff's stated concerns, "we need not and do not review the Council's interpretation of the statute, or advise on the merits of [plaintiff's First and Fifth Amendment] constitutional challenge.").[8]

---

[7] The *amici* set forth various arguments regarding justiciability and the weight that should be afforded the June 5 Letter. *See* Brief of the Medical Information Working Group ["MIWG"] as *Amicus Curiae* in Support of Plaintiffs, Dkt. No. 35, at 21-25; *Amicus Curiae* WLF's Memorandum of Law in Support of Plaintiffs' Motion for Preliminary Injunction, Dkt. No. 43, at 18-21; Brief of *Amicus Curiae* Pharmaceutical Research and Manufacturers of America ["PhRMA"] in Support of Plaintiffs' Motion for Preliminary Injunction, Dkt. No. 48, attached to the Declaration of Guy Petrillo dated June 17, 2015, at 17-21. However, none of the *amici* cites any authority to the contrary of that described above. Nor do they cite any applicable authority to support their apparent position that FDA is not entitled to provide clarification to Amarin about the communications at issue during the course of this litigation; to the contrary, it is entirely appropriate for FDA to provide such information to Plaintiffs and the letter narrowed the scope of the dispute before this Court.

[8] Plaintiffs also cannot show a credible threat of prosecution with respect to two of the regulations on which they rely to argue that FDA expanded the reach of the FDCA to prohibit truthful speech. Pl. Br. at 10-11. The FDCA requires prescription drug advertisements to contain "a true statement" of "such . . . information in brief summary relating to side effects, contraindications, and effectiveness" as FDA may require by regulation. 21 U.S.C. § 352(n). For clarification, 21 C.F.R. § 202.1(*l*)(2) describes the distinction between labeling as opposed to advertising, provided that the other statutory requirements for labeling are met. This regulation

Nor can the Doctor Plaintiffs show that their rights to receive information are injured in any way. *See In re Dow Jones & Co.*, 842 F.2d 603, 608 (2d Cir. 1988) (the right to receive speech is "entirely derivative" of the rights of the speaker). Accordingly, all allegations that rely on Amarin's incorrect assumption that it could not disseminate summaries of the ANCHOR trial results and certain reprints under any circumstances are not justiciable.[9]

Nor have Plaintiffs shown a live controversy as to their FCA claim, given their own representations of the facts, or as to their Fifth Amendment claim, in light of the June 5 Letter. These issues are discussed in further detail below in Sections V.B. and V.C.[10]

V. Plaintiffs Are Not Entitled to a Preliminary Injunction Because They Are Not Likely to Succeed on the Merits

A preliminary injunction is an extraordinary and drastic remedy and is never awarded as

---

does not, as asserted by Plaintiffs, *see* Pl. Br. at 10-11, expand the statutory definition of labeling. *See Kordel*, 335 U.S. at 350. In addition, 21 C.F.R. § 202.1(e)(4)(i)(a) provides that statements of effectiveness in advertisements "shall not recommend or suggest" unapproved uses, but it does not proscribe any speech outside that specific context. FDA does not rely on either of these regulations to support its authority over manufacturer communications related to unapproved uses of approved prescription drugs, *see* London Decl. Ex. N (Revised Good Reprint Practices Draft Guidance, § II) (providing a summary of the authority FDA relies on). Accordingly, the FDA does not intend to initiate an enforcement action applying either regulation to Amarin's proposed speech. Woodcock Decl. ¶ 30.

[9] FDA policy recognizes that health care payors, such as formulary committees and insurance companies, also have an interest in obtaining information about unapproved uses. For example, FDA's Unsolicited Requests Guidance applies to requests made by any person or entity that is "completely independent" of the relevant manufacturer, specifically including "health care organizations" and "formulary committees." *See* London Decl. Ex. O (Unsolicited Requests Guidance). However, because Amarin raises only an as-applied challenge regarding communications with health care providers, not payors, this issue is beyond the scope of this lawsuit. *See* MIWG Br. at 7 (raising this issue).

[10] The Government's response to the Complaint is due on July 27, 2015. The Government reserves the right to move to dismiss the Complaint in whole or in part based on these or other arguments, or, if it files an answer, to subsequently move for judgment on the pleadings.

of right. *Munaf v. Geren*, 553 U.S. 674, 689-90 (2008). "[P]laintiff[s] seeking a preliminary injunction must establish that [they are] likely to succeed on the merits, that [they are] likely to suffer irreparable harm in the absence of preliminary relief, that the balance of equities tips in [their] favor, and that an injunction is in the public interest." *Winter v. NRDC*, 555 U.S. 7, 20 (2008); *see Salinger v. Colting*, 607 F.3d 68, 79-80 (2d Cir. 2010). Where the moving parties seek a mandatory injunction that alters the status quo, and that will affect government action taken in the public interest pursuant to a statutory scheme, the movants must make an even more compelling demonstration of entitlement to preliminary relief than is normally required. *Cacchillo v. Insmed, Inc.*, 638 F.3d 401, 406 (2d Cir. 2011). Moreover, a court deciding a preliminary injunction motion "should pay particular regard for the public consequences in employing the extraordinary remedy of injunction." *Winter*, 555 U.S. at 24.

A. Amarin's Proposed Speech Is Not Unconstitutionally Infringed

As explained in the June 5 Letter, the communications at issue are either potentially misleading (at best) or potentially evidence of a new intended use. Because Plaintiffs do not claim that Amarin has a right to disseminate misleading information, the only issue before the Court is whether the First Amendment permits the Government to rely on Amarin's dissemination of the communications at issue in conjunction with its distribution of Vascepa as evidence that Amarin intends a new use for Vascepa.[11] It unquestionably does: the evidentiary use of speech to prove intent is constitutional under the First Amendment. In the alternative,

[11] Plaintiffs do not dispute that Amarin cannot disseminate false or misleading statements about Vascepa. *See* Pl. Br. at 18-19, Compl. ¶¶ 122, 125-26. Although the communications at issue are not inherently misleading, whether they will actually be misleading depends on future factual contingencies whose outcome cannot presently be known. Similarly, it cannot be known whether the communications at issue will constitute evidence of intended use. Such determinations must be made on a case-by-case basis, depending on an analysis of the surrounding circumstances.

even if the Court were to apply the *Central Hudson* factors for restrictions on commercial speech (it should not), FDA's application of its statutory and regulatory authorities to Amarin's proposed speech is permissible because it advances substantial public health interests and is narrowly tailored.

1. The First Amendment Allows the Government to Rely on Amarin's Dissemination of the Communications at Issue as Evidence of Intended Use

FDA has not approved Vascepa to reduce the risk of coronary heart disease because Amarin has not provided substantial scientific evidence supporting the effectiveness of the drug for that indication, the showing required by the FDCA for approval of new drugs. *See* 21 U.S.C. § 355(d) & (e); *Hynson*, 412 U.S. at 613-14. Amarin nevertheless wishes to communicate to healthcare professionals, in conjunction with its distribution of Vascepa, that "[s]upportive but not conclusive research shows that EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease." Compl. ¶ 124. Amarin relies primarily on the results of a clinical trial, the "JELIS trial" to suggest that scientific support for the heart disease claim has increased since FDA evaluated it for dietary supplements. Compl. ¶ 44. That trial, however, had numerous design limitations and, during Amarin's administrative appeal, FDA determined that Amarin could not use the results of the JELIS trial as support for or against the use of triglyceride levels as a substitute for cardiovascular risk reduction. Rosebraugh Decl. ¶¶ 25-27. Despite these findings, Amarin seeks to disseminate the heart disease claim in conjunction with the ANCHOR trial results, which would "perpetuate the unsubstantiated claim that Vascepa confers a clinical benefit by lowering triglyceride levels in patients with cardiovascular disease or at risk for

cardiovascular disease and on statin therapy." Woodcock Decl. ¶ 37. The First Amendment does not require that result.[12]

To appreciate why Amarin's First Amendment claim regarding the heart disease claim is without merit, it is critical to understand the regulatory significance of speech by manufacturers regarding unapproved uses of approved drugs. As the Second Circuit held in *Caronia*, the FDCA does "*not* prohibit[] and criminaliz[e] the truthful off-label promotion of FDA-approved prescription drugs." 703 F.3d at 168-69 (emphasis added). Thus, the issue in this case is not whether it would be constitutional for the FDCA to make truthful speech regarding unapproved uses a crime. The FDCA does not do so.

Instead, the role of truthful speech regarding unapproved uses is strictly an evidentiary one. "It is unlawful for a manufacturer to introduce a drug into interstate commerce with an intent that it be used for an off-label purpose."[13] *Wash. Legal Found. v. Henney*, 202 F.3d 331, 332 (D.C. Cir. 2000). And it is likewise unlawful for a manufacturer to distribute a drug in interstate commerce if the drug's labeling lacks adequate directions for its intended uses. *See supra*, Section III. Under the FDCA a manufacturer's intended uses for a drug "may be derived or inferred from labeling, promotional material, advertising, and 'any other relevant source.'"

---

[12] MIWG's claim that FDA purportedly restricts "manufacturers' ability to communicate certain truthful, non-misleading information about on-label uses" is not relevant to this dispute, which, as raised by Amarin, concerns solely communications about off-label (*i.e.*, unapproved) uses of Vascepa. MIWG Br. at 9-10. Moreover, communications regarding on-label (*i.e.*, approved) uses of drugs involve a different set of regulatory issues as well as separate guidance documents than those involved in this case. *See, e.g.*, Risk Information Guidance Link: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM400104.pdf.

[13] Evidence of a new intended use for Vascepa would establish only one element of an FDCA violation. For example, to establish an FDCA violation under 21 U.S.C. § 331(a), the Government also would have to prove the distribution of Vascepa in interstate commerce.

Nat'l Nutritional Foods, 557 F.2d at 334. Thus, when a manufacturer engages in speech regarding an unapproved use, such speech is potentially relevant to determining whether the unapproved use is an intended one, with the regulatory consequences for the distribution of the drug that flow from such a determination.

The use of a company's speech as a basis for inferring intent under the FDCA has repeatedly been approved by the courts, including the Second Circuit. *See, e.g.*, *Nat'l Nutritional Foods*, 557 F.2d at 334; *Nutritional Health Alliance v. Shalala*, 144 F.3d 220, 228 (2d Cir. 1998); *United States v. Storage Spaces Designated Nos. "8" and "49,"* 777 F.2d 1363, 1366-67 (9th Cir. 1985); *Action on Smoking & Health v. Harris*, 655 F.2d 236, 238-39 (D.C. Cir. 1980); *United States v. Millpax, Inc.*, 313 F.2d 152, 154 (7th Cir. 1963). There is no room for Amarin to argue that this evidentiary use of manufacturer speech offends the First Amendment.

Indeed, the Supreme Court and the D.C. Circuit both have rejected claims, like Amarin's, that the First Amendment prohibits the Government from using a defendant's speech as evidence of intent. *See Wisconsin v. Mitchell*, 508 U.S. 476 (1993); *Whitaker v. Thompson*, 353 F.3d 947 (D.C. Cir. 2004). In *Mitchell*, a criminal defendant's sentence was enhanced on the ground that his actions were racially motivated. 508 U.S. at 480. The government proved his racial animus by introducing evidence of his speech. *Id.* The defendant argued that enhancing his sentence on the basis of his speech violated the First Amendment. *Id.* at 481. The Supreme Court unanimously rejected that argument, 508 U.S. at 479, holding categorically that "[t]he First Amendment . . . does not prohibit the evidentiary use of speech to establish the elements of a crime *or to prove motive or intent*." *Id.* at 489 (emphasis added).

Whitaker, in turn, relied on *Mitchell* to reject a First Amendment challenge in an FDCA case—one in which a dietary supplement manufacturer challenged FDA's decision that it could

not make labeling claims that showed the product was intended to treat a disease and therefore was a drug. 353 F.3d at 948-49. The D.C. Circuit determined that the manufacturer's proposed claims were not protected commercial speech, holding that "th[e] use of speech to infer intent, which in turn renders an otherwise permissible act unlawful, is constitutionally valid" and hence "it is constitutionally permissible for the FDA to use speech [by the manufacturer] . . . to infer intent for purposes of determining that [the manufacturer's] proposed sale . . . would constitute the forbidden sale of an unapproved drug." *Id.* at 953; *accord United States v. Article of Drug Designated B-Complex Cholinos Capsules*, 362 F.2d 923, 927 (3d Cir. 1966); *United States v. Cole*, No. 3:13-CV-01606-SI, 2015 WL 471594, at *4 (D. Or. Feb. 5, 2015); *United States v. Livdahl*, 459 F. Supp. 2d 1255, 1267-68 (S.D. Fla. 2005); *United States v. Lane Labs-USA, Inc.*, 324 F. Supp. 2d 547, 579-80 (D.N.J. 2004).

There is nothing novel or controversial about these decisions. Evidentiary use of a party's speech to draw inferences about the party's intent is routinely approved in this Circuit. *See, e.g.*, *United States v. Pierce*, No. 13-3687-CR, 2015 WL 2166141, at *6 (2d Cir. May 11, 2015) (Chin, J.) (use of defendant's rap lyrics as evidence of motive in RICO case did not violate First Amendment because "here the speech is not 'itself the proscribed conduct.'" (quoting *Caronia*, 703 F.3d at 161)); *Sassaman v Gamache*, 566 F.3d 307, 312 (2d Cir. 2009) (discriminatory intent in employment discrimination case); *United States v. Sisti*, 91 F.3d 305, 313 (2d Cir. 1996) (intent to obstruct in criminal obstruction case); *United States v. Lee*, 916 F.2d 814, 818 (2d Cir. 1990) (intent to abandon property in narcotics distribution case).

In the face of this well-established law, Plaintiffs rely almost exclusively on the Second Circuit's decision in *Caronia* to try to establish likelihood of success on the merits. *See* Pl. Br. at 16-20. *Caronia*, however, did not decide whether it would be constitutionally permissible for the

Government to consider speech to be evidence of intended use. Indeed, citing *Mitchell*, 508 U.S. at 489, *Caronia* assumed, without deciding, that "the government *can* offer evidence of a defendant's off-label promotion to prove a drug's intended use." 703 F.3d at 161 & n.8 (emphasis added).

That is all that the FDA reserved the right to do here in its June 5 Letter—the right to consider the speech at issue as potential evidence of intended use in connection with a misbranded or unapproved new drug charge. As explained above, it is settled that speech *may* be relied on as evidence in this fashion. The Court need go no further to dispose of Amarin's First Amendment claim.

2. The First Amendment Allows the Government to Prohibit Any False or Misleading Statement About Vascepa

Commercial speech does not enjoy any constitutional protection if it is false or misleading, and Amarin does not assert a constitutional right to market Vascepa in a misleading manner. *See* Pl. Br. 18-19, Compl. ¶¶ 122, 125-26; *Central Hudson*, 447 U.S. at 563; *Caronia* 703 F.3d at 164, 167; *see also United States v. Harkonen*, 510 F. App'x 633, 636 (9th Cir. 2013); *United States v. Caputo*, 517 F.3d 935, 940 (7th Cir. 2008). As the June 5 Letter explains, summaries of studies that are biased or omit material information would be misleading. June 5 Letter at 6. It would similarly be misleading for Amarin to suggest or imply, for example, that studies using products other than Vascepa were studies of Vascepa itself. *Id.* at 8. Also misleading would be a suggestion 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. Rosebraugh Decl. ¶ 25-27; Woodcock Decl. ¶ 37. And if Amarin were to disseminate the ANCHOR summaries, journal articles, and the

heart disease claim in a misleading manner in connection with the distribution of Vascepa, such conduct undisputedly would not be protected by the First Amendment.

3. The Challenged FDCA Provisions Meet First Amendment Standards for Regulation of Commercial Speech As Applied To Amarin

As *Mitchell* and *Whitaker* demonstrate, courts do not consider the evidentiary use of speech to show intent to be a regulation of speech and, accordingly, they do not analyze such use under *Central Hudson*. The Court thus need not and should not even consider *Central Hudson* and *Caronia*. But, even if the use of speech as evidence of intent had not received such overwhelming and specific judicial imprimatur as to control the outcome here, the FDCA and its implementing regulations would pass muster even if analyzed under *Central Hudson* as commercial speech restrictions.[14]

Central Hudson permits governmental restrictions on commercial speech that advance a "substantial" government interest and are no "more extensive than is necessary to serve that interest." 447 U.S. at 566. This standard does not require "the least restrictive" regulatory means, nor a perfect fit between means and ends. *See Clear Channel Outdoor, Inc. v. City of New York*, 594 F.3d 94, 104 (2d Cir. 2010). "[W]hat is 'require[d] is a fit between the legislature's ends and the means chosen to accomplish those ends—a fit that is not necessarily perfect, but reasonable; that represents not necessarily the single best disposition but one whose

[14] In their brief, Plaintiffs "recognize that *Central Hudson*'s intermediate scrutiny standard controls here but reserve[d] the right to argue that strict scrutiny applies." Pl. Br. at 16 n.7. PhrMA nevertheless asserts in its *amicus* brief that the restrictions at issue are "presumptively unconstitutional." PhrMA Br. at 13 (citing *Sorrell*, 131 S. Ct. at 2665 and *Caronia*, 703 F.3d at 162-63). While no level of First Amendment scrutiny should be applied to the restrictions at issue here, *see supra*, Section V.A.1, to the extent any is applied, it should be *Central Hudson*. This position is supported by *Caronia*, which applied *Central Hudson* even after concluding that in the circumstances of that case the government's construction of the relevant provisions of the FDCA regarding misbranding imposed "content- and speaker-based restrictions on speech." *Caronia*, 703 F.3d at 164, 165, 166-69.

scope is in proportion to the interest served.'" *Id.* (quoting *Bd. of Trustees v. Fox*, 492 U.S. 469, 480 (1989)). The narrow tailoring requirement is met so long as the regulation "promotes a substantial government interest that would be achieved less effectively absent the regulation, and is not substantially broader than necessary to achieve the government's interest." *Marcavage v. City of New York*, 689 F.3d 98, 106 (2d Cir. 2012) (quoting *Ward v. Rock Against Racism*, 491 U.S. 781, 799-800 (1989) (internal quotation marks omitted)).

FDA here has established that applying the FDCA to the communications at issue in this case would further important public health interests, *see generally* Rosebraugh and Woodcock Decls., a showing that greatly exceeds even the *Central Hudson* test and a finding that the Court need not make to rule for the Government. Rather, even under *Central Hudson*, the Court merely must "judge the validity of the restriction in this case by the relation it bears to the general problem" of maintaining the safety and reliability of the nation's drug supply. *Greater New Orleans Broad. Ass'n, Inc. v. United States*, 527 U.S. 173, 194 n.8 (1999) (quoting *United States v. Edge Broadcasting Co.*, 509 U.S. 418, 429-430 (1993)) ("To be sure, in order to achieve a broader objective such regulations may incidentally, even deliberately, restrict a certain amount of speech not thought to contribute significantly to the dangers with which the Government is concerned."); *see also* S REP. 1744, at 35-36 (discussing main purposes of 1962 Amendments) (London Decl. Ex. Z).

To the extent the Court applies the *Central Hudson* factors, which it should not in light of the above discussion regarding the use of speech as evidence of intent, the outcome in *Caronia* is not controlling. *Caronia* did not involve speech that was shown at trial to be potentially false or misleading and did not involve the use of speech as evidence of intent. Instead, it involved the constitutionality of a "complete and criminal ban on off-label promotion." 703 F.3d at 167.

Caronia addressed only the legal theory presented to the jury there—*i.e.*, jury instructions and the Government's closing argument that "left the jury to understand that Caronia's speech was itself the proscribed conduct." *Id.* at 161. The Court of Appeals expressly did not rule on the constitutionality of using off-label promotion as evidence of intended use,[15] *id.* at 161 & n.8, and its First Amendment holding was confined to truthful, non-misleading speech, *id.* at 165 n.10.

Moreover, unlike here, the *Caronia* court did not have the benefit of a Government declaration demonstrating that the communications at issue might be misleading. *Caronia*, 703 F.3d at 168; *contrast* Woodcock Decl. ¶ 30-31, 37, 41 (addressing the potentially misleading nature of the communications at issue here). And—also unlike here—the *Caronia* court was not presented with any declarations explaining how the communications at issue would undermine the premarket approval regime and the attendant public interests it furthers, and why various potential alternatives would fail to protect those interests. *Contrast* Woodcock Decl. ¶¶ 42-52.

In concluding that "[t]he government's interests could be served equally well by more limited and targeted restrictions on speech," 703 F.3d at 168, *Caronia* acknowledged that there could be a different result in a future case that, like this one, presented narrower speech restrictions (assuming *arguendo* that this case involves speech restrictions). To fail to give weight to these many and important distinctions would render a dead letter the *Caronia* panel's caution that "we do not hold, of course, that the FDA cannot regulate the marketing of

[15] The Court of Appeals in *Caronia* assumed without deciding that the government may offer evidence of off-label promotion to prove the intended use of a drug, but did not rule on the issue because it concluded that the case as presented to the jury did not rely on speech solely as evidence of intent. 703 F.3d at 161.

prescription drugs."[16] *Id.* at 169. Accordingly, *Caronia* does not control the *Central Hudson* analysis.

a) The Requirement That Drugs Be Safe and Effective for Each of Their Intended Uses Directly Advances Substantial Public Health Interests

When the government restricts truthful commercial speech, it must identify a substantial governmental interest for doing so, and the restriction must directly advance that interest. *Central Hudson*, 447 U.S. at 566. The government interest requirement unquestionably is met here, as there can be no doubt that the government "interests in drug safety and public health are substantial." *Caronia*, 703 F.3d at 166; *accord Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 369 (2002) ("Preserving the effectiveness and integrity of the FDCA's new drug approval process is clearly an important governmental interest, and the Government has every reason to want as many drugs as possible to be subject to that approval process."). In turn, Dr. Woodcock's declaration describes in detail how FDA's contemplated application of its authorities directly advances these substantial interests. Woodcock Decl. ¶¶ 4-22, 31, 33-38. As explained above, no similar showing was made in *Caronia*.

The numerous public health interests at stake here are unquestionably substantial. First, the Government has a substantial interest in motivating robust scientific research that allows for the evaluation of whether a drug is safe and effective for a particular use. Because of the considerable time and resource commitment required to complete rigorous studies to support a new approval (and many of those studies ultimately fail), manufacturers might well decide not to

[16] If this Court relies on *Caronia* in entering a preliminary injunction, then such injunction should address only the possibility of a *criminal* enforcement action against Amarin, because *Caronia*'s holding was limited to only the criminal provisions of the FDCA. *See Caronia*, 703 F.3d at 163 ("Criminal regulatory schemes, moreover, warrant even more careful scrutiny."); *id.* at 167 (noting availability of non-criminal penalties as alternative).

pursue such studies if they were free to market drugs by making unsubstantiated claims about unapproved uses.[17] *See* Woodcock Decl. ¶ 5. FDA's premarket approval and misbranding provisions advance public health by motivating firms to develop robust scientific data regarding the safety and efficacy of each particular proposed use of a given drug. *See* Woodcock Decl. ¶¶ 6-7. By encouraging companies to develop robust scientific data, in fact, the FDCA actually *furthers* the First Amendment interest in fostering a marketplace of ideas.

Second, Congress determined that FDA must review the safety and effectiveness of *each* intended use of certain medical products *before* the product is introduced into interstate commerce for that use. Such premarket review can *prevent* harm; post-market remedies are often taken only after harm has occurred. *See* Woodcock Decl. ¶¶ 8-13; *see also USV Pharm. Corp. v. Weinberger*, 412 U.S. 655, 665 (1973) (describing pre-1962 post-market enforcement as a "slow, cumbersome method" and "utterly unsuited to the need"); *Drug Industry Antitrust Act Hearings*, at 171 (London Decl. AA).

Third, the history of public health tragedies caused by medical products demonstrates the need to prevent unscrupulous players from making deceptive or unsubstantiated claims about medical products. This very potential for harm caused Congress to direct FDA, as a government agency with the appropriate scientific expertise, to independently review applications for premarket approval and subject them to robust standards. *See* Woodcock Decl. ¶¶ 14-15; *see also*, *e.g.*, S. REP. No. 1744, at 37 ("Leading physicians testified that . . . the marketing of a safe

[17] Indeed, before the 1962 Amendments, companies typically did not conduct definitive, rigorous studies of drug effectiveness before widely promoting and distributing them. *See* ADMINISTERED PRICES: DRUGS: REPORT OF THE SEN. COMM. ON THE JUDICIARY, MADE BY ITS SUBCOMM. ON ANTITRUST AND MONOPOLY, PURSUANT TO S. RES. 52, S. REP. NO. 448, 87th Cong. 182, 187, 188 & n.87, 189, 203 (1961) (London Decl. BB).

but ineffective drug may well be positively injurious to the public health. When an ineffective drug is prescribed, it is usually in place of an older but effective drug.") (London Decl. Ex. Z).

Fourth, the Government has a substantial interest in ensuring that drugs bear labeling that contains both accurate information and adequate instructions for use. As part of the drug approval process, FDA approves labeling that conveys important information related to the safe and effective use of the product for its intended use, such as indications, dosage, precautions, warnings, and contraindications, as well as information regarding the level of efficacy for each approved intended use. *See* 21 U.S.C. §§ 355(b) & (d), 352(f)(1); Woodcock Decl. ¶ 17. If a manufacturer distributes a drug for an unapproved use, in violation of 21 U.S.C. § 355(a), then by definition the drug lacks FDA-approved labeling for that use; without such labeling, each physician would bear the burden of trying to evaluate the universe of available data—in its highly variable quality—to determine not just whether to use the drug, but how specifically to administer and monitor it. Woodcock Decl. ¶ 17. Additionally, if a manufacturer distributes a drug for a new intended use, the only way for the manufacturer to avoid liability for misbranding is to demonstrate the safety and efficacy of the drug for the new use through the drug approval process and to implement new labeling that provides adequate directions for use as part of that process. *See* 21 U.S.C. § 352(f)(1); 21 C.F.R. §§ 201.5, 201.100(c)(1). The Government's ability to treat a manufacturer's speech regarding the use of its drug as evidence of intended use (under either a misbranding theory or an unapproved new drug theory) is thus indispensable to implementing the statutory goals of providing labeling with adequate directions for the intended uses of drugs and to ensure the accuracy of drug labeling.

Fifth, the regulatory scheme advances the governmental interest in ensuring that physicians have access to reliable information about the safety and efficacy of drugs. In enacting

the 1962 Amendments, Congress found that even though firms were already prohibited from making false or misleading statements about drugs, they nonetheless frequently manipulated the presentation of information to healthcare professionals in a distorted way to encourage greater use of the product, including for unapproved uses that may have been unsafe or ineffective. *See, e.g.*, *Drug Industry Antitrust Act Hearings* at 67 (expert testimony that "the physician is bombarded with seductive advertising which fails to tell the truth, the whole truth, and nothing but the truth" which can lead to prescriptions of drugs in an unsafe or ineffective manner) (London Decl. Ex. AA); *id.* at 173 ("Obviously, the doctor, no matter how vigilant, cannot protect Mrs. Smith's safety if he has to rely on misinformation."); S. REP. No. 448, at 192-98 (company promoted antibiotic for broad uses despite possibly fatal side effect of anaplastic anemia, misrepresenting nature of FDA-required warning) (London Decl. Ex. BB); *id.* at 202-22 (companies misrepresented safety of steroid drug and diabetes drug that had severely harmful side effects). FDA therefore monitors the marketing of approved drugs to determine, among other things, whether it is false, misleading, or evidence of a new intended use. *See* Woodcock Decl. ¶ 18.

Moreover, before 1962, reliable information about the safety and efficacy of the vast majority of drugs simply did not exist, *see supra* footnote 17, and Congress required drug companies to generate that information so that it could be made available to physicians. Congress heard testimony from the Secretary of Health, Education, and Welfare that a physician's ability to make treatment decisions for his patients requires "the availability of truthful and complete information" about the effectiveness of new drugs. *Drug Industry Antitrust Act Hearings*, at 173 (London Decl. Ex. AA); *see also id.* at 76; S. Rep. 1744, at 33 (One of 1962 Amendments' three main goals was "[t]o provide physicians with better and more

adequate information about drugs and correlatively to reduce the dissemination of information which is false and misleading.") (London Decl. Ex. Z).

The prohibition on advertising of compounded drugs struck down in *Thompson v. Western States Medical Center*, 535 U.S. 357, 374 (2002), and the prohibition on drug firms purchasing and using prescriber-identifying prescription information struck down in *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653, 2670-71 (2011), can be distinguished on this ground. In *Sorrell*, the restriction was motivated by a "fear that people would make bad decisions if given truthful information." 131 S.Ct. at 2670. In *Western States*, the Court held that the speech restriction could not be justified "by a fear that advertising compounded drugs would put people who do not need such drugs at risk by causing them to convince their doctors to prescribe the drugs anyway." 535 U.S. at 374. (As explained in Part V.A.1, *supra*, those cases can also be distinguished on the ground that this case does not involve a restriction on speech, but involves only the use of speech as evidence of intent, and so *Central Hudson* does not apply.)

Although *Central Hudson* does not require that all of the government's substantial interests be advanced in every case, *see Greater New Orleans*, 527 U.S. at 194, 194 n.8, that showing can be made in this case. As described above, Amarin's distribution of Vascepa for an unapproved use would undermine the premarket approval requirements and the public health interests that those requirements advance. If this Court were to authorize Amarin to make the potentially misleading heart disease claim that Amarin proposes here, for example, Amarin would have much less of an incentive to conduct the REDUCE-IT trial. Woodcock Decl. ¶ 34. If it were possible to circumvent the drug approval process, there would be a strong financial incentive to do so—as noted above, drug clinical trials are enormously expensive and time-consuming, and there is no guarantee that they will demonstrate that the drug is safe and

effective for the investigated use.[18] Although Amarin has stated that it intends to complete the REDUCE-IT trial, *see, e.g.*, Compl. ¶ 67, if Amarin were to stop the REDUCE-IT trial, the medical and scientific community would continue to be deprived of the robust scientific data promised by the trial regarding the safety and efficacy of Vascepa for the use related to cardiovascular disease, as well as the benefit of FDA's independent and rigorous premarket review. *Id.* ¶¶ 34-35. In addition, Vascepa would continue to lack labeling with accurate information about and adequate instructions for the use related to cardiovascular disease. *Id.* ¶ 36.

Amarin's distribution of Vascepa for an unapproved use could mislead physicians and cause them to make ill-informed prescription decisions. *See* Woodcock Decl. ¶ 37. For example, on its face, the heart disease claim does not advise physicians to prescribe Vascepa as an adjunct in combination with statins. Physicians could misapprehend the claim, especially if made in isolation, to mean that Vascepa can be prescribed in lieu of statin therapy, but statin therapy is proven to reduce the risk of cardiovascular events while Vascepa is not. Woodcock Decl. ¶ 37. Thus, the relief requested by Amarin could cause patients not to receive a drug that

[18] The financial incentives clearly are significant; indeed, Amarin's recent SEC filings describe payment agreements that seemingly incentivize executives to avoid the need to complete this sort of testing. After FDA rescinded the SPA agreement for the ANCHOR trial (and while Amarin's appeal of this rescission was pending), *see* London Decl., Ex. J, Amarin offered an incentive of $150,000 if certain officers "secured a declaratory judgment from a court of competent jurisdiction on or before December 31, 2014[,] confirming the Company's ability to inform physicians of the clinical data from the Company's ANCHOR Phase III clinical trial notwithstanding an FDA failure to approve the Company's NDA for the ANCHOR indication by December 31, 2014." London Decl. Ex. W (excerpt from Form DEF 14A Proxy Statement at 30 (April 30, 2014)). Amarin's Proxy Statement for the period ending on July 6, 2015, extended the incentive bonuses to the officers if "the Company is able to expand its right to market Vascepa such as through inclusion of the clinical data from the Company's ANCHOR clinical trial in the Vascepa label for the current (MARINE) indication on or before December 31, 2015. London Decl. Ex. X (excerpt from Form DEF 14A Proxy Statement at 45-46 (April 24, 2015)).

has been approved as safe and effective for reducing the risk of cardiovascular disease, such as a statin. *Id.* In addition, the statement—"Supportive but not conclusive research shows that EPA and DHA may reduce the risk of coronary heart disease"— draws conclusions from the research relating to EPA and DHA without providing the underlying research itself. *See* Woodcock Decl. ¶ 41. It therefore invites physicians to rely on the conclusions drawn by the manufacturer instead of analyzing and interpreting the data using their own professional judgment. *Id.* Finally, Amarin's presentation of the heart disease claim in conjunction with its dissemination of the ANCHOR trial summary or reprints about the ANCHOR trial could lead physicians to conclude that the "[s]upportive but not conclusive research" referenced in the heart disease claim includes the ANCHOR trial results when, in fact, the ANCHOR trial results "do not 'show that EPA . . . may reduce the risk of coronary heart disease.'" *Id.* ¶ 37. This use of 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.*

Amarin argues that the FDCA does not directly advance public health interests, because FDA does not object to dietary supplement firms using Amarin's proposed heart disease claim on EPA-containing dietary supplements.[19] Pl. Br. at 19-20. Amarin ignores the critical reality

[19] Plaintiffs also appear to argue that public health interests are not directly advanced because HHS authorizes reimbursement under federal health care programs for some unapproved uses. Pl. Br. at 21. This is incorrect. The two different regulatory schemes at issue here—HHS's determinations regarding whether particular drug treatments are reimbursable and FDA's role in approving drugs—are complementary and it is logical that health plan coverage decisions allow physicians flexibility in treating patients whereas drug-approval and marketing decisions hinge on the different considerations set forth in the Woodcock Declaration. *See* Woodcock Decl. ¶ 45 ("There would be no governmental interest in virtually eliminating the prescribing of unapproved uses for one subset of the population [those under Medicaid or Medicare] but having it continue for the remainder of the population.").

that drugs present markedly different considerations from dietary supplements. *See* Woodcock Decl. ¶¶ 30-31, 33. When the D.C. Circuit directed FDA to apply a scientific substantiation standard for claims regarding dietary supplements that was lower than the statutory standard for drug claims, it noted that drugs "appear to be in an entirely different category" than dietary supplements. *Pearson v. Shalala*, 164 F.3d 650, 656 & n.6 (D.C. Cir. 1999). A drug is "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease." 21 U.S.C. § 321(g)(1)(B). In contrast, dietary supplements are merely intended to maintain healthy dietary practices. *See* 21 U.S.C. § 321(ff); June 5 Letter at 9 & n. 23. Drugs also are typically administered to a more vulnerable population than the general population that may use dietary supplements. *See* Dietary Supplement Health and Education Act of 1994, Pub. L. 103-417, 108 Stat. 4325, Sec. 2 Findings (Oct. 25, 1994). Here, for example, Amarin is seeking to market Vascepa as a drug intended to treat patients who are already being treated with statins to lower cholesterol, but continue to have or be at risk for cardiovascular disease. Yet, FDA has found on multiple occasions that the heart disease claim did not meet the statutory standard of significant scientific agreement as the claim is based on "less persuasive studies." Woodcock Decl. ¶ 33. The heart disease claim thus presents risks, because, as the D.C. Circuit observed in *Pearson*, "the potential harm [posed by drugs] presumably is much greater" than that posed by dietary supplements. 164 F.3d at 656 n.6.

These considerations amply justify a more cautious approach to drug approval and promotion, and the applicable statutory scheme recognizes this necessity. Unlike drugs, there is no statutory requirement of premarket approval for dietary supplements to be distributed. *See* 21 U.S.C. § 301 *et seq.* In addition, as a result of *Pearson*, claims about dietary supplements are held to a much lower standard (credible evidence) than the robust evidentiary requirement for

drugs (substantial evidence) or the intermediate standard that FDA applies to reprints. *See* 21 U.S.C. § 355(d) & (e); Woodcock Decl. ¶¶ 31-32. Unlike for drug claims, qualified health claims "can be made [for dietary supplements and foods] under some circumstances even when the weight of the scientific evidence is against the claim, provided there is some credible evidence supporting it." Woodcock Decl. ¶ 33. Indeed, the June 5 Letter advised Amarin that if it "were to repackage and re-label [its] product as a dietary supplement" and ensure that other relevant conditions were met, "FDA would not object to your inclusion on that dietary supplement of the" heart disease claim. June 5 Letter at 10. Plaintiffs thus conflate two separate regulatory regimes and seek to make Amarin subject only to the aspects of each regime that it finds convenient—an approach that is unsupported by law and contrary to logic and sound public health policy.

b) The FDCA as Applied to Vascepa Is Narrowly Drawn and Not More Excessive Than Necessary; Any Alternative Would Be Ineffective or Impractical

The FDCA and its regulations are narrowly tailored to promote important public health interests without placing unnecessary burdens on First Amendment interests. *See* Woodcock Decl. ¶¶ 20-22, 24. They encourage robust scientific research that leads to medical advances and enriches the marketplace of ideas. At the same time, they do not reach all, or even virtually all, truthful and non-misleading speech by manufacturers regarding unapproved uses of their drugs. Assuming other statutory requirements are met, the dissemination of information about an unapproved use would not, by itself, cause a violation of the FDCA when such information is neither false nor misleading and is not relevant, or sufficient, to infer a new intended use.

The touchstone for determining the regulatory consequences of truthful speech about unapproved uses is the concept of intended use. Statements in a manufacturer's labeling about

an unapproved use of an approved drug do not trigger the FDCA's premarket approval requirements unless they "prescribe[]," "recommend[]," or "suggest[]" the unapproved use, thereby potentially showing that the use is an intended one. *See* 21 U.S.C. §§ 321(p), 355(a). Similarly, a manufacturer's statements about unapproved uses do not render the drug misbranded for lack of adequate directions for use unless they establish, by themselves or together with other evidence, that the unapproved use is an intended one. *See* 21 U.S.C. § 352(f)(1). If the contents of the manufacturer's speech and the surrounding circumstances do not show that the manufacturer intends the unapproved use, then the manufacturer is free to engage in the speech without exposing itself to liability under the Act. FDA's guidance documents offer assistance to manufacturers by identifying circumstances in which the dissemination of information regarding unapproved uses is *not* regarded as establishing an intended use and therefore does not render the manufacturer liable for distribution of an unapproved or misbranded drug. These safe harbors, which have their roots both in the underlying statutory and regulatory scheme and in FDA's responsible administration of that scheme, provide room for manufacturers to disseminate truthful and non-misleading scientific information about unapproved uses in ways that are not a mere pretext for promotion of the unapproved use. In the June 5 Letter, FDA has further clarified how it would apply the legal framework and its policies to Amarin's proposed speech.

The FDA's application of the FDCA to the communications at issue is fully consistent with the First Amendment, and the June 5 Letter makes clear that Amarin retains numerous avenues to disseminate truthful and non-misleading information relating to unapproved uses of Vascepa, including most of the communications proposed in this action. In addition, to the extent the Doctor Plaintiffs want information regarding unapproved uses of Vascepa, they are free to ask Amarin, and FDA would not rely on Amarin's truthful and non-misleading response

as evidence of intended use or as a false and misleading communication that misbranded the product.[20] June 5 Letter at 5 n.13. Finally, FDA has examined alternative approaches (only one of which is suggested by Plaintiffs) and, as explained below, has rejected them as impractical, ineffective, unrealistic, or based on inaccurate assumptions.

i) Plaintiffs' Proposed Reliance on Disclaimers by Drug Manufacturers Would Be Ineffective

FDA has considered and finds inadequate and unacceptable Plaintiffs' only proposed more narrow alternative approach, namely, permitting or requiring disclaimers. Pl. Br. at 20. Governmental restrictions of commercial speech are appropriate where the government has determined that less restrictive alternatives would be ineffective. *Cf. Fox*, 492 U.S. at 478 ("[W]e have been loath to second-guess the Government's judgment" regarding need for particular regulations of commercial speech.)

As FDA concluded was true here, warnings and disclosures can help to provide material information regarding data and their value, but they are not always effective in curing misleading impressions. Woodcock Decl. ¶ 48. Nor do they protect all of the public health interests underlying premarket review. *Id.* For example, relying on disclaimers would permit firms to bypass the premarket review process for new intended uses once the product was approved for any use by disclosing that the use is unapproved or including certain warnings. *Id.* This would undermine the Government's ability to incentivize robust research, to require premarket safety and effectiveness review for each use, and to develop appropriate instructions for use. *Id.* In this case, for example, Amarin could forego the REDUCE-IT trial and not pursue an sNDA for the

[20] Further, a summary of the ANCHOR study has been published, *see* Woodcock Decl. ¶ 39, and Amarin has made the results of the ANCHOR study available on its corporate website and distributed it widely at scientific conferences. *See* London Decl. ¶¶ 29-30, Ex. Y.

now-unapproved use related to cardiovascular disease. *Id.* ¶ 34. Disclaimers, moreover, would do nothing to address the problems caused by the distribution of drugs that lack adequate directions for use.

In holding that disclaimers are appropriate for dietary supplements, the D.C. Circuit took pains to emphasize that dietary supplements are different from drugs. *Pearson*, 164 F.3d at 656 & n.6. As *Pearson* recognizes, prescription drugs can lead to serious physical harm when used for an inappropriate condition or in the wrong way. In the context of drugs, disclaimers are not sufficient to cure the potentially misleading effect of conclusory statements, especially when they are based on weak scientific evidence. Woodcock. Decl. ¶¶ 37, 41, 48. Therefore, it is wrong to conclude, as Amarin appears to, *see* Pl. Br. at 20, that the logic of *Pearson* can be applied to drugs.

ii) Other Alternatives Including All Identified in *Caronia* Likewise Would Be Ineffective and Unfeasible and Are Not Even Proposed by Plaintiffs

Plaintiffs fail to identify or advance any other suggested alternative measures that they believe would meet governmental public health needs while imposing fewer restrictions on Plaintiffs' speech or ability to obtain information from Amarin. In discharging its regulatory responsibilities, however, FDA has reviewed other alternatives—including all of those identified in *Caronia*, 703 F.3d at 168—but has found them all inadequate to meet public health needs, and therefore not viable less restrictive alternatives to the regulatory approach adopted by FDA.[21]

First, relying on Government-issued or mandated warnings or disclaimers or specific use prohibitions will not adequately protect the public health. As noted, when a manufacturer begins

[21] As explained above, the *Caronia* court had no record of FDA's position on these alternatives, as the Woodcock Declaration provides here.

to distribute a drug for an unapproved use, there may be insufficient reliable information to determine whether the drug is safe or effective for that use. By the time information is known regarding which (if any) unapproved uses of a drug are safe and effective, as opposed to dangerous or worthless, it is already too late as some consumers have already been exposed or harmed. Woodcock Decl. ¶ 46; *see also* Aaron S. Kesselheim, Michelle M. Mello, *Prospects for Regulation of Off-Label Drug Promotion in an Era of Expanding Commercial Speech Protection*, 92 N.C. L. REV. 1539, 1594 (2014) ("It defies understanding how the FDA could develop "safety tiers" for off-label uses of drugs since by very definition these are uses for which all of the data that manufacturers purport to have amassed are not provided to the FDA for review."). The same obstacle would be present if the Government attempted to identify and prohibit especially dangerous or concerning unapproved uses. Woodcock Decl. ¶ 46.

Such an alternative would restrict the FDA to the pre-1962 reality of pursuing false or misleading drug claims after the fact, by enforcing the FDCA's misbranding provisions, but that method was utterly ineffective. *See USV Pharm. Corp.*, 412 U.S. at 665. Before the enactment of the Kefauver-Harris Amendments, "good medical practice [was] hampered, and the consumer [was] misled until, perhaps years later, the Government ha[d] gathered the necessary evidence to sustain its burden of proving the [misbranding] violation in court." *Id.*

Meanwhile, it would be similarly non-viable to require drug manufacturers to list all potential indications in their initial new drug application, because, quite simply, all potential uses of a drug are not known when a drug is first approved. Woodcock Decl. ¶ 47 (providing example where study of new uses for already approved drug led to important medical advance). Requiring all possible indications to be known or identified at the time of the new drug

application would delay approval of appropriate new drug applications and reduce incentives for drug firms to develop and seek approval of new medical treatments. *Id.*

Another possibility discussed in *Caronia*, limiting the volume or percentage of a drug's sales intended for unapproved uses, would be arbitrary and unsafe. There is no medical or scientific basis for approving a drug use contingent on a sales volume limit. *See* Woodcock Decl. ¶ 44. Such a ceiling would harm some consumers by denying them access to a treatment being made available to an FDA-prescribed number of others, and, perhaps more worryingly, would authorize unproven uses that ultimately may well prove dangerous or worthless. *See id.* Even unapproved uses that generate small sales can pose serious public health risks—for example, by diverting patients with serious illnesses from effective to ineffective drugs. *See id.* ¶ 15. In addition, there is no practical way for FDA to establish the baseline for what volume or percentage of a drug's current sales are for approved uses or unapproved uses. *See id.* ¶ 44. Prescriptions written by health-care providers do not ordinarily reflect whether a drug was prescribed for an approved or unapproved use; requiring such diagnostic information to be included would raise privacy concerns; the reason a drug is prescribed generally is not revealed in Medicare or Medicaid reimbursement claims; and it would be impossible to determine which over-the-counter drugs are purchased for unapproved uses, since only the consumer knows the use. *See id.*

Taxing sales for unapproved uses more heavily also is not a viable alternative approach. Doing so would disincentivize unapproved uses without making them categorically unavailable, would pose the same administrability and enforceability problems as a use-based sales limit, and, perhaps most importantly, would be less effective than the current regime, because the bulk of

the new tax burden would likely be borne by patients rather than manufacturers.[22] This proposal, therefore, would substantially reduce manufacturers' incentives to obtain FDA approval for new uses, by replacing restrictions on distributing drugs for unapproved uses with only a modest increase in the cost of doing business. *See* Woodcock Decl. ¶ 52. In addition, because this proposal would affect all unapproved uses indiscriminately, it places a financial burden on even those patients for whom an unapproved use is truly medically necessary.

Education campaigns or "reminders" of potential tort liability likewise would not be an adequate substitute for the current regime. As explained above, Congress enacted the 1962 Amendments because after-the-fact remedies such as tort liability and Government enforcement actions were inadequate to protect the public health and safety. That remains the case today, and reminding physicians and drug manufacturers about the well-known fact that tort liability exists would be equally inadequate.[23] In addition, to the extent this alternative had any effect at all, it could discourage health care providers from the prescribing of all unapproved uses, and could interfere with appropriate, individually-customized treatment decisions. Woodcock Decl. ¶ 51.

Another non-viable alternative proposed in *Caronia* is to educate physicians and patients about how to evaluate drug health claims. Drug firms present truthful but incomplete information which, by reason of its incompleteness (whether due to lack of completed rigorous

---

[22] Consumers would bear the brunt of the tax burden because patient demand for prescription drugs tends to be highly inelastic. *See, e.g.*, Simonsen, Skipper & Skipper, *Price Sensitivity of Demand for Prescription Drugs*, Economics Working Paper 2010-3, School of Economics and Management, Aarhus University (Jan. 15, 2010) <ftp://ftp.econ.au.dk/afn/wp/10/wp10_03.pdf>.

[23] *See* Michelle M. Mello et al., *"Health Courts" and Accountability for Patient Safety*, 84 MILBANK Q. 459, 459-60, 472-73 (2006) (noting current "malpractice crisis" and describing how physicians' approaches to patients are shaped by liability pressures); *see also, e.g.*, *Bruesewitz v. Wyeth LLC*, 562 U.S. 223, 226-28 (2011) (Congress enacted National Childhood Vaccine Injury Act due to "massive increase in vaccine-related tort litigation" which increase caused leading drug companies to withdraw from childhood-vaccine market).

studies or inconclusive results), is impossible for anyone to evaluate accurately. *See* Woodcock Decl. ¶ 50. Even if complete information somehow were disseminated, no education campaign could equip countless individual physicians and patients with the tools, background, and specialized expertise in statistics, pharmacokinetics, biomedical engineering, and other fields required to evaluate the risks and benefits of a new intended use. *See id.*

For all of these reasons, no alternative approach would adequately advance the government's substantial public health interest. As such, the current regime is as narrowly tailored as is practicable and cannot be considered more extensive than necessary.

B. Applying the FDCA to Amarin's Proposed Communications Does Not Violate Plaintiffs' Rights Under the Fifth Amendment

Using a manufacturer's dissemination of information about unapproved new uses for approved drugs, particularly as applied to Amarin's proposed communications about Vascepa, is not impermissibly vague, and Plaintiffs' as-applied due process challenge should be rejected. Amarin argues that FDA's regulation leaves Amarin "in the dark" about what it may and may not say, Pl. Br. at 23, and that this "lack of clarity" as to what "off-label promotion, if any, is legally permitted," is "unacceptable" under the Due Process Clause of the Fifth Amendment, Pl. Br. at 22.[24] But this argument ignores the existing guidance that FDA has issued for the industry,

[24] Because Amarin brings an as-applied due process challenge, Pl. Br. at 15, Amarin's statement that "other drug manufacturers [are] in the dark about what they may or may not say," Pl. Br. at 23, should be disregarded. Similarly, MIWG's arguments that drug manufacturers do not know whether their hypothetical speech generally is prohibited or not under FDA's regulations and guidance, *see* MIWG Br. at 13-21, are outside the scope of this dispute. Specifically, MIWG attempts to convert Amarin's as-applied Fifth Amendment challenge to a facial challenge. *See* MIWG Br. at 20 (complaining that "no other manufacturer may rely" on the letter to Amarin). Even if its arguments were appropriately raised, they are without merit. To succeed in a vagueness challenge, a plaintiff "must demonstrate that the law is impermissibly vague in *all* of its applications." *Village of Hoffman Estates v. Flipside, Hoffman Estates, Inc.*, 455 U.S. 489,

which is applicable to the speech Amarin proposes to make, as well as the subsequent explicit application of that guidance set forth in the June 5 Letter as to which of Amarin's proposed communications about Vascepa FDA would consider as evidence that Amarin is introducing a misbranded or unapproved new drug into interstate commerce.[25] June 5 Letter at 1-10. Particularly in light of the June 5 Letter—which expressed views that Amarin could have sought prior to filing this lawsuit but did not—Amarin cannot now say that it has no notice of the conduct which could expose it to possible enforcement action.

As an initial matter, for the reasons described in Section IV, Plaintiffs have not shown a live controversy regarding their purported constitutional violation as to most of their proposed communications, because there is no credible threat of prosecution. *See Frank v. United States*, 78 F.3d 815, 831-32 (2d Cir. 1996) (holding Fifth Amendment vagueness claims to be non-justiciable due to the lack of a "'credible threat' of criminal charges" in light of, among other things, a memorandum issued by the Office of Legal Counsel confirming that the individual would not be subject to criminal liability; the court noted that "however informal, [the memorandum] has been proffered on numerous occasions as the government's position, suggesting that criminal charges against [the class including cross-appellant] are exceedingly unlikely"), *vacated*, 521 U.S. 1114, *aff'd on reh'g*, 129 F.3d 273 (2d. Cir.1997); *Rafferty*, 131

---

497 (1982). Not even with help from MIWG do Plaintiffs make such a showing, and for this reason, a facial challenge fails.

[25] FDA issues guidance to clarify its interpretation of its regulations. *See* 21 U.S.C. § 371 (describing procedures for "guidance documents that set forth initial interpretations of a statute or regulation, changes in interpretation or policy that are of more than a minor nature, complex scientific issues, or highly controversial issues"); 21 C.F.R. § 10.115 ("Guidance documents are documents prepared for FDA staff, applicants, sponsors, and the public that describe the agency's interpretation of or policy on a regulatory issue.").

F.3d at 221 ("Since the commitments made by the Judicial Council resolve the concerns raised by Mr. Rafferty, we need not and do not review the Council's interpretation of the statute, or advise on the merits of Mr. Rafferty's [First and Fifth Amendment] constitutional challenge.").

Moreover, Plaintiffs cannot succeed on the merits of their asserted due process violation because they have ample notice of what conduct may give rise to possible prosecution. Under the Due Process Clause, a statute is impermissibly vague "if it fails to provide people of ordinary intelligence a reasonable opportunity to understand what conduct it prohibits [or] if it authorizes or even encourages arbitrary and discriminatory enforcement." *VIP of Berlin, LLC v. Town of Berlin*, 593 F.3d 179, 186-87 (2d Cir. 2010) (internal quotation marks omitted). "[T]he evaluation of whether a statute is vague as applied to a litigant must be made with respect to the litigant's actual conduct and not with respect to hypothetical situations at the periphery of the statute's scope." *Id.* at 189 (internal quotation marks and alterations omitted). As the Supreme Court has explained, "[o]bjections to vagueness . . . rest on the lack of notice, and hence may be overcome in any specific case where reasonable persons would know that their conduct is at risk." *Maynard v. Cartwright*, 486 U.S. 356, 361 (1988). When, as here, "the agency is willing to give pre-enforcement advice to [affected parties] concerned with the applicability" of the rules, and has provided examples (in that case, in published cease-and-desist orders), that is a "persuasive" factor in determining that the rules are not impermissibly vague. *United States v. Sun & Sand Imports, Ltd.*, 725 F.2d 184, 187 (2d Cir. 1984).

Plaintiffs here have more than sufficient notice as to what is permitted and what is not. The June 5 Letter directly addresses Amarin's proposed communications, and provides advice that is even clearer and more precise than the advice discussed in *Sun & Sand Imports* and other cases. *See Advance Pharma., Inc. v. United States*, 391 F.3d 377, 397 (2d Cir. 2004)

("[D]efendants not only had 'the ability to clarify' any ambiguity in the language of the challenged reporting requirement; they in fact had such language clarified for them in no less than three meetings with federal authorities."); *Marchi v. Bd. of Coop. Educ. Servs. of Albany*, 173 F.3d 469, 480 (2d Cir. 1999) (considering specific guidance provided to plaintiff as relevant to vagueness inquiry); *Toy Manufacturers of America, Inc. v. Consumer Product Safety Commission*, 630 F.2d 70, 78-79 (2d Cir. 1980) (rejecting vagueness challenge in part due to ability to "know in advance how to avoid an unlawful course of action" by obtaining review from the Consumer Products Safety Commission). These cases are consistent with *FCC v. Fox Television Stations, Inc.*, 132 S. Ct. 2307, 2318 (2012), a case that Plaintiffs cite, which explains that the regulatory history and guidelines from the agency were relevant to the question of whether the networks had sufficient notice that their broadcasts "were a violation of [18 U.S.C.] § 1464 *as interpreted and enforced by the agency*." (emphasis added).

Finally, regardless of the June 5 Letter, it should have been obvious to Amarin that its proposed use of the heart disease claim found on dietary supplements and foods is not authorized for prescription drugs under the FDCA and accompanying regulations. This claim refers to an unapproved new use on its face, and is permitted for dietary supplements through FDA's exercise of enforcement discretion based on credible evidence. Woodcock Decl. ¶¶ 31, 33. There is no question that claims based on such a low level of scientific substantiation are not authorized for drugs. *Id.* ¶ 33. "[B]ecause the statute is judged on an as-applied basis, one whose conduct is clearly proscribed by the statute cannot successfully challenge it for vagueness." *United States v. Spy Factory*, 951 F. Supp. 450, 466 (S.D.N.Y. 1997) (quoting *United States v. Nadi*, 996 F.2d 548, 550 (2d Cir. 1993)). Indeed, the Complaint itself reveals that Plaintiffs were aware that by making some of the proposed communications at issue, "they

[would be] treading perilously close to the line of lawful conduct." *Spy Factory*, 951 F. Supp. at 477; *see, e.g.*, Compl. ¶¶ 163-67, 175-80. Accordingly, Plaintiffs' vagueness challenge should fail because "'reasonable persons would know that their conduct is at risk.'" *United States v. Strauss*, 999 F. 2d 692, 698 (2d Cir. 1993) (quoting *Maynard v. Cartwright*, 486 U.S. 356, 361 (1988)).

C. The Government's Interpretation of the False Claims Act Raises No First Amendment Concerns

Amarin's request that the Government be enjoined from enforcing the False Claims Act, 31 U.S.C. §§ 3729-3733, against it for the speech that it proposes is both unnecessary and unwarranted under the law. The FCA is the United States' primary tool to redress fraud on the Government. Section 3729(a)(1)(A) provides for liability where the defendant "knowingly presents, or causes to be presented, a false or fraudulent claim for payment or approval." Section 3729(a)(1)(B) provides for liability where the defendant "knowingly makes, uses, or causes to be made or used, a false record or statement material to a false or fraudulent claim." *United States ex rel. Pervez v. Beth Israel Med. Ctr.*, 736 F. Supp. 2d 804, 811 (S.D.N.Y. 2010). The falsity element may be met by showing that the claim was submitted for an unapproved use that is not reimbursable by federal health care programs.

Amarin correctly observes that federal health care programs may reimburse for unapproved uses that are medically accepted indications and that are supported by a citation in statutorily-approved compendia. Pl. Br. at 12, 21 & n.11. Amarin also states that the use of Vascepa to reduce persistently high triglycerides in adult patients is supported by such a citation. *Id.* at 13. Accordingly, it is difficult to see how, assuming the truth of the facts alleged in the complaint, *e.g.*, where the indication is actually supported by a medical compendium and there is no other contention of falsity, a false claim could or would arise. Plaintiffs thus lack standing to

raise this claim, based on the lack of any purported actual and non-hypothetical injury redressable by this litigation, *Frank*, 78 F.3d at 822, and are seeking an impermissible advisory opinion, *Cargill, Inc. v. Charles Kowsky Resources, Inc.*, 949 F.2d 51, 56 (2d Cir. 1991) ("A case or controversy does not exist when the factual events forming the basis of a claim have not yet occurred.").

Even if there were a justiciable issue as to the FCA, any FCA enforcement action would not implicate the First Amendment. The FCA does not prohibit speech; rather, it is a remedy for conduct that knowingly[26] causes the submission of a false claim for payment to the Government. *See* 31 U.S.C. § 3729(a)(1)(A); *see also United States ex rel. Nevyas v. Allergan, Inc.*, No. 09-432, 2015 WL 3429381, at *1 n.1 (E.D. Pa. May 26, 2015) (rejecting First Amendment challenge to FCA predicated on violations of the Anti-Kickback Statute because it is the company's conduct, and not its speech, that is at issue). As a statutory matter, it is irrelevant whether a party causes the submission of a false claim by words, by conduct, or by a combination of both. *See* 31 U.S.C. § 3729(a)(1)(A) & (B). The FCA does not restrict the speech of those fraudulently seeking payment from the government any more than the antitrust laws restrict the speech of parties to an agreement to illegally restrain trade. The examples that Plaintiffs cite are consistent with the use of the FCA to penalize conduct, namely causing or submitting a false claim, as opposed to mere promotion.[27] Moreover, as discussed in Section

[26] The FCA defines "knowingly" as acting with actual knowledge, in deliberate ignorance or with reckless disregard as to the truth or falsity of the information. 31 U.S.C. § 3729(b)(1)(A).

[27] *See* Statement of Interest, *United States ex rel. Matthew Cestra v. Cephalon, Inc.*, 10 Civ. 6457 (S.D.N.Y. 2013) ("'[W]hen a manufacturer engages in the marketing of drugs for indications that are not FDA approved for that drug or not otherwise supported by a compendium listing, its conduct may cause false non-covered claims to be submitted to federal health care programs, and liability under the FCA may lie.'"); Statement of Interest filed in *United States ex rel. Frank*

V.A.1, *supra*, there is no First Amendment bar to the use of speech as evidence in support of an element of the violation. *See Mitchell*, 508 U.S. at 489; *Giboney v. Empire Storage & Ice Co.*, 336 U.S. 490, 502 (1949) ("[I]t has never been deemed an abridgement of freedom of speech or press to make a course of conduct illegal merely because the conduct was in part initiated, evidenced, or carried out by means of language, either spoken, written, or printed.").

Amarin is simply wrong that the company is at risk because its speech "without more" creates liability under the FCA. Pl. Br. at 13. This ignores the fact that to bring an FCA action, the Government is required to prove all of the elements of the FCA, including falsity, materiality, scienter, and causation.[28] Put another way, the Government must prove that Amarin caused doctors to submit materially false claims to the Government for payment for non-covered uses that were ineligible for payment, and did so with the requisite scienter. Amarin has failed to show that, to the extent it were to be exposed to FCA liability, such exposure would raise any concerns under the First Amendment. Amarin's request for injunctive relief on this basis should be denied.[29]

VI. Plaintiffs Will Not Suffer Irreparable Injury Absent a Preliminary Injunction, the Equities Tip in the Government's Favor, and a Preliminary Injunction Is Not in the Public Interest

To attempt to meet their "irreparable harm" burden, Plaintiffs rely on a presumption of

---

Solis v. Millennium Pharmaceuticals, Inc., 09 Civ. 3010 (E.D. Cal. 2014) (explaining that promotion "can be *evidence* of [the] defendant's having caused physicians to submit false claims").

[28] Amarin's proposed "'belt and suspenders' disclaimer reminding doctors to prescribe reimbursable drugs," Pl. Br. at 24, is no doubt allowed under the FCA. Such statements would be considered along with other evidence in assessing potential liability under the FCA.

[29] No court has conducted a *Central Hudson* analysis in an FCA case in which a company has raised a First Amendment challenge, and Amarin's invocation of that analysis here is misplaced as the FCA does not restrict speech.

irreparable injury flowing from purported First Amendment violations, as opposed to showing specific facts identifying any particular actual or imminent injury that they are suffering. *See* Pl. Br. at 24-25. The June 5 Letter, however, makes clear that Amarin is free to engage in virtually all of its proposed speech without fear of civil or criminal liability, and FDA's guidance has long stated that FDA does not object when manufacturers respond to requests from physicians, such as the Doctor Plaintiffs, with information on unapproved uses. *See* June 5 Letter at 5 n.13. And, as explained above, the FDA's application of the FDCA to Amarin fully comports with the First Amendment, and therefore necessarily does not cause any irreparable harm.

In sharp contrast, FDA and the public have much to lose should a preliminary injunction be entered; as the applicable legal test puts it, both the "balance of equities" and the "public interest" decisively favor denying Plaintiffs' motion. Enjoining the agency here 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; that state of regulatory affairs could again exist if the Court were to establish such precedent for Amarin. *See supra,* Sections III and V.A.3 (discussing background of and need for current regime, and insufficiency of potential less restrictive alternatives). And doing so also would seriously harm the many public interests that the current drug approval regime serves, including, most fundamentally, the assurance that medical professionals and patients now have that drugs are safe and effective for each of their intended uses. *See* Woodcock Decl. ¶¶ 4-22, 31, 33-38, 41. Thus, the public and the government interest are best served by denying the preliminary injunction, thereby upholding FDA's authority to regulate the approval of drugs for each intended use.

VII. Conclusion

For the foregoing reasons, Plaintiffs' request for a preliminary injunction should be denied.

Dated: New York, New York
June 23, 2015

Respectfully submitted,

PREET BHARARA
United States Attorney
Southern District of New York

/s Ellen London
By: ELLEN LONDON
Assistant United States Attorney
86 Chambers Street
New York, New York 10007
Tel.: (212) 637-2737
Fax: (212) 637-2702
Email: ellen.london@usdoj.gov

BENJAMIN C. MIZER
Principal Deputy Assistant Attorney General
Civil Division

JONATHAN F. OLIN
Deputy Assistant Attorney General

SCOTT R. MCINTOSH
Civil Appellate Section

MICHAEL S. BLUME
Director
Consumer Protection Branch

ANDREW E. CLARK
Assistant Director

KERALA T. COWART
Trial Attorney
Consumer Protection Branch
U.S. Department of Justice
P.O. Box 386
Washington, DC 20044

Tel.: (202) 353-3881
Email: kerala.t.cowart@usdoj.gov

WILLIAM B. SCHULTZ
General Counsel

ELIZABETH H. DICKINSON
Associate General Counsel
Food and Drug Division

ANNAMARIE KEMPIC
Deputy Chief Counsel for Litigation

KAREN SCHIFTER
Senior Counsel
JULIE DOHM
Associate Counsel
U.S. Dept. of Health & Human Services
Office of the General Counsel
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002