U.S. Department of Justice

United States Attorney
Southern District of New York

86 Chambers Street

June 8, 2015

BY ECF
The Honorable Paul A. Engelmayer
United States District Judge
Thurgood Marshall United States Courthouse
40 Foley Square
New York, New York 10007

Re: *Amarin Pharma, Inc., et al. v. United States Food & Drug Administration et al.*
No. 15 Civ. 3588 (PAE)

Dear Judge Engelmayer:

This Office represents the United States Food & Drug Administration ("FDA"), the United States, and the remaining defendants named in their official capacity (together the "Government") in the above-referenced case. In accordance with the Court's Order dated June 2, 2015 [Docket No. 23], the Government is filing the FDA's regulatory letter (attached as Exhibit A) that was provided to Plaintiffs on June 5, 2015, and that responds to issues raised in Plaintiffs' complaint.

Respectfully submitted,

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EXHIBIT A

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51, Room 6133
Silver Spring MD 20993

June 5, 2015

Amarin Pharma, Inc.
1430 Route 206
Bedminster, NJ 07921

Attention: Steven Ketchum, Ph.D.
President of Research and Development

Dear Dr. Ketchum:

FDA has reviewed the Complaint you recently filed regarding information you would like to disseminate about your drug product Vascepa, eicosapentaenoic acid ("EPA"), an omega-3 fatty acid. More specifically, you describe your proposed communications in paragraph 124 of your Complaint and Exhibits A and B to the Complaint. Although you did not ask for our views before filing the Complaint (as other pharmaceutical companies sometimes do, *see, e.g.*, 21 C.F.R. § 202.1(j)(4)), we are taking the opportunity to formally communicate our views to clarify the application of our current thinking to the specific facts presented here.

As described in greater detail below, FDA does not have concerns with much of the information you proposed to communicate. 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.[1] We welcome any further inquiry Amarin may have regarding sharing information about the unapproved uses of its drug products.

Background

1. Vascepa's Approved Indication for Severe Hypertriglyceridemia

Vascepa is a purified ester of EPA derived from fish oil. FDA approved Vascepa in July 2012 as a drug to be used as an adjunct to diet to reduce triglyceride ("TG") levels in adult patients with severe hypertriglyceridemia, defined as TG ≥500 mg/dL ("very high TG levels"). The approved dose for this indication is 4 grams per day. The primary rationale for treating individuals with

[1] Among other things, the Federal Food, Drug, and Cosmetic Act ("FDCA") prohibits the introduction (or causing the introduction) into interstate commerce of a new drug that has not complied with requirements for approval (21 U.S.C. § 331(d)), or any drug that is misbranded (21 U.S.C. §331(a)). These provisions and their implementing regulations include prohibitions on introducing (or causing the introduction) into interstate commerce of a prescription drug that is intended for a use that has not been approved by FDA, even if that drug is approved for a different use.

very high TG levels is to reduce the risk of pancreatitis. In this context, improvement in TG is used as a surrogate to predict lowering the risk of pancreatitis.

2. Vascepa's Unapproved Indication for Mixed Dyslipidemia in Statin-Treated Patients

Amarin also sought FDA approval to market Vascepa for another use, namely to treat patients with TG levels between 200 mg/dL and 499 mg/dL ("high TG levels") who are already being treated with statins to lower cholesterol.[2] The primary rationale for treating statin-treated patients with this range of TG levels with a second drug is to further reduce the risk of cardiovascular events, such as cardiovascular morbidity or mortality, from cardiovascular disease ("CVD"). Amarin designed the "ANCHOR trial" to assess the effect of Vascepa on TG levels in statin-treated patients with well-controlled low-density lipoprotein-cholesterol ("LDL-C") levels and high TG levels. In this context, changes in TG levels were used as a surrogate to predict lowering the risk of cardiovascular events.

a. Amarin's ANCHOR and REDUCE-IT SPA Agreements

Amarin conducted the ANCHOR trial under a Special Protocol Assessment ("SPA") agreement with FDA.[3] Although FDA accepted changes in TG levels as a surrogate endpoint for reducing CVD risk when it entered into the SPA agreement, FDA also advised Amarin that on-going cardiovascular outcomes trials ("CVOTs") would provide important additional information regarding the adequacy of TG levels as a surrogate. Specifically, FDA stated:

> Although levels of non-HDL-C correlate with risk for CVD in some studies, we are not aware of any prospective, controlled clinical trial data demonstrating that pharmacological reduction of non-HDL-C (or TG) with a second drug in patients with elevated TG levels at LDL goal on statin therapy significantly reduces the residual risk for CVD. The AIM-HIGH, ACCORD, and IMPROVE-IT studies, while not designed to address this specific gap in knowledge, will provide important information on the incremental benefit of adding a second lipid-active drug to statin therapy.[4]

To address FDA's concerns, Amarin also entered into a separate SPA agreement for the REDUCE-IT trial to evaluate the effects of Vascepa in patients on statin therapy who have high TG levels and either have CVD or are at high risk for CVD.[5] The primary efficacy endpoint in

[2] A statin is defined as "any of a group of drugs (as lovastatin and simvastatin) that inhibit the synthesis of cholesterol and promote the production of LDL-binding receptors in the liver resulting in a usually marked decrease in the level of LDL and a modest increase in the level of HDL circulating in blood plasma." Statin Definition, Merriam-Webster.com, http://www.merriam-webster.com/dictionary/statin (last visited June 4, 2015).

[3] ANCHOR Trial Special Protocol Assessment Agreement, from Eric Colman, Deputy Division Director, Division of Metabolism and Endocrinology Products, Office of Drug Evaluation II, Center for Drug Evaluation and Research, FDA, to Peggy Berry, Vice President, Regulatory Affairs, Amarin Neurosciences, Ltd. (July 6, 2009). The ANCHOR Trial SPA agreement was subsequently amended. Letter from Eric Colman, Deputy Division Director, Division of Metabolism and Endocrinology Products, Office of Drug Evaluation II, Center for Drug Evaluation and Research, FDA, to Peggy Berry, Vice President, Regulatory Affairs, Amarin Neurosciences, Ltd. (May 12, 2010).

[4] Minutes to July 14, 2008, pre-IND Meeting at 8.

[5] REDUCE-IT Trial Special Protocol Assessment Agreement, from Eric Colman, Deputy Division Director, Division of Metabolism and Endocrinology Products, Office of Drug Evaluation II, Center for Drug Evaluation and Research, FDA, to Peggy Berry, Vice President, Regulatory Affairs, Amarin Neurosciences, Ltd. (Aug. 5, 2011).

REDUCE-IT is the occurrence of the first major adverse cardiovascular event, such as cardiovascular morbidity or mortality.

b. The Scientific Developments Regarding the TG-CVD Relationship

After Amarin initiated the ANCHOR study, data from three ongoing CVOTs — ACCORD-Lipid, AIM-HIGH, and HPS2-THRIVE — became available.[6] Each of these trials failed to demonstrate incremental cardiovascular benefit of a second lipid-altering drug (fenofibrate or formulations of niacin) when added to statin-treated patients with well-controlled LDL-C. Although these trials investigated the effects of niacin and fenofibrate, FDA determined that the accumulation and totality of the available scientific data and information no longer meets the level of evidence necessary to the use of decreases in TG levels in statin-treated patients as a surrogate for reduction in CVD risk.

c. Amarin's Supplemental New Drug Application

During the same timeframe in which the data from the CVOTs became available, Amarin conducted and completed the ANCHOR trial. The ANCHOR trial was an adequate and well-controlled study to determine whether Vascepa lowers TG levels in statin-treated patients with well-controlled LDL-C levels and high TG levels. The results demonstrated a statistically significant reduction in TG over placebo (mineral oil). Based on the ANCHOR trial results, and following 50% enrollment in the REDUCE-IT trial, Amarin submitted a supplemental new drug application ("sNDA") requesting approval for Vascepa as an adjunct to diet and in combination with a statin to reduce TG, non-HDL-C, Apo B, LDL-C, TC, and VLDL-C in adult patients with mixed dyslipidemia and CHD or a CHD risk equivalent.[7]

d. The Advisory Committee's 9 to 2 Vote Against Approval of Amarin's Pending sNDA for Vascepa

FDA convened an advisory committee to seek outside expert consultation regarding the experts' level of confidence that the ANCHOR results would translate into a reduction in cardiovascular risk among the target population, and whether Vascepa's effects in the target population were sufficient to grant approval for co-administration with statin therapy for treatment of patients similar to the ANCHOR population, prior to completion of REDUCE-IT.[8] Among other things,

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The REDUCE-IT Trial SPA Agreement was subsequently amended. Letter from Peggy J. Berry, Vice President, Regulatory Affairs and Clinical Quality, Amarin Pharma, Inc., to Mary Parks, Director, Division of Metabolism and Endocrinology Products, Center for Drug Evaluation and Research, FDA re: Request for Amendment to SPA Agreement (Apr. 2, 2013).

[6] For a description of the CVOTs, *see* Formal Dispute Resolution Appeal Denial Letter I from Curtis Rosebraugh, Office of Device Evaluation II, Office of New Drugs, Center for Drug Evaluation and Research, FDA, to Steven Ketchum, President of Research and Development, Amarin Pharma, Inc., at 7-8 & App. B (Apr. 22, 2014).

[7] Letter from Peggy J. Berry, Vice President, Regulatory Affairs and Clinical Quality, Amarin Pharma, Inc., to Mary Parks, Director, Division of Metabolism and Endocrinology Products, Center for Drug Evaluation and Research, FDA re: NDA 202057 S-005 (Feb. 21, 2013).

[8] Summary Minutes of the Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (October 16, 2013), *available at* http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM378970.pdf.

the committee discussed the results of the ANCHOR study and of the three failed CVOTs and their potential impact on Amarin's pending sNDA for Vascepa. The committee voted 9 "no" and 2 "yes" on the question of whether Vascepa should be approved for this indication prior to the completion of the REDUCE-IT trial.

e. Rescission of the ANCHOR SPA Agreement

Following the advisory committee meeting, FDA's review division rescinded the ANCHOR SPA agreement.[9] FDA's review division concluded that a change in TG levels is no longer sufficient to establish the effectiveness of a drug intended to reduce cardiovascular risk in statin-treated subjects with high TG levels. FDA's review division denied Amarin's request for reconsideration, and the rescission decision was upheld during two subsequent levels of formal dispute resolution on the grounds that (1) no adequate and well-controlled trial has demonstrated a cardiovascular benefit resulting from drug-induced lowering of TG in statin-treated patients, and (2) three recent clinical trials failed to show additional cardiovascular benefit of drugs even though each drug had clearly lowered TG levels in statin-treated patients.[10]

Rescission of a SPA agreement is a rare occurrence. Of the approximately 1,000 SPA agreements entered into by FDA and sponsors of investigational new drug applications over the last seven years, only ten have been rescinded. The rarity of SPA agreement rescission indicates that FDA does not take the rescission process lightly or without due consideration.

In addition, the indications for co-administration with a statin were removed from labeling of other lipid-lowering drugs (Trilipix, Niaspan) because these indications were also approved based on evidence that the products lowered TG levels. Similarly, the results of a statin add-on study, which was similar to the ANCHOR study, were removed from the clinical studies section of the labeling for Lovaza. These actions further demonstrate that FDA is acting in the best interest of the public health and treating lipid-lowering drugs consistently based on the strongest and most current science.

f. FDA's Decision Not To Approve the Pending sNDA for Vascepa

FDA determined that it cannot approve Amarin's sNDA in its current form because there are insufficient data to support lowering TG levels as a surrogate for reducing CVD risk in statin-treated patients with well-controlled LDC-C levels and high TG levels.[11] FDA advised Amarin

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[9] SPA Agreement Rescission Letter from Eric Colman, Deputy Division Director, Division of Metabolism and Endocrinology Products, Office of Drug Evaluation II, Center for Drug Evaluation and Research, to Peggy Berry, Vice President, Affairs and Clinical Quality, Amarin Pharma, Inc. (Oct. 29, 2013).

[10] Formal Dispute Resolution Appeal Denial II Letter from John Jenkins, Director of Office of New Drugs, Center for Drug Evaluation and Research, FDA, to Steven Ketchum, President of Research and Development, Amarin Pharma, Inc. (Sept. 11, 2014); Formal Dispute Resolution Appeal Denial Letter I from Curtis Rosebraugh, Office of Device Evaluation II, Office of New Drugs, Center for Drug Evaluation and Research, FDA, to Steven Ketchum, President of Research and Development, Amarin Pharma, Inc. (Apr. 22, 2014); Minutes of the December 16, 2013 Type A Meeting at 10.

[11] Complete Response Letter from James P. Smith, Division of Metabolism and Endocrinology Products, Office of New Drugs, Center for Drug Evaluation and Research, FDA, to Steven Ketchum, President of Research and Development, Amarin Pharma, Inc. (Apr. 27, 2015).

that to obtain approval, it would need to provide evidence that Vascepa reduces the risk of major adverse cardiovascular events in patients at high risk for CVD, with high TG levels and well-controlled LDL-C levels, and on statin therapy. FDA also told Amarin that the final results from the REDUCE-IT trial could be submitted to satisfy this deficiency. Since then, Amarin has committed to continuing the REDUCE-IT trial and has stated that it expects that the trial will be completed in 2017, with results expected to be available in 2018. *See* Compl. ¶ 67.

We note that, while FDA and Amarin were engaged in discussions over the course of several years regarding the content of the FDA-approved labeling for Vascepa, Amarin did not ask about and we did not discuss Amarin's distribution of information that is not within the FDA-approved labeling.

Discussion

As your Complaint acknowledges (Compl. ¶ 137), FDA has issued guidance documents to describe some of the circumstances when it would not rely on a manufacturer communication regarding unapproved uses of approved drugs to be evidence of intended use and/or false or misleading.[12] As these documents reflect, FDA "recognizes the value to health care professionals of truthful and non-misleading scientific or medical publications on unapproved new uses." Revised Good Reprint Practices Draft Guidance at 6. It appears that virtually all of the communications you propose to disseminate fall within the scope of these existing guidance documents.[13] Furthermore, as you also may know, FDA is currently engaged in a comprehensive review of its regulations and guidance documents regarding manufacturers' dissemination of information regarding their medical products, and new guidance will be

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[12] FDA, *Revised Draft Guidance for Industry, Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices* (Feb. 2014), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM387652.pdf ("Revised Good Reprint Practices Draft Guidance"); FDA, *Draft Guidance for Industry Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices* (Dec. 2011), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf ("Draft Unsolicited Requests Guidance"); FDA, *Good Reprint Practices for Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices* (Jan. 2009), http://www.fda.gov/oc/op/goodreprint.html ("Good Reprint Practices Guidance"). The Revised Good Reprint Practices Draft Guidance was issued in response to stakeholder requests to extend the 2009 Good Reprint Practices Guidance to medical reference texts and clinical practice guidelines. Revised Good Reprint Practices Draft Guidance at 6.

[13] In addition to the proposed communications that are covered by the Good Reprint Practices Guidance discussed below, the Draft Unsolicited Requests Guidance is relevant to your claims. That guidance states that "FDA has long taken the position that firms can respond to unsolicited requests for information about FDA-regulated medical products by providing truthful, balanced, non-misleading, and non-promotional scientific or medical information that is responsive to the specific request, even if responding to the request requires a firm to provide information on unapproved or uncleared indications or conditions of use. If responses to unsolicited requests fall within these parameters, FDA has not expected those responses to meet regulatory requirements for promotional labeling or advertising and has not considered these responses as evidence of intended use." Draft Unsolicited Requests Guidance at 6. Accordingly, to the extent health care professional such as 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.

forthcoming.[14] Because this lawsuit was filed before FDA had the opportunity to issue a new guidance that is relevant to your proposed communications and to express its views regarding your proposed communications, FDA is taking this opportunity to explain how its existing guidance and current thinking applies to your proposed communications. Our views are informed in part by the unusual combination of circumstances presented here, including, but not limited to, the design and results of the ANCHOR study, the rescission of the SPA agreement based on the developing science, the safety profile of Vascepa, and Amarin's commitment to complete the REDUCE-IT trial. Under these circumstances, FDA does not intend to object to Amarin's proposed communications if made in the manner and to the extent described below.

1. Distribution of the Results of the ANCHOR Study

In your Complaint, you allege that you would like to provide healthcare professionals with, among other things, information regarding the results of the ANCHOR study (Compl. ¶ 124). We note that there are existing journal articles regarding the ANCHOR study, including at least one that summarizes its results. *See* Ballantyne CM, Bays HE, Kastelein JJ, Stein E, Isaacsohn JL, Braeckman RA, Soni PN. Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high triglycerides (from the ANCHOR study). Am. J. Cardiol. 2012; 110:984-992. This is the type of reprint that is squarely covered by FDA's current reprints policy, as reflected in both the 2009 and 2014 reprints guidance documents. As long as the distribution of that reprint is accompanied with the disclosures and is disseminated in the manner summarized below, FDA would not consider it false or misleading or its distribution to be evidence of intended use.

FDA also has no objection to your providing other truthful and non-misleading summaries of the results of the ANCHOR trial. As the reprints guidance documents suggest, FDA believes that an unabridged or unaltered publication is more likely to be complete and balanced (and, therefore, less likely to be misleading) than a communication that excerpts, summarizes, highlights, or otherwise alters a publication because these latter types of alterations may omit material information. In addition, the act of altering a document may introduce bias, for example, by emphasizing particular aspects of the document while deemphasizing or omitting others. Here, we have reviewed the text of Exhibit B and find that it does not raise those types of concerns. Although we would not necessarily have agreed to include Exhibit B in its entirety in FDA-approved labeling if the indication had been approved, as long as the distribution of Exhibit B is accompanied with the disclosures and is disseminated in the manner summarized below, FDA would not consider it false or misleading or rely on the distribution as evidence of intended use.

To the extent you choose to provide a summary that is different from Exhibit B, FDA would not consider it false or misleading or its distribution evidence of intended use if the summary remains factual, does not omit material information, and does not otherwise introduce bias. In particular, the communication could be misleading if it implied or suggested that the ANCHOR study supports the conclusion that lowering triglyceride levels lowers the risk of CVD in patients already treated with statins or that available evidence establishes that there is a clinical benefit in lowering TG levels for patients with high TG levels. We also believe that to avoid being misleading any summary would show not only the differences between Vascepa and the mineral

[14] Citizen Petition Response from Leslie Kux, J.D., Assistant Commissioner for Policy, FDA, to Alan R. Bennett, Ropes & Gray, et al., Docket Nos. FDA-2011-P-0512 and FDA-2013-P-1079 (June 6, 2014) and update (Dec. 22, 2014), available at http://www.regulations.gov/#!documentDetail;D=FDA-2011-P-0512-0009.

oil placebo, but also the changes from baseline to endpoint in each of the treatment groups, as you have done in Exhibit B.

We agree with your proposal to include disclosures that describe the limitations of the data and the existence of other relevant data (Compl. ¶ 124); such disclosures help to provide an accurate and balanced presentation and ensure that the information will be properly understood. We believe that the following disclosures would be appropriate:

- Vascepa is not approved to reduce the risk of coronary heart disease;
- The effect of Vascepa on the risk of cardiovascular mortality and morbidity has not been determined;
- Vascepa is not approved for the treatment of statin-treated patients with mixed dyslipidemia and high (> 200 mg/dL and < 500 mg/dL) triglyceride levels. FDA declined to approve this indication because the available evidence does not establish that reducing triglycerides with a drug reduces the risk of cardiovascular events among patients already treated with statins;
- Recent cardiovascular outcome trials (ACCORD-Lipid, AIM-HIGH, and HPS2-THRIVE) each failed to demonstrate incremental cardiovascular benefit of adding a second lipid-altering drug (fenofibrate or formulations of niacin), despite reducing triglyceride levels, among statin-treated patients with well-controlled low-density lipoprotein-cholesterol; and
- Any potential financial or affiliation biases between the firm and those who conducted the ANCHOR study.[15]

To further protect against misleading the audience, FDA recommends:[16]

- Providing a copy of the current FDA-approved labeling;
- Providing a copy of the above-referenced reprint (when a summary of the ANCHOR trial is distributed);
- Distributing such information in educational or scientific settings, and not including such information with or attached to promotional or marketing materials; and
- Distribution by persons with the appropriate background or training to accurately communicate this scientific information.

FDA also agrees with your proposal to limit your audience to health care professionals, and not to include the information in direct-to-consumer advertising (Compl. ¶¶ 121-122).

2. Distribution of Additional Reprints

[15] FDA would not object to the inclusion of the following additional statements that you propose to make (Compl. ¶ 124) so long as they remain truthful and non-misleading:

- A cardiovascular outcomes study of Vascepa designed to evaluate the efficacy of Vascepa in reducing cardiovascular mortality and morbidity in a high risk patient population on statin therapy is currently underway;
- Vascepa may not be eligible for reimbursement under government healthcare programs, such as Medicare or Medicaid, to reduce the risk of coronary heart disease or for treatment of statin-treated patients with mixed dyslipidemia and high (> 200 mg/dL and < 500 mg/dL) triglyceride levels. We encourage you to check that for yourself.

[16] *See, e.g.*, Revised Good Reprint Practices Draft Guidance § III.A; Good Reprint Practices Guidance § IV.B.

In your Complaint, you allege that you would like to distribute "peer-reviewed scientific publications relevant to the potential effect of EPA on the reduction of the risk of coronary heart disease" (Compl. ¶ 124 and Exhibit A). Again, these are the types of publications covered by the existing guidance, which recommends that any manufacturer disseminated reprints: "address adequate and well-controlled clinical investigations that are considered scientifically sound by experts with scientific training and experience to evaluate the safety or effectiveness of the drug or device. These can include historically controlled studies, pharmacokinetic (PK) and pharmacodynamic (PD) studies, and meta-analyses if they are testing a specific clinical hypothesis." Good Reprint Practices Guidance § IV.A. Under this policy, manufacturer-distributed reprints should not include opinion pieces, such as letters to the editor, with little or no substantive discussion of the relevant investigation or data. As long as the distribution of these reprints is accompanied with the disclosures and is disseminated in the manner summarized in this paragraph and in the previous section, FDA would not consider their distribution to be evidence of intended use.

However, some practices with respect to the distribution of reprints may render the communication false or misleading. In order to avoid that situation, we note some recommendations here. For example, "a distributed journal article should not be characterized as definitive or representative of the weight of credible evidence derived from adequate and well-controlled clinical investigations if it is inconsistent with the weight of credible evidence or if a significant number of other studies contradict the conclusions set forth in the article." Revised Good Reprint Practices Draft Guidance at 8. Similarly, a communication should not state or imply that studies conducted using products other than Vascepa were studies of Vascepa itself, nor should a communication state or imply that these studies establish that Vascepa will reduce the risk of coronary heart disease. Rather, to ensure that your communications are not false or misleading, we recommend that they expressly disclose when studies were conducted using products other than Vascepa (in particular when those other products contain active ingredients that are different from the icosapent ethyl — an ester of EPA — that is contained in Vascepa) and that the results of the studies may not be applicable to Vascepa. Indeed, you have emphasized in your complaint and as your position in other litigation that Vascepa is distinct from other products that contain EPA.[17]

3. Qualified Health Claim for Conventional Foods and Dietary Supplements

In your Complaint, you also state that you would like to make the following qualified health claim for Vascepa: "Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease" (Compl. ¶ 124). FDA has issued letters stating its intent to exercise enforcement discretion for the use of this claim in the labeling of certain conventional foods and dietary supplements that contain EPA and DHA.[18]

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[17] Compl. n.13; *Amarin Pharms. Ireland Ltd. v. FDA*, No. 14-cv-00324 (RDM), 2015 WL 3407061, at *5 (D.D.C. May 28, 2015).

[18] Letter Responding to Health Claim Petition dated November 3, 2003 (Martek Petition): Omega-3 Fatty Acids and Reduced Risk of Coronary Heart Disease (Docket No. 2003Q-0401) (Sept. 8, 2004), http://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm072932.htm ("Martek Petition Response"); Letter Responding to Health Claim Petition dated June 23, 2003 (Wellness petition): Omega-3 Fatty Acids and Reduced Risk of Coronary Heart Disease (Docket No. 2003Q-0401) (Sept. 8, 2004), http://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm072936.htm ("Wellness Petition Response").

With respect to the quoted claim as applied to conventional foods and dietary supplements, FDA found as far back as 1993 that there is not significant scientific agreement as to the validity of the relationship between omega-3 fatty acids and reduced risk of coronary heart disease.[19] Because the evidentiary standard for FDA to authorize a health claim by statute and regulation is "significant scientific agreement,"[20] and the FDCA forbids the use of unauthorized health claims in food labeling, the agency declined to permit the use of health claims about omega-3 fatty acids and reduced risk of coronary heart disease in the labeling of conventional foods and dietary supplements. This decision, as applied to dietary supplements, was challenged in *Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999), and the D.C. Circuit directed FDA, among other things, to reconsider the relationship between omega-3 fatty acids and reduced risk of coronary heart disease and to permit the claim unless the agency could show that no disclaimer could prevent the claim from misleading consumers. Upon reconsideration, the agency concluded in 2000, and again in 2004, that there was still no significant scientific agreement that omega-3 fatty acids reduce the risk of coronary heart disease; yet, as a result of *Pearson*, the agency currently does not object to the above phrasing of the claim for dietary supplements or conventional foods, provided that certain conditions are met.[21]

That this claim may, through the exercise of FDA's enforcement discretion, appear in the labeling of conventional foods and dietary supplements, but not in the labeling of drugs, is a consequence of the different regulatory regimes, established by statute and regulation, for these products. As a result of *Pearson*, FDA exercises enforcement discretion with respect to qualified health claims that have been reviewed by FDA and found to be supported by credible evidence, even when the evidence falls short of the significant scientific agreement standard for health claims on conventional foods and dietary supplements.[22] This low level of scientific evidence for qualified health claims resulting from *Pearson* and its progeny should not be extended to claims for drugs, which require substantial evidence of effectiveness to support approval for each approved use, *see* 21 U.S.C. § 355, because dissemination of information with such a low level of scientific weight could undermine the important public health interests served by the premarket approval requirements for drugs under the FDCA.[23] These important public health interests include: (1) creating incentives to develop robust scientific data regarding the safety and efficacy of a drug for a particular use; (2) requiring review of those data before the

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[19] *See* Food Labeling: Health Claims and Label Statements: Omega-3 Fatty Acids and Coronary Heart Disease, 58 Fed. Reg. 2682 (Jan. 6, 1993); Food Labeling: Health Claims for Dietary Supplements, 58 Fed. Reg 53,296 (Oct. 14, 1993); Food Labeling: Health Claims for Dietary Supplements, 59 Fed. Reg. 436 (Jan. 4, 1994).

[20] The significant scientific agreement standard is prescribed by statute for conventional food health claims. *See* 21 U.S.C. § 343(r)(3)(B)(i). By regulation, FDA adopted the same standard for dietary supplements. *See* 21 C.F.R. 101.14(c).

[21] Martek Petition Response; Wellness Petition Response; Letter from Christine J. Lewis, Ph.D., FDA, to Jonathan W. Emord, Esq., Emord & Associates, P.C., "Letter Regarding Dietary Supplement Health Claim for Omega-3 Fatty Acids and Coronary Heart Disease" (Docket No. 91N-0103), October 31, 2000.

[22] *See Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims* (Jan. 2009), http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm073332.htm.

[23] *Pearson* recognized that drugs are an "entirely different category" from dietary supplements and did not extend its holding to drugs. 164 F.3d at 661 n.6. Notably, there is no premarket approval for dietary supplements.

marketing of the product for that use to prevent harm to patients, and to ensure that healthcare providers have a sound basis for making treatment decisions before the use is widespread; (3) providing for the review of safety and efficacy data by an independent body to ensure that claims are appropriately supported; (4) requiring the development of labeling that provides information necessary for the safe and effective use of the product; and (5) preventing firms from misleadingly marketing their products.

Vascepa, as a prescription drug, must be shown to be safe and effective for its intended use in its intended population before it can be lawfully distributed in interstate commerce — unlike EPA-containing dietary supplements which do not undergo premarket review and are intended to assist the general population in maintaining healthful dietary practices. Amarin has not demonstrated with substantial evidence that Vascepa is effective to reduce the risk of coronary heart disease in statin-treated patients who have CVD or are at risk for CVD. Yet, the qualified health claim that Amarin seeks to use for Vascepa will suggest to physicians that Vascepa may be effective for that use in those patients. To the extent a physician misapprehends the evidence underlying the qualified health claim Amarin seeks to use for Vascepa and prescribes Vascepa instead of a more effective treatment, the patient — already with CVD or at risk for CVD — could be harmed. For example, although it may not be Amarin's intent, the use of the qualified health claim could lead physicians to prescribe Vascepa in lieu of promoting healthy dietary and lifestyle changes or prescribing statin therapy, which is proven to reduce the risk of cardiovascular events. Thus, including the qualified health claim in connection with your distribution of Vascepa would be potentially harmful to the public health, and FDA would consider such conduct to be potentially misleading or potential evidence of intended use.

If, however, you were to repackage and re-label your product as a dietary supplement and ensure that all the conditions set forth in the Martek and Wellness Petition Responses cited in footnote 18 were met, FDA would not object to your inclusion on that dietary supplement of the qualified health claim referenced above. Alternatively, if you wanted to distribute your product, repackaged and relabeled as a dietary supplement, with a different claim, you could petition for a new qualified health claim.

Conclusion

In sum, FDA would not consider your dissemination of summaries of the results of the ANCHOR studies and reprints in the manner described above to be false or misleading or their distribution to be evidence of intended use. And, although FDA would potentially consider your inclusion of the qualified health claim referenced in paragraph 124 of your Complaint in connection with your distribution of Vascepa as misleading or as evidence of an intent to market the product for an unapproved use, you could make such a claim in connection with the distribution of your product if you were to repackage and re-label it as a dietary supplement.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration

cc: Joel Kurtzberg, Esq.
Cahill Gordon & Reidel LLP