What is Amarin's view on the June 19, 2019 CFSAN evaluation of proposed qualified health claims applicable to food and dietary supplement products containing the omega-3 acids?

The U.S. Food and Drug Administration (FDA) Office of Nutrition and Food Labeling Center for Food Safety and Applied Nutrition (CFSAN, pronounced sif'-san), which regulates food, dietary supplements and cosmetics, announced today results of its evaluation of proposed qualified health claims applicable to food and dietary supplement products containing the omega-3 acids, EPA and DHA. The claims were submitted in 2014 by a trade organization that represents manufacturers of omega-3 dietary supplement products, The Global Organization for EPA and DHA. CFSAN concluded that there is insufficient and inconclusive data to make anything other than highly qualified health claims regarding omega-3 dietary supplement products.

Amarin does not anticipate that this announcement from CFSAN will have any significant impact on the use or sale of Vascepa® (icosapent ethyl) capsules.

Amarin agrees with CFSAN that any conclusive suggestion that omega-3 supplements benefit cardiovascular health is dubious. In contrast, Vascepa's benefits are proven. This CFSAN result is consistent with Amarin's stated view for many years. Amarin and CFSAN's perspectives were recently supported by multiple meta-analyses that have called any such conclusion into serious question.[1] In fact, the European Medicines Agency (EMA) also noted recent negative outcomes studies with other EPA and DHA containing drug products – known as omega-3 fatty acid mixtures (e.g., Omacor® 1-gram, known in the US as Lovaza®). The EMA has concluded that omega-3 fatty acid medicines (specifically, Omacor/Lovaza and other DHA/EPA mixtures) are not effective in preventing further heart attack and blood vessel problems in patients who have had a heart attack.[2]

The studies evaluated by CFSAN were generally of dietary supplements containing EPA and DHA. Such studies covered decades of published reference data. The degree of evidence generally sought by CFSAN for food products is significantly lower than is required by the FDA's Center for Drug Evaluation and Research (CDER), which is responsible for efficacy and safety evaluations of drugs. Had this been an application for a drug, a response from FDA of insufficient and inconclusive data would typically result in non-acceptance or rejection of a drug application. CFSAN, in its response, did not evaluate studies of Vascepa in its assessment. Because Vascepa has been developed as a drug product to treat disease,

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[1] *See* Theingi Aung, et al., Associations of Omega-3 Fatty Acid Supplement Use with Cardiovascular Disease Risks: Meta-analysis of 10 Trials Involving 77,917 Individuals, JAMA Cardiology (published online January 31, 2018) David S. Siscovick et al., *Omega-3 Polyunsaturated Fatty Acid (Fish Oil) Supplementation and the Prevention of Clinical Cardiovascular Disease: A Science Advisory From the American Heart Association*, 135 CIRCULATION e867 – e884, Table 8 (2017), http://circ.ahajournals.org/content/early/2017/03/13/CIR.0000000000000482 ("available evidence does not support the use of [omega-3] supplements in the general population who are not at high risk for [cardiovascular disease]"); *see also* Ethan M. Balk et al., *Omega-3 Fatty Acids and Cardiovascular Disease: An Updated Systematic Review*, EVIDENCE REPORT/TECHNOLOGY ASSESSMENt No. 223, at vi (Aug. 2016), https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/fatty-acids-cardiovascular-disease_research.pdf (concluding that omega-3 supplements do not affect "major adverse [cardiovascular] events, all-cause death, sudden cardiac death, coronary revascularization, atrial fibrillation, or [blood pressure]" *in populations at risk for, or with cardiovascular disease*, or in "general healthy populations"); Asmaa S. Abdelhamid et al., *Omega-3 Fatty Acids for the Primary and Secondary Prevention of Cardiovascular Disease*, COCHRANE DATABASE OF SYSTEMATIC REVIEWS, 1, 3 (July 2018), https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003177.pub3/full

[2] EMA Determination, December 14, 2018 at https://www.ema.europa.eu/documents/referral/omega-3-fatty-acid-medicines-omega-3-fatty-acid-medicines-no-longer-considered-effective-preventing_en.pdf

studies of Vascepa have been, and are being, evaluated separately by CDER. A PDUFA target date of September 28, 2019 has been set by the review division within CDER for Amarin's pending supplemental new drug application which seeks to expand the indicated use of Vascepa based on data from the REDUCE-IT™ cardiovascular outcomes study.

Separate from CFSAN rejecting the proposed claims for omega-3 dietary supplements, note that manufacturing requirements for dietary supplements regarding issues such as quality, quantity of stated content, stability and consistency are not as stringent as those for drugs.[3] Omega-3 dietary supplements, in particular, have been subject to significant scrutiny for their manufacturing quality for issues such as spoilage and oxidation. These issues can lead to degradation of the fragile omega-3 acids, evidenced in part by a fishy odor, that can lead to important health and safety concerns.[4] EPA and DHA are fragile molecules and the clinical effects of these molecules may vary if they are spoiled, oxidized or otherwise damaged during manufacture or storage.

In rejecting the proposed claims and effectively permitting, in substitute, highly qualified claims, CFSAN stated that overall the evidence evaluated was inconclusive and highly inconsistent. As noted by CFSAN,

> Consistency of the findings among similar and different study designs is important for evaluating causation and the strength of the evidence. Lack of consistency among studies evaluating the same substance-disease relationship weakens the strength of the evidence. Therefore, [CFSAN] concludes that while there is some credible evidence suggesting that combined intake of EPA and DHA from conventional foods and dietary supplements may reduce the risk of hypertension by lowering blood pressure, this evidence is inconclusive and highly inconsistent.

To prevent consumer deception about the strength of the science underlying the new claim, the qualified health claims must be accompanied by a disclaimer or other qualifying language that accurately describes the low level of scientific evidence supporting the claim. For example, the statements CFSAN permitted require that each statement also note the following limitation: "However, FDA has concluded that the evidence is inconsistent and inconclusive."

CFSAN included in its response comments reflecting that adequate dose is important. It stated that even to make a qualified health claim (e.g., that the product "may" provide a benefit but that evidence of such is inconsistent and inconclusive), the product must contain at least 0.8 grams of EPA and DHA (combined total) as the minimum amount per serving for a conventional food or dietary supplement.

Emphasis that evidence is inconsistent and inconclusive is a repeated and central theme to qualified health claims with respect to omega-3 dietary supplements. CFSAN expressed that it intends to exercise enforcement discretion for the following qualified health claims regarding EPA and DHA when the claims

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[3] *See* 21 C.F.R. pts. 210, 211 (drug good manufacturing practices), *to* 21 C.F.R. pt. 111 (dietary supplement good manufacturing practices)).

[4] *See Supplements and Safety*, S34 E3, Frontline, PBS (Jan. 2016) at 39:30, *available at* http://www.pbs.org/video/frontline-supplements-and-safety/ (last accessed June 19, 2019) (discussing the difference between FDA-approved omega-3 drug products and fish oil dietary supplements, and related negative effects of oxidized lipids in fish oil). *See also* R. Preston Mason and Samuel C.R. Sherratt, *Omega-3 fatty acid fish oil dietary supplements contain saturated fats and oxidized lipids that may interfere with their intended biological benefits*, Biochemical and Biophysical Research Communications (2016).

are used in the labeling of conventional foods and dietary supplements consistent with the letter of enforcement discretion:

> 1. Consuming EPA and DHA combined may help lower blood pressure in the general population and reduce the risk of hypertension. However, FDA has concluded that the evidence is inconsistent and inconclusive. One serving of [name of the food or dietary supplement] provides [ ] gram(s) of EPA and DHA.
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> 2. Consuming EPA and DHA combined may reduce blood pressure and reduce the risk of hypertension, a risk factor for CHD (coronary heart disease). However, FDA has concluded that the evidence is inconsistent and inconclusive. One serving of [name of the food or dietary supplement] provides [ ] gram(s) of EPA and DHA.
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> 3.a. Consuming EPA and DHA combined may reduce the risk of CHD (coronary heart disease) by lowering blood pressure. However, FDA has concluded that the evidence is inconsistent and inconclusive. One serving of [name of the food or dietary supplement] provides [ ] gram(s) of EPA and DHA.
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> 3.b. Consuming EPA and DHA combined may reduce the risk of CHD (coronary heart disease) by reducing the risk of hypertension. However, FDA has concluded that the evidence is inconsistent and inconclusive. One serving of [name of the food or dietary supplement] provides [ ] gram(s) of EPA and DHA.
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> 4. Research shows that consuming EPA and DHA combined may be beneficial for moderating blood pressure, a risk factor for CHD (coronary heart disease). However, FDA has concluded that the evidence is inconsistent and inconclusive. One serving of [name of the food or dietary supplement] provides [ ] gram(s) of EPA and DHA.

The qualified health claims announced today are consistent with FDA's past practice in this area. Since 2004 the FDA has exercised enforcement discretion for the qualified health claim "Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease" under certain circumstances. If this matter pertained to a drug rather than the lower burden of evidence standard of a product classified as food, not even a qualified claim would likely be allowed regarding such products as CDER has consistently held that the risk of a product outweighs its benefits when benefit of the product has not been established.

Amarin is proud of the scientific rigor of its development and testing of Vascepa as an ethical drug. We believe that the clinical effect and safety of Vascepa is distinct from any product. The purpose of a drug, in treating serious disease, is distinct from dietary supplements which are not intended or approved for such use. As reinforced by this review by CFSAN, despite decades of study and use, dietary supplements cannot claim there is adequate support for effectiveness or safety in the treatment of cardiovascular risk. While some people may elect to use dietary supplements, they should not be relied on to help prevent cardiovascular risk. Patients should consult with their physician for treatment of cardiovascular risk.

Amarin remains fully committed to defending the Vascepa franchise against any company that seeks to mislead the public and cardiovascular patients in need by fraudulently leveraging the landmark REDUCE-IT™ study results or the REDUCE-IT or Vascepa names for profit. See Amarin Investor FAQ: *What is Amarin*

doing to protect the Vascepa® franchise against dietary supplement manufacturers that mislead the public by referencing REDUCE-IT™ or Vascepa®? (updated May 7, 2019)