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March 5, 2018

Via Electronic Submission (www.regulations.gov)

The Honorable Seema Verma, M.P.H.
Administrator
Centers for Medicare & Medicaid Services
Department of Health and Human Services
Attn: CMS-2017-0163
7500 Security Boulevard
Baltimore, MD 21244

Re: CMS-2017-0163; Advance Notice of Methodological Changes for Calendar Year (CY) 2019 for Medicare Advantage (MA) Capitation Rates, Part C and Part D Payment Policies and 2019 Draft Call Letter – Proposal to Permit Substitution of Prescription Drugs with OTC Drugs and Dietary Supplements

Dear Administrator Verma:

Amarin Pharma, Inc. (Amarin) appreciates the opportunity to comment on the Part D provisions of the proposed draft Call Letter titled, "Advance Notice of Methodological Changes for Calendar Year (CY) 2019 for Medicare Advantage (MA) Capitation Rates, Part C and Part D Payment Policies and 2019 Draft Call Letter." These comments are focused on the proposal by CMS to permit Part D Plans (PDPs) to substitute for *prescription* drugs *over-the-counter* (OTC) drugs and dietary supplements (the latter of which is regulated as food). More specifically, CMS on page 197 of the Draft Call Letter (Part II) proposes to allow PDPs: "***to include additional OTC products such as dietary supplements and cough medicines,*** without the requirement that either product offset the use of a Part D drug."[1]

We respectfully urge the Agency to reject the proposal as it applies to dietary supplements. In fact, CMS should not sanction (and instead should explicitly prohibit) any efforts by PDPs to substitute dietary supplements for prescription drugs. The proposed substitution is contrary to the Part D provisions in the Social Security Act, and more fundamentally, it would endanger the public health. As explained below, dietary supplements are not equivalent to, and cannot be substituted for, prescription drugs; they cannot be used to treat, prevent, cure, or mitigate disease; and there is no requirement that dietary supplement manufacturers demonstrate that they are safe or effective, or even labeled appropriately before the products are marketed. Thus, if CMS were

[1] Available at https://www.cms.gov/Medicare/Health-Plans/MedicareAdvtgSpecRateStats/Downloads/Advance2019Part2.pdf (emphasis added).

to treat dietary supplements as being substitutable for drugs, it would risk Plans causing harm, rather than providing treatment, to Medicare beneficiaries.

The proposal, as it applies to dietary supplements, would contradict recommendations from numerous professional societies, including the American Diabetes Association (ADA)[2] and the American Society of Health System Pharmacists[3] – both of which advise against the routine use of dietary supplements in patients with medical conditions. These recommendations warn against the use of dietary supplements for medical treatment because the clinical evidence does not generally support a beneficial role in improving outcomes.

We appreciate that CMS may have confused dietary supplements with OTC drugs because both are available without prescription and on drug store shelves. But, they are distinct. OTC drugs, like prescription drugs, are subject to stringent federal oversight and cannot be marketed unless they are safe and effective and labeled appropriately. The same is not true for dietary supplements.

I. Dietary Supplements Cannot Meet the Definition Of "Covered Part D Drug," And Permitting Substitutions Would Be Contrary To The Social Security Act

As an initial matter, dietary supplements do not meet the definition of "covered Part D drug" in the Social Security Act.[4] That term is defined in pertinent part as "a *drug* that may be dispensed only upon a *prescription* and that is described in subparagraph (A)(i), (A)(ii), or (A)(iii), of [S]ection 1927(k)(2)."[5] Significantly, Section 1927(k)(2)(A)(i) specifically includes "drugs" that have been approved by FDA pursuant to Section 505 of the Federal Food, Drug & Cosmetic Act (FDCA),[6] and the other two referenced provisions refer to "drugs" that are otherwise legally marketed under the FDCA.[7] For that reason alone, CMS should not sanction any Part D drug plan substituting a dietary supplement for a physician-prescribed prescription drug.

Beyond the statutory limitations of the Social Security Act, however, "drugs" and "dietary supplements" are wholly different products subject to wholly different statutory provisions and regulatory regimes. "Drugs" must meet strict standards for safety, efficacy, and manufacturing. They are for the treatment of illness and disease, which is why they are prescribed by physicians and covered under the Part D benefit. In contrast, "dietary supplements" are a type of "food."[8] Unlike "drugs," "dietary supplements" are not intended to treat, prevent, cure, or mitigate disease.[9] Indeed, FDA, on its own website, cautions consumers that: "[i]t is not legal to market a dietary supplement product as a treatment or cure for a specific disease, or to alleviate the

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[2] Lifestyle Management: Standards of Medical Care in Diabetes - 2018. Diabetes Care. 2018;41(Suppl. 1):S38–S50.
[3] ASHP Statement on the Use of Dietary Supplements, https://www.ashp.org/-/media/assets/policy-guidelines/docs/statements/use-of-dietary-supplements.ashx?la=en&hash=51A155A1F5354D4B9145C5677E685F1590F5015C
[4] *See* 42 U.S.C. § 1395w-102(e).
[5] *Id.* (emphasis added).
[6] 21 U.S.C. § 355.
[7] *See* 42 U.S.C. § 1396r-8(k)(2)(A).
[8] 21 U.S.C. § 321(f), (ff).
[9] *Compare* 21 U.S.C. § 321(g), with §§ 343(r)(6), 321(ff).

symptoms of a disease."[10] Rather, "dietary supplements" are intended for nutritional purposes, to supplement the diet.[11]

We appreciate cost is an important consideration. But cost is not a sufficient justification to deny patients the safeguards developed through decades of legislation to improve public health through the FDA's drug review and approval process. It is inconceivable that any Part D Plan's Pharmacy & Therapeutics Committee could reach a medical judgment that a dietary supplement could replace a prescription drug or otherwise be used to treat an illness or other medical condition. CMS should not sanction such activity – particularly under the guise of the *Medicare* prescription drug benefit. Beneficiaries expect that their benefit will be to treat their illnesses, and substituting dietary supplements in place of drugs is not providing treatment. In fact, it significantly risks aggravating medical conditions and causing new harm to the beneficiary. CMS instead should explicitly prohibit Part D Plans from using supplements at all.

II. Dietary Supplements Are Not Drugs, And Permitting Substitutions Would Endanger The Public Health

A. Drugs And Dietary Supplements Have Different Purposes And They Are Subject To Very Different Levels Of Federal Oversight

As mentioned, drugs and dietary supplements are not the same, and they are not interchangeable in purpose. Moreover, they are subject to wholly different levels of oversight. Drugs are subject to stringent FDA oversight to ensure their efficacy, safety, and manufacturing quality, and dietary supplements are not.

The path to drug approval is long. It typically starts with laboratory and animal tests to evaluate how the drug works and to determine whether it is likely to be safe in humans, and then it is followed by extensive adequate and well-controlled clinical testing.[12] Once the clinical trials are conducted, the sponsor may submit an application for drug approval to FDA, and if the agency believes that the drug is safe and effective, that the proposed labeling is appropriate, and that manufacturing methods assure that the drug's identity, strength, quality, and purity, then the agency will approve the drug.[13]

By contrast, dietary supplements are regulated as "food,"[14] and as such, they are not subject to FDA approval; they do not need to be tested for safety and effectiveness before being marketed; and FDA does not review their labeling before the products are marketed, such that the labeling may contain false statements about safety or effectiveness or may omit important safety

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[10] FDA 101: Dietary Supplements, https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm050803.htm

[11] *See* 21 U.S.C. § 321(ff)(1).

[12] *See, e.g.*, FDA Website, Development & Approval Process (Drugs), https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ CMS should also consider the impact of its proposal on new drug development, given that recent data indicate that the average cost to bring a new drug to market has grown considerably ($1.99B compared with $1.19B in 2010) in the last seven years, and that the number of new drugs brought to market by large pharmaceutical manufacturers has declined in that time period. *See A new future for R&D? Measuring the return from pharmaceutical innovation 2017,* Deloite Centre for Health Solutions (2018).

[13] 21 U.S.C. § 355.

[14] *Id.* § 321(f), (ff).

information, including warnings and contraindications.[15] Furthermore, dietary supplement manufacturing and distribution are not subject to the same stringent requirements as drugs with respect to quality, stability or consistency. In fact, independent reports have shown that the contents of dietary supplements are often inconsistent with their labels and inconsistent batch to batch.[16]

Moreover, a recent summary of research conducted by the National Institutes of Health (NIH) confirmed that dietary supplements lack in treatment value. Despite investing more than $250 million to $300 million annually, NIH research on dietary supplements generally failed to demonstrate beneficial effects on health. According to the recent summary of "this extensive investment: 'most of the larger NIH-supported clinical trials of [dietary supplements] failed to demonstrate a significant benefit compared to control groups.'"[17] Simply put, the evidence conclusively shows that dietary supplements cannot be used for treatment.

In addition, dietary supplements should not be confused with OTC "drugs," because both are available without a prescription, on drug store shelves. OTC "drugs," like prescription "drugs" cannot be marketed unless they are safe and effective and labeled appropriately in accordance with FDA requirements for OTC drugs. An OTC drug can be marketed legally only if FDA either approves a new drug application for the drug, or if the drug conforms to an OTC monograph, which is like a recipe for a drug that lists acceptable ingredients, doses, formulation, and labeling statements – including contraindications and warnings.[18]

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[15] For that reason, numerous organizations urge Americans to refrain from the use of dietary supplements in place of prescription drugs. The American Pharmacist Association (APhA), for example, advises patients "While omega-3 dietary supplements can be an important part of consumer wellness, unlike regulated prescription and OTC drugs, dietary supplements are not required to meet strict FDA drug standards for safety, efficacy, and manufacturing and are not intended to treat serious medical conditions like VHTG. Patients should consult with their doctor about appropriate FDA-approved drug therapy." APhA convenes stakeholders on appropriate omega-3 fish oil use for VHT, APhA, https://www.pharmacist.com/apha-convenes-stakeholders-appropriate-omega-3-fish-oil-use-vht Similarly, the Preventive Cardiovascular Nurses Association (PCNA), in their patient handout regarding the use of omega-3 products notes: "Dietary supplements are not regulated by the Food and Drug Administration (FDA) in the same way as medications" and "the prescription and the supplement are not the same. Only take a supplement if approved by your nurse or doctor." Triglycerides: What You Need To Know, PCNA, http://pcna.net/docs/default-source/default-document-library/triglycerides-sheet.pdf?sfvrsn=0

[16] *See* Scientific Reports (January 25, 2015): Fish oil supplements in New Zealand are highly oxidised and do not meet label content of n-3 PUFA available at http://www.nature.com/srep/2015/150121/srep07928/full/srep07928.html (finding that 69% of fish oil supplements studied contained less than 2/3 the active ingredients listed on the label (generally, EPA and DHA)); *See also* United States Government Accountability Office Testimony Before the Special Committee on Aging, U.S. Senate HERBAL DIETARY SUPPLEMENTS Examples of Deceptive or Questionable Marketing Practices and Potentially Dangerous Advice (May 26, 2010), available at https://www.gao.gov/new.items/d10662t.pdf; and A.G. Schneiderman Announces Agreement With GNC To Implement Landmark Reforms For Herbal Supplements https://ag.ny.gov/press-release/ag-schneiderman-announces-major-nationwide-agreement-nbty-herbal-supplement-maker; and https://ag.ny.gov/press-release/ag-schneiderman-announces-agreement-gnc-implement-landmark-reforms-herbal-supplements.

[17] Cohen PA. The Supplement Paradox: Negligible Benefits, Robust Consumption. JAMA. 2016;316(14):1453-1454.

[18] *See* 21 U.S.C. § 355; 21 C.F.R. pt. 330; FDA Website, Drug Applications for Over-the-Counter-Drugs, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/Over-the-CounterDrugs/default.htm

B. *The Former-Attorney General And FDA Have Cautioned That "Substituting" Dietary Supplements For Proven Drugs Could Substantially Harm The Public Health.*

Based on the enormous differences in the federal oversight of drugs and dietary supplements, the former-Attorney General Lynch observed in connection with a dietary supplement enforcement sweep:

> What many Americans don't know is that dietary supplements are *not subject to testing [by FDA] before they reach the store shelves – meaning that every day, millions of Americans are ingesting substances whose safety and efficacy are not guaranteed. Some of these supplements are simply a waste of money, promising results that they can't deliver or advertising ingredients that they don't contain. And too often, these supplements don't just abuse consumer trust – they also endanger public health. Some contain harmful ingredients, causing consumers to fall ill. Others falsely claim to cure illness and disease, leading patients to use them as a substitute of proven therapies they may need. But whether these supplements are deceptive or dangerous, the fact remains that too many companies are making profits by misleading – and in some cases harming – American consumers.*[19]

FDA, on its website, posts similar cautionary statements about dietary supplements. Such statements include:

- *"Dietary supplement manufacturers do not have to get the agency's approval before producing or selling these products."*[20]

- *"Federal law does not require dietary supplements to be proven safe to FDA's satisfaction before they are marketed."*[21]

- "For most claims made in the labeling of dietary supplements, the law does not require the manufacturer or seller to prove to FDA's satisfaction that the claim is accurate or truthful before it appears on the product."[22]

- "In general, FDA's role with a dietary supplement product begins after the product enters the marketplace. That is usually the agency's first opportunity to take action against a

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[19] Attorney General Lynch Discusses Department's Efforts to Protect Consumers From Unsafe Dietary Supplements, Department of Justice, Office of Public Affairs, March 8, 2016, https://www.justice.gov/opa/pr/attorney-general-lynch-discusses-departments-efforts-protect-consumers-unsafe-dietary

[20] FDA 101: Dietary Supplements, https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm050803.htm

[21] *Id.* (emphasis added).

[22] *Id.*

product that presents a significant or unreasonable risk of illness or injury, or that is otherwise adulterated or misbranded."[23]

- **"Using supplements improperly can be harmful.** Taking a combination of supplements, using these products together with medicine, or *substituting them in place of prescribed medicines could lead to harmful, even life-threatening, results.*"[24]

- **"Some supplements can have unwanted effects before, during, or after surgery.** For example, bleeding is a potential side effect risk of garlic, ginkgo biloba, ginseng, and Vitamin E. In addition, kava and valerian act as sedatives and can increase the effects of anesthetics and other medications used during surgery. Before surgery, you should inform your health care professional about all the supplements you use."[25]

Significantly, both the former-Attorney General and FDA itself have specifically cautioned that "substituting" dietary supplements for proven drugs could substantially harm the public health. Given these consistent federal statements, Medicare beneficiaries will at best be confused, and at worst will feel deceived and frustrated, if they are forced onto supplements to treat their illnesses before they can access the prescriptions written for them by their doctors. It is simply inconsistent for CMS to permit Plans to do so in the name of the Medicare drug benefit.

Consider, for example a dietary supplement containing kava, which is marketed for relaxation and to promote stress relief, such as Kavana's Kava Kava (see image below).[26] *If such supplements were substituted for FDA-approved drugs, such as antidepressants, the patients receiving the supplements would likely be grossly under-treated. Although kava kava may promote relaxation and stress relief – although even that has not been proven to FDA – it has not been proven to treat depression. Nor, to our knowledge, has it been shown by scientific evidence to be comparable to antidepressants.*

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[23] *Id.*

[24] *Id.* (emphasis added). *See also* Geller AI, et al. N Engl J Med. 2015;373:1531-40; Cohen PA. Hazards of hindsight--monitoring the safety of nutritional supplements. N Engl J Med. 2014;370(14):1277-80.

[25] FDA 101: Dietary Supplements, https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm050803.htm

[26] Kavana Kava Kava, available at https://www.amazon.com/Kavana-Supplements-Extract-Supplement-Capsules/dp/B015NLOMJK/ref=sr_1_7_a_it?ie=UTF8&qid=1519225557&sr=8-7&keywords=Kava

Indeed, as discussed in more detail in Section III below, FDA's regulatory scheme attempts to protect against this type of substitution. Even marketing a dietary supplement with promotional claims indicating the product can be used as a substitute for a drug (or marketing the product with promotional claims suggesting that the product can be used to treat, prevent, cure or mitigate disease), renders the product an illegal unapproved "drug" under the FDCA.[27]

C. *Even When Dietary Supplements Are Derived From Similar Products As Drugs, They May Be Less Efficacious For The Treatment Of Disease – Or Not Efficacious At All.*

Kava kava is far from the only example. Amarin markets Vascepa® (icosapent ethyl) capsules in the United States. Vascepa®, an FDA-approved drug comprised of a single molecule omega-3 acid, is derived and highly purified from fish. It is a pure, single omega-3 acid that is synthetically produced to be a significantly more potent omega-3 product than dietary supplements containing common fish oil or krill oil. The eicosapentaenoic acid (the omega-3 fatty acid commonly known as "EPA") in Vascepa® is in ethyl ester form (E-EPA), unlike common fish oil. Vascepa® is FDA approved for use as an adjunct to diet to reduce triglyceride levels in adult patients with severe hypertriglyceridemia, based on substantial evidence from controlled clinical trials.[28]

Natural sources of EPA, such as common fish or krill oil, on their face, are much less potent. A consumer would have to consume a likely intolerable amount of common fish oil or common krill oil in an effort to even get the same dosage of E-EPA in Vascepa®. For example, a 350 mg capsule of MegaRed® Omega-3 Krill Oil contains approximately 50 mg of natural EPA in each

[27] 21 C.F.R. § 101.93(g)(2).

[28] *See* Vascepa® Full Prescribing Information, https://www.vascepa.com/assets/pdf/Vascepa_PI.pdf (hereinafter "Vascepa® Full Prescribing Information").

capsule,[29] whereas a 1 gram capsule of Vascepa® contains 1000 mg of E-EPA.[30] *Given that the FDA-approved dose of Vascepa®* to reduce triglyceride levels in adult patients with severe hypertriglyceridemia is 4000 mg per day (*e.g.*, two, 1 gram capsules twice a day), consumers would have to take approximately 80 capsules of MegaRed® Omega-3 Krill Oil daily to get a similar dose of EPA from that product as they would get from four, 1 gram capsules of Vascepa®. And, significantly, even if patients were willing to take 80 capsules of MegaRed® Omega-3 Krill Oil, or another common fish oil, per day (and it is unlikely that they would be willing to do so), there would be no assurance that it would either have the same effect as Vascepa® or that such a large volume of common krill oil is safe.[31]

Yet, it would not be shocking to imagine, if CMS were to permit the use of dietary supplements in substitution for prescription drugs, that certain Part D Plans might try substitute fish oil in patients suffering from cardiovascular disease instead of the prescription drugs that they need. By doing so, part D Plans would be misleading patients. In fact, a recent meta-analysis of large cardiovascular outcomes trials published in JAMA demonstrated that dietary supplement doses of fish oil have no cardiovascular benefit.[32] (Ironically, the costs of using a dietary supplement to achieve an adequate dose of EPA equivalent to 2 grams of Vascepa® may also be higher than the prescription itself, a point that likely would be lost on Part D plans).

Finally, even when dietary supplements and drugs both contain similar components, they may have wholly different active moieties (i.e., the functional part of a drug molecule), which may make them have different risk/benefit profiles. For example, FDA has explicitly determined that Lovaza®, an FDA-approved drug that contains a mixture of omega-3 fatty acids in the ethyl ester form, has a different "active ingredient" and a different "active moiety" than Vascepa®, which is almost 100% E-EPA.[33] Thus, common fish or krill oil dietary supplements, which unlike Vascepa®, contain multiple fatty acids – have a wholly different active moiety than Vascepa®.

D. Dietary Supplements Pose Particular Threats To The Public Health When Their Labeling Omits Important Contraindications, Warnings, Or Other Information

As mentioned, there is no guarantee that dietary supplements are safe or effective, and FDA does not review the labeling of dietary supplements before they are marketed to make sure that the labeling is not false or misleading. Moreover, there is no FDA requirement that dietary supplement labeling contain relevant warnings and contraindications.

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[29] *See* MegaRed Website, https://www.schiffvitamins.com/product/megared-superior-omega-3-krill-oil-350mg-65-ea-020525104342

[30] *See* Vascepa® Full Prescribing Information.

[31] Mason RP, Sherratt SCR. Omega-3 fatty acid fish oil dietary supplements contain saturated fats and oxidized lipids that may interfere with their intended biological benefits. Biochem Biophys Res Commun. 2017;483(1):425-429.

[32] Aung T, et al. Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks: Meta-analysis of 10 Trials Involving 77 917 Individuals. JAMA Cardiol. 2018 Jan 31. doi: 10.1001/jamacardio.2017.5205. [Epub ahead of print].

[33] *See* FDA Letter to Robert A. Dormer, Hyman, Phelps & McNamara, regarding Vascepa's Exclusivity Determination, dated May 31, 2016.

Significantly, FDA requires warnings and contraindications to be listed in *drug* labeling,[34] but not in dietary supplement labeling. In fact, only five statements are required for dietary supplement labeling: (1) the statement of identity, (2) the net quantity, (3) the nutrition labeling, (4) the ingredient list, and (5) the name and place of the manufacturer.[35] Because information regarding warnings and contraindications is not included in dietary supplement labeling, physicians and Medicare beneficiaries in the Part D program may not know that there are safety issues associated with a product.

For example, as mentioned, FDA's website warns that "bleeding is a potential side effect risk of garlic, ginkgo biloba, ginseng, and Vitamin E . . . [and that] kava and valerian act as sedatives and can increase the effects of anesthetics and other medications used during surgery."[36] Yet, the labeling for many of those products does not contain such warnings. Again, consider Kavana's Kava Kava product, for example. That product, which is marketed on Amazon, contains no warnings about the potential hazards of using the product prior to surgery.[37]

Similarly, the labeling for this ginkgo biloba dietary supplement (below) lacks a warning specific to the bleeding risk associated for ginkgo biloba, that is referenced on FDA's website.

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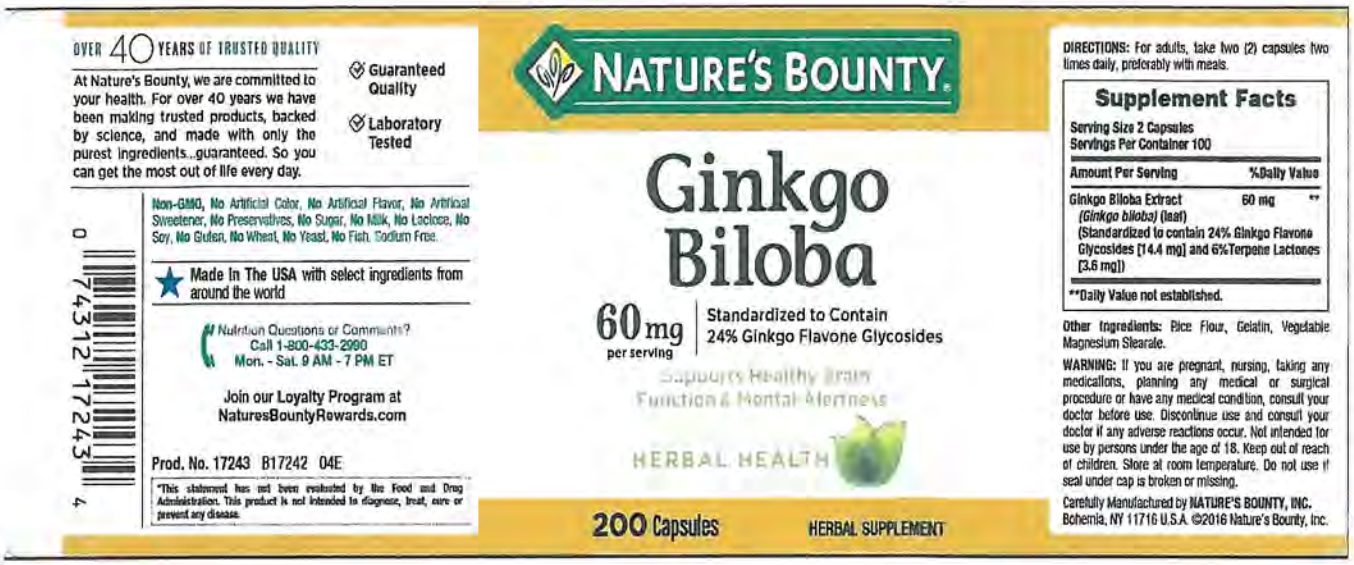
[34] 21 C.F.R. § 207.56.

[35] *See id.* §§ 101.3(a), 101.105(a), 101.36, 101.4(a)(1), 101.5; see also Guidance For Industry: A Dietary Supplement Labeling Guide (April 2005).

[36] FDA 101: Dietary Supplements, https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm050803.htm

[37] https://www.amazon.com/Kavana-Supplements-Extract-Supplement-Capsules/dp/B015NLOMJK/ref=sr_1_1_sspa?ie=UTF8&qid=1519250723&sr=8-1-spons&keywords=kava+kava&psc=1 (last checked February 21,2018)



In addition, many manufacturers of dietary supplements containing fish oil, or omega-3, fail to provide consumers with the following critical warnings and disclosures that FDA-approved prescription drugs containing omega-3 are required to provide.

- Increased Bad Cholesterol (for products that contain DHA) – It is well understood in the medical community that omega-3 products that include DHA can raise levels of bad cholesterol (LDL-C) in diseased patients for which omega-3 drugs are typically prescribed.[38] Accordingly, manufacturers of prescription omega-3 drug products that contain DHA, such as Lovaza®, are required to include the following statement, or similar language, in the Warnings and Precautions section of the prescribing information: "In some patients, LOVAZA increases LDL-C levels. LDL-C levels should be monitored periodically during therapy with LOVAZA."[39]

- Increased Liver Enzymes - Increases in certain liver enzymes have been observed in patients with poor liver function who are taking omega-3 prescription drug products.[40] The FDA-approved "Patient Information" for such drugs instructs patients to tell their doctor if they have liver problems before taking the medication and alerts patients to the fact that their doctor should do liver function tests because certain liver enzyme levels may increase while they are taking the products.[41]

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[38] *See* Weintraub, H. Overview of Prescription Omega-3 Fatty Acid Products for Hypertriglyceridemia. Postgraduate Medicine. 2014; 126:7-18 ("Weintraub"); see also FDA Medical Review of Omtryg, FDA Reference ID 3413782 at p. 19, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204977Orig1s000TOC.cfm ; *see also* Wei MY, Jacobson TA. Curr Atheroscler Rep. 2011;13:474–483.

[39] Lovaza Prescribing Information, https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Lovaza/pdf/LOVAZA-PI-PIL.PDF

[40] *See, e.g.,* Lovaza Prescribing Information, https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Lovaza/pdf/LOVAZA-PI-PIL.PDF

[41] *See id.*

- Prolonged Bleeding Time – All prescription omega-3 drugs are required to state under the "Drug Interactions" section in their labeling that some published studies with omega-3 have demonstrated prolongation of bleeding time, and to advise physicians that patients receiving treatment with these and other drugs affecting coagulation (*e.g.*, anti-platelet agents) should be monitored periodically.[42]

That products marketed as dietary supplements that also contain DHA do not use this warning is particularly unconscionable because: (1) many consumers take omega-3 products to help with *cardiovascular health*, and (2) bad cholesterol (LDL-C), is an FDA-recognized surrogate for *increased cardiovascular risk.*[43]

One example of labeling for an omega-3 supplement that omits this type of information is immediately below.

In addition, FDA requires FDA-approved omega-3 drug products marketed with claims indicating that the products can lower triglyceride levels in statin treated patients with persistently high triglyceride levels to provide certain disclosures to avoid misleading patients.[44] These disclosures, for example, include a statement that there is uncertainty with regard to whether lowering triglyceride levels in this patient group has a beneficial effect on overall cardiovascular health. No such disclosure is required regarding dietary supplements.

III. Any CMS Policy That Encourages the Substitution of Prescription Drugs with "Dietary Supplements" Would Be in Violation of Other Federal Laws

[42] *See id.*

[43] *See* Weintraub.

[44] *See Amarin Pharma, Inc., et al. v. Food & Drug Administration, et al.* (1:15-cv-03588-PAE) (S.D.N.Y.); *see also Amarin Pharma, Inc., et al. v. Food & Drug Administration, et al.* (1:15-cv-03588-PAE) (S.D.N.Y.) (March 8, 2016) (Stipulation and Order of Settlement).

As referenced above, pursuant to the FDCA and its implementing regulations, a dietary supplement cannot be marketed with a "disease claim" (*i.e.*, a claim that the product is intended to treat, prevent, cure, or mitigate a disease) without invoking unlawful "drug" status.[45] Moreover, FDA regulations specifically provide that "disease claims" include claims that a purported dietary supplement is a substitute for a "product that is a therapy for a disease."[46] If this were not the case – if products marketed as dietary supplements could be marketed with "disease claims" or as substitutes for drugs – then a large number of products could evade FDA's drug approval process and manufacturers would have no incentive to invest in the scientific research that would otherwise be necessary for drug approval.[47] Given that these products cannot be marketed with disease claims, it follows that Part D plans should not be *using* these products to treat disease.

Congress and FDA clearly do not intend for dietary supplements to be widely used to treat disease or widely used as substitutes for drugs. Any CMS policy that explicitly or even implicitly could be interpreted (and would be understood) to encourage dietary supplements to be substituted for drugs, therefore, would stand as an obstacle to Congress' and FDA's objectives, ultimately undermining the provisions in the FDCA intended to drive scientific investigation and undermining the drug approval requirement.[48]

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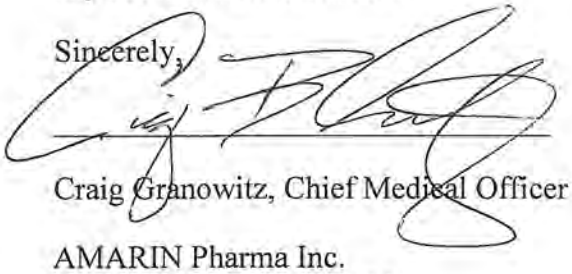
We appreciate that CMS may have intended only to permit OTC drugs to be substituted for prescription drugs – and not dietary supplements as well. Because both products can be bought off the shelf, it is a common mistake for many to refer to "OTCs and supplements" together, or indeed to incorrectly assume that they are the same. However, as demonstrated above, there is a world of difference between drugs – including OTC drugs – and dietary supplements. As such, and whatever CMS opts to do in permitting PDPs to use OTC drugs in lieu of prescription drugs, it should ban the use of dietary supplements in the Part D program.

We thank you for consideration of these comments, and welcome any questions or follow up that you may have. Please feel free to contact me at craig.granowitz@amarin.com if we can provide any additional information.

Sincerely,



Craig Granowitz, Chief Medical Officer

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[45] 21 U.S.C. §§ 321(g)(1)(B), 343(r); 21 C.F.R. § 101.93(g).
[46] 21 C.F.R. § 101.93(g)(2)(vi).
[47] *See* 21 U.S.C. § 355(a).
[48] *See* 21 U.S.C. § 355(a).