July 8, 2019

Submitted via Regulations.gov

Divisions of Docket Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

CITIZEN PETITION

Medical Research Collaborative, LLC submits this petition under 21 C.F.R. § 10.30 of the Federal Food, Drug, and Cosmetic Act (FDCA), to request that the Commissioner of Food and Drugs (Commissioner) take the actions identified in section A below.

A. Actions Requested

Medical Research Collaborative respectfully requests of the Commissioner that ethyl ester, re-esterified triglyceride, free-fatty acid (aka "carboxylic-acid"), mono- and di-glyceride forms of omega-3 fatty acids be officially ruled by the FDA as being dietary ingredients.

B. Statement of Grounds

In a bid to have the right to purchase high-purity omega-3 supplements stripped from U.S. consumers, Amarin Corp. attempted to circumvent the jurisdiction granted by Congress to the USFDA by issuing a Complaint to the ITC to judge all such supplements as "drugs" and not "dietary supplements." It is clear that high-purity ethyl ester eicosapentaenoic acid (EPA-E) was in use as a dietary ingredient well before the Investigational New Drug Application (IND) for Vascepa (no. 102,457 [1]) was granted. Thus, code 21 USC 321(ff)(3)(B) of the FD&C Act[2] does not preclude high-purity EPA-E as a dietary ingredient in that regard. However, Amarin argued more broadly that products containing ethyl ester forms (also re-esterified triglyceride (rTG) and other forms that use a transesterification step as part of their

[1] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202057orig1s000clinpharmr.pdf
[2] https://codes.findlaw.com/us/title-21-food-and-drugs/21-usc-sect-321.html

formulation) of EPA and/or docosahexaenoic acid (DHA) and other fatty acids, are not dietary supplements as defined by the FD&C Act, and further, that their use historically as such only came after these semi-synthetic versions of omega-3 fatty acids were granted INDs.[3]

> "Amarin's Complaint: In August 2017, Amarin filed a complaint with the Commission alleging that certain competitors are falsely labeling or deceptively describing synthetically produced omega-3 products as (or for use in) "dietary supplements" when the products are in fact "drugs" that have not been approved for sale or use in the United States. Appx19–29. (Amarin's complaint applied only to a small group of synthetically modified products, not to the majority of fish oil dietary supplements.) Amarin alleged that those acts constitute unfair acts or unfair methods of competition under Section 337 of the Tariff Act. Appx24 ¶ 1; see 19 U.S.C. § 1337. Amarin also asserted that those unfair acts violate Section 43(a) of the Lanham Act because falsely labeling or deceptively describing drugs as (or for use in) dietary supplements deceives consumers and others in the supply chain regarding the nature of the product. Appx24 ¶ 1; see 15 U.S.C. § 1125(a)(1). Amarin alleged that its domestic-industry commercial interests were being injured as a result of certain competitors' false and deceptive representations concerning the nature and characteristics of their imported products. Appx115–126."

FDA interprets the FD&C Act as defining a "dietary supplement" as that containing one or more "dietary ingredients," further delineated as follows:[4]

> "As defined in section 201(ff)(1) of the FD&C Act (21 U.S.C. 321(ff)(1)), a "dietary ingredient" is any one of the following:
>
> > (A) A vitamin;
> > (B) A mineral;
> > (C) An herb or other botanical;
> > (D) An amino acid;
> > (E) A dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
> > (F) A concentrate, metabolite, constituent, extract, or combination of any ingredient described in (A), (B), (C), (D), or (E)."

This includes synthetic or semi-synthetic forms of vitamins, minerals and amino acids. However, synthetically or semi-synthetically produced botanicals, and even esterified omega-3s (as well as other esterified nutrients) at some point may not be deemed to be dietary ingredients (FDA hasn't issued final guidance on this yet). In their natural forms, EPA and DHA are considered essential fatty acid nutrients, fitting in the category: *"a dietary substance for use by man to supplement the diet by increasing the total dietary intake…"* But in esterified form, they may not be deemed thus.

From the latest FDA-draft guidance on this topic as of July 2019:[5]

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[3] https://investor.amarincorp.com/static-files/a39c4d56-8aa5-424c-9490-8f7b43777f19

[4] https://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/UCM515733.pdf

"5. *If I alter the chemical structure of a dietary ingredient, is the new substance still a dietary ingredient?*

It depends. Altering the chemical structure of a dietary ingredient (e.g., creation of new stereoisomers, addition of new chemical groups **as in esterification**) creates a new substance that is different from the original dietary ingredient. The new substance is not considered to be a dietary ingredient merely because it has been altered from a substance that is a dietary ingredient and, therefore, is in some way related to the dietary ingredient.

In some cases, however, the new substance may independently qualify for one of the dietary ingredient categories listed in section 201(ff)(1) of the FD&C Act. For example, taurine is the end product of the metabolism of the amino acid cysteine. It is thus a metabolite of an amino acid and fits one of the definitions of a dietary ingredient (see 21 U.S.C. 321(ff)(1)(D), (F)). The enzymatic or synthetic processing of cysteine or any other dietary ingredient would be an appropriate method for the manufacture of a metabolite of a dietary ingredient like taurine for use in a dietary supplement…"

The language in the above mention seems to suggest that an esterified product is not deemed to be a dietary ingredient, but it is not definitive. It asserts only that the esterified form is a "new substance" and that this "new substance is not considered to be a dietary ingredient *merely because* it has been altered from a substance that *is* a dietary ingredient…" It does not explicitly state that this new substance *"is not a dietary ingredient,"* only that it is a "new substance" that cannot be deemed a dietary ingredient solely (aka "merely") on the basis that its unaltered form *is* a dietary ingredient. That does not preclude other rationale for it to potentially be considered a dietary ingredient. As such, some or all esterified products could still fall in line with the requirement to be reported as a New Dietary Ingredient (NDI), which is the main subject matter of this draft guidance document the mention is found in, entitled, *"Dietary Supplements: New Dietary Ingredient Notifications and Related Issues: Guidance for Industry."*

As an aside, we wonder here if FDA did not instead mean *transesterification* [6] when they wrote "esterification" above, as the latter is also a natural process and frequent result of human metabolism[7] (as is "re-esterification"[8]). In fact, any process (metabolic or otherwise) that results in an ester being made is technically an 'esterification process.' This occurs when, for example, a fatty acid is combined with an alcohol (such as ethanol, glycerol, etc.).[9] Triglycerides are thus fatty acid esters of glycerol, formed as a result of esterification.[10]

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[5] https://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/UCM515733.pdf

[6] https://chem.libretexts.org/Bookshelves/Organic_Chemistry/Supplemental_Modules_(Organic_Chemistry)/Esters/Reactivity_of_Esters/Transesterification

[7] https://www.ahajournals.org/doi/full/10.1161/01.atv.15.11.1819

[8] http://www.jlr.org/content/31/8/1423.long

[9] https://www.sciencedirect.com/topics/food-science/esterification

[10] https://chem.libretexts.org/Courses/University_of_Kentucky/UK%3A_CHE_103_-_Chemistry_for_Allied_Health_(Soult)/Chapters/Chapter_14%3A_Biological_Molecules/14.2%3A_Lipids_and_Triglycerides

The *"It depends"* mention in the draft guidance above relating to metabolites might therefore still be applicable to esterified forms of EPA and DHA, but not *ethyl* ester forms, which cannot be achieved as a result of human metabolism (no naturally occurring *ethanol*). However, so called "monoglyceride omega-3s" would appear to fit the excepted clause,[11, 12, 13, 14, 15, 16] along with free-fatty acid[17] (aka "carboxylic-acid") and rTG forms, as we will elaborate on forthcoming.

The draft guidance clarifies that if a product was in use before Oct. 1994, it may be "grandfathered in," and not required to be reported as a "New Dietary Ingredient" (NDI). Yet, the guidance also states that an ingredient must first be defined as a "dietary ingredient" to then be either an NDI or not. Thus, the main question (and it is an open question) is whether or not the FD&C Act precludes ethyl ester forms (and potentially rTG and other forms that first rely upon a transesterification step) of EPA and DHA being deemed "dietary ingredients."

Another mention by FDA in a letter to AIBMR Life Sciences brought up in Amarin's appeal is also relevant.

[To AIBMR]:

> "Based on the information in your submission, it is unclear if "fatty acid esters, derived from anchovy or menhaden oil" which you intend to market under the trade name Provinal™ is a "dietary ingredient" within the meaning of21 U.S.C. 32l(ff)(l). For example, synthetic fish oil fatty acid ethyl esters do not fit within the statutory definition of "dietary ingredient" because they are not constituents of a dietary substance for use by man under section 201(ff) (l)(F). Therefore, FDA cannot determine, at this time, whether your product contains a dietary ingredient that may lawfully be marketed as a dietary supplement."

However, once again we are met with open-ended phrases such as "*it is unclear if*…" and "FDA *cannot determine, at this time*, whether your product contains a dietary ingredient (DI)…" FDA acknowledges that ethyl ester forms of fatty acids (including omega-3s, such as EPA and DHA) may lie outside the statutory definition of a DI, but do not go one step further and outright state they are *not* DIs. They conclude only it is "unclear" and "cannot be determined at this time." That leaves open a future determination by FDA that EPA-E and DHA-E are DIs.

According to the FD&C Act as interpreted by FDA, synthetic vitamins, minerals, and amino acids are considered dietary ingredients despite their synthetic nature. But that does not mean all other synthetic ingredients are precluded as DIs. For instance, FDA mentions "vanillin" and "cinnamic acid" as synthetic botanical constituents that are considered "dietary ingredients," due to their long-standing use in food products and very safe track record. The same could potentially be said of ethyl ester omega-3s, included in food products for many years now.[18]

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[11] https://pubs.rsc.org/en/Content/ArticleLanding/2018/CP/C8CP04256J#!divAbstract
[12] https://link.springer.com/article/10.1007/BF01569662
[13] http://thriveveteranscenter.com/wp-content/uploads/2018/08/Fish-Oil.pdf
[14] https://patents.google.com/patent/US5935828A/en
[15] https://store.amymyersmd.com/products/complete-omega-3-softgels
[16] https://neptunecorp.com/en/what-we-do/ingredients/maxsimil/
[17] https://patents.google.com/patent/US9050309B2/en
[18] https://onlinelibrary.wiley.com/doi/pdf/10.1002/lite.201400004

In a warning letter to an "ethyl ester creatine" merchant, there is found no mention of the substance itself being deemed as not qualifying as a dietary ingredient, only issues regarding labeling and quality control.[19] If FDA deemed ethyl ester creatine to not be a DI, it would be most straightforward for them to have notified the merchant that they were selling a "drug," not a "dietary ingredient." The omission of such may in one respect be interpreted as a concession, or at least as carefully leaving room for a future determination to regard certain ethyl ester products as dietary ingredients.

The following from the draft guidance in question may allow reconstituted (aka "re-esterified") TG (rTG) forms, which return EPA-E/DHA-E to their original TG-form components as found in nature (plus some metabolites) and absent any ethanol, to be considered DIs:

> "If reagents used during processing are likely to make covalent changes to components in the mixture during processing, you should determine **whether the new material is still a dietary ingredient**. For example, use of a large amount of an oxidizing acid like sulfuric acid to process a botanical mixture may create a new "semi-synthetic" mixture that is no longer a mixture of **components that were present in the original plant**. Therefore, the mixture would **no longer** be a dietary ingredient."

Contrariwise, it could be said that "components that were present in the original plant" that are part of the "new material" *are* dietary ingredients, despite the semi-synthetic nature of the composition.

A description of rTG (and other forms) is as follows:[20]

> "DHA and EPA supplements can be given as free fatty acids (FFA), natural and reconstituted triglycerides and ethyl esters. Natural fish oil triglycerides (nTG) correspond to 100% triglycerides whereas chemically reconstituted triglycerides (rTG), as defined in the European Pharmacopeia are a mixture of monoglyceride (MG),12 diglyceride (DG) and triglycerides with triglyceride being the main component (>60%)."

Nordic Naturals' products take advantage of a process that yields an even higher percentage of TG in the final composition:[21]

> "Until recently, Nordic Naturals fish oil products contained up to 60% triglycerides (with the remaining 40% comprised of diglycerides and monoglycerides). Now, however, we have perfected the technology that allows us to reassemble 93% of the fatty acids in our fish oils into the triglyceride form (with only 7% monoglycerides and diglycerides)."

They also provide helpful graphics to illustrate the components and their metabolism:

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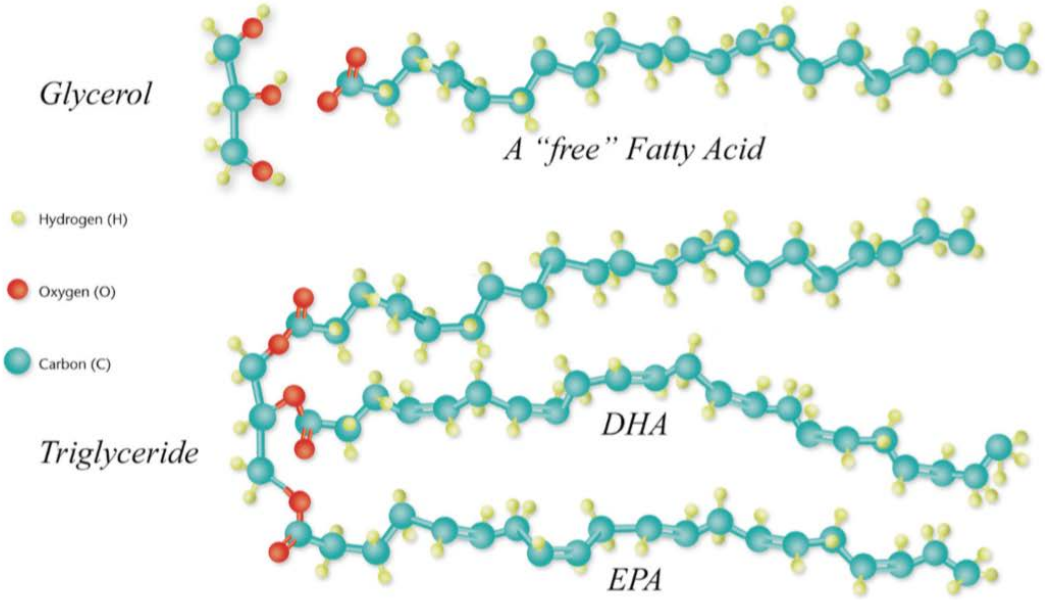
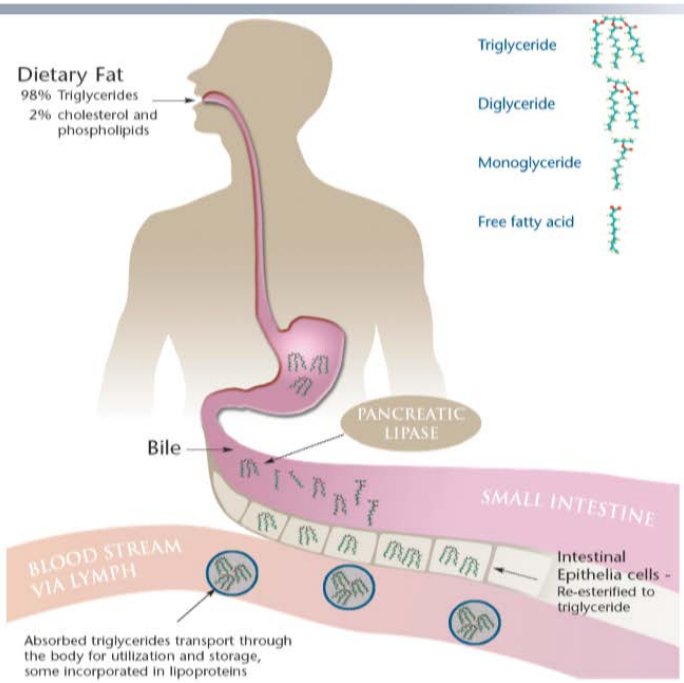
[19] https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2014/ucm421502.htm
[20] http://apjcn.nhri.org.tw/server/APJCN/19/4/499.pdf
[21] http://www.promedics.ca/site/downloads/Nordic%20rTGtrifoldLOW.pdf

Essential Omega-3 Fatty Acids



Absorption - designed to digest triglycerides



Thus, the rTG form is a mixture of what exists in the "original" fish oil, with a lesser percentage of the components that are known metabolites as the body breaks down TGs into free fatty acids (FFA) and monoglycerides, with some diglycerides also present[22] (thus, monoglyceride, diglyceride, and FFA forms of omega-3s that rely on a previous transesterification step may also be included in this discussion). Re-esterification is part of this natural metabolism process, with ethanol absent in the final composition.[23] Therefore, by our reading of FDA guidance, rTG forms of EPA/DHA should pass muster as dietary ingredients, due to being comprised of 1) mostly TG forms, which are present in the "original" nutrient source (i.e. anchovy, sardines, etc.), and 2) metabolites of a dietary ingredient: monoglyceride and diglyceride EPA/DHA. The process also need not take place in the human body:

> "A metabolite that has been synthesized from another dietary ingredient would be a dietary ingredient under section 201(ff)(1)(F) and could be used as a dietary ingredient in a dietary supplement. Although the definition of a metabolite requires human ingestion of the dietary ingredient to increase the production or flux of the metabolite in the human body, it does not require the metabolism to actually take place in a human being during the manufacture of a dietary ingredient. A metabolite may be synthetically produced, provided that the starting material is a dietary ingredient and the production process mimics the metabolic process in the body following ingestion."

The only detraction to this argument appears to be the last sentence in the above, which might exclude rTG forms in a very strict reading, as an intermediary transesterification process does occur that breaks off the glycerol "backbone" and causes the resultant free fatty acids to cleave to ethanol. This greatly helps concentrate the EPA and/or DHA present in the crude batch via subsequent molecular distillation. But the final rTG product form contains only natural EPA-TG and/or DHA-TG and metabolites of EPA-TG/DHA-TG.

Whether ethyl ester forms of EPA and DHA (whereby the free fatty acids remain cleaved to ethanol) are dietary ingredients would not be defensible by this argument, however. Yet by extension, it may be. FDA has stated the following with regard to ethyl alcohol in goods or in the manufacture of foods:[24]

> "Practically and scientifically, pure ethyl alcohol synthesized from natural gas or petroleum products does not differ from that obtained by fermentation with subsequent distillation. Furthermore, foods in which one is used cannot be distinguished objectively from those in which the other is used.
>
> POLICY:
>
> Synthetic ethyl alcohol may be used as a food ingredient or in the manufacturing of vinegar or other chemicals for food use, within limitations imposed by the Federal Food, Drug, and Cosmetic Act, the Alcohol Administration Act, and regulations promulgated under these acts."

Also, the human body metabolizes the consumption of alcohol and fatty acids to make "fatty acid ethyl esters" (FAEE), which in this case cannot then be considered synthetic.[25]

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[22] http://www.jbc.org/content/281/1/491.full.pdf
[23] https://www.ncbi.nlm.nih.gov/pubmed/2280183
[24] https:/www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074550.htm
[25] http://www.jlr.org/content/42/7/1025.full

> "A number of intracellular proteins have been isolated from different sources and shown to catalyze esterification of fatty acids to ethanol (12–14). By aminoterminal-sequence analysis, it was shown that two of these purified FAEE synthases are apparently identical to liver microsomal carboxylesterase ES-10, the predominant carboxylesterase in rat liver (15, 16). Other enzymes such as pancreatic cholesterol ester synthase (17) and pancreatic carboxylester synthase (18) also have been shown to possess some FAEE synthesizing activity. FAEE also can be synthesized by transesterification of ethanol and fatty acyl-CoA, a reaction catalyzed by acylcoenzyme A:ethanol O-acyltransferase (AEAT)."

Beyond these observations, there is room for interpretation of the following mention from the current draft guidance:

> "**Synthetic** vitamins, minerals, and amino acids are recognized as dietary ingredients **because** a vitamin, mineral, or amino acid **is defined by its nutritional function** (its **ability to provide nutrients** to the human body), **not by its state of matter** like a botanical."

For example, a synthetically produced amino acid, i.e. L-carnitine, which is often taken as a weight-loss supplement,[26] is considered a DI based upon its ability to provide L-carnitine to the human body, and the identification of L-carnitine as a "nutrient" itself—as opposed to a synthetic botanical such as echinacea, which cannot in and of itself be considered a "nutrient"—and furthermore, *"A substance that has been synthesized in a laboratory or factory **has never been part of an herb or other botanical** and, therefore, is not a dietary ingredient under section 201(ff)(1)(C) of the FD&C Act."* But EPA-E and DHA-E *were* "part of" a natural food source, and further, are directly assimilated in and used by the human body as nutrients (essential fatty acids). Therefore, it may be more apt to consider EPA and DHA in a similar category as "vitamins, minerals and amino acids," or perhaps more succinctly for them all: *nutrients*. Certainly, the end result is the same—500 mg of EPA-E and 500 mg of NTG EPA will both result in increases in serum EPA levels, which the human body will utilize as it needs. This is similar to various forms of vitamin E, in fact, available in natural, synthetic and semi-synthetic forms.[27, 28]

Furthermore, one could argue that since semi-synthetic and synthetic fats of various kinds have long been used as dietary ingredients, such as hydrogenated oil (common fat bound to hydrogen) and "Olestra" (a sucrose polyester), and because EPA/DHA are fatty acids themselves, that a semi-synthetic modification of these falls under the same category of DI.

Amarin's goal was to get the Federal Circuit to remand the Complaint back to the ITC, charging them to investigate the matter in the hopes that they would rule ethyl ester fatty acids, including any that rely on a transesterification step (rTG forms, etc.), are drugs and not dietary supplements, despite their safe use for decades as dietary supplements across the globe. That would have, unwittingly to millions of Americans, stripped the US consumer of their right to these forms of omega-3s (and presumably other ethyl ester supplements), as nearly all high-purity forms of omega-3s must rely on a transesterification step to achieve high percentage yields of EPA and/or DHA. The ITC would have then had to decide whether to infer from the FDA draft guidance or not, and whether it should be concluded that EPA-E is *not* a dietary ingredient, but exclusively a drug, from its interpretation of the FD&C Act. This was in our

[26] https://www.ncbi.nlm.nih.gov/pubmed/27335245
[27] https://www.naturalproductsinsider.com/heart-health/many-forms-vitamin-e
[28] https://acgrace.com/natural-vs-synthetic-vitamin-e/

view a clear move to stifle fair competition, and to monopolize access to a product they did not even invent (the process to make high purity EPA-E was discovered by Nissui in the early 1980s, and used to make Epadel from ca. 1990 onwards [29]), potentially in violation of federal antitrust laws,[30] and with full disregard to the fact that Congress has solely charged the FDA with the ministerial role of interpreting and applying the FD&C Act.[31]

The FDA issued the following statement to the ITC on the case:[32]

> "FDA respectfully submits that the Commission should decline to initiate the requested investigation. As pled, Complainants' claims—unfair methods of competition under the Tariff Act based on false advertising under the Lanham Act and violations of the Federal Food Drug and Cosmetics Act ("FDCA")—can succeed only if the Commission finds that Respondents' products are unapproved "new drugs" rather than "dietary supplements" under the FDCA. The Complaint here is predicated on open questions of law and policy on which FDA has not reached final conclusions. Any such findings by the Commission on those issues may conflict with later determinations by FDA. Further, through the Complaint, Complainants attempt an unlawful private FDCA enforcement action based on Complainants' allegations, not on FDA's findings. As detailed below, because Congress has authorized only FDA to initiate FDCA enforcement actions, the FDCA precludes claims that would require the adjudicator to interpret, apply, or enforce the FDCA. For Complainants to succeed on any of their claims, the Commission would have to do all three of those things."

In agreeance with the declaration from the FDA above, the Federal Circuit issued a ruling against Amarin Corp., 2-1, with the dissenting opinion not disagreeing with the ruling of the majority necessarily, but only in that the dissenting justice viewed the case to be outside the Federal Circuit's jurisdiction, that the grounds upon which an appeal to the decision by the ITC weren't even met. The dissenting justice's view pertains to a subtlety of law, whereby only the ITC's "final determination" may be appealed, not their decision "not to institute an investigation."[33] The majority ruled that the ITC was correct in not instituting the investigation as the subject matter lied outside their jurisdiction. In essence, it was a majority verdict against Amarin, and was essentially thrown out of court.

FDA is currently working on a master list of those "grandfathered-in dietary ingredients," including all products that are considered "dietary ingredients" and are exempted from reporting as NDIs by FDA.[34] If ethyl ester forms of omega-3s make it onto the list, then that would resolutely absolve manufacturers of the same.

In the final part of the approved drug/investigational drug exclusion from the definition of a "dietary supplement" is the provision, *"unless the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this Act."* In FDA's Draft

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[29] http://www.nissui.co.jp/english/corporate/frontier/15/index.html
[30] https://www.ftc.gov/tips-advice/competition-guidance/guide-antitrust-laws/antitrust-laws
[31] https://www.fda.gov/about-fda/fda-basics/what-difference-between-federal-food-drug-and-cosmetic-act-fdc-act-fda-regulations-and-fda-guidance
[32] https://wlflegalpulse.files.wordpress.com/2017/11/fda-letter-to-usitc.pdf
[33] http://www.cafc.uscourts.gov/sites/default/files/opinions-orders/18-1247.Opinion.5-1-2019.pdf
[34] https://www.fda.gov/downloads/Food/NewsEvents/WorkshopsMeetingsConferences/UCM581835.pdf

Guidance for Industry: *Dietary Supplements: New Dietary Ingredient Notifications and Related Issues IV. D. 8 (July 2011)*, FDA provides its interpretation of this language as follows:

> "The general rule is that an article that has been authorized for investigation as a new drug or as a biologic before being marketed as a food or as a dietary supplement cannot be marketed as a dietary supplement if substantial clinical investigations of the article have begun and the existence of such investigations has been made public. FDA can create an exception to this prohibition by regulation, but only if the agency finds that the use of the article in dietary supplements would be lawful. To date, no such regulations have been issued. The appropriate mechanism to request such a regulation is to file a citizen petition under 21 CFR 10.30."

Hence, the grounds upon which this citizen petition is being filed.

The long history of safe use, both infused in food products and as the essential and predominant component of omega-3 dietary supplements, of ethyl ester omega-3s and other high-purity forms of omega-3s, including rTG, FFA, mono- and di-glyceride forms, that rely upon a transesterification step, should in our view qualify these substances to be officially ruled by the FDA as dietary ingredients, just as vanillin and cinnamic acid are, as in every manner, except officially acknowledged by the FDA, these omega-3 ingredients are in fact currently and widely being used as dietary ingredients, with the goal of supplying essential fatty acid nutrients to the bodies of those that consume them.

We think the vast majority of US citizens, who have enjoyed and derived benefit from such ingredients/supplements for decades now, would wholeheartedly agree. Indeed, the fact that the omega-3 market is now a multi-billion-dollar US industry speaks in stead of an overwhelming majority vote in this regard. We ask the Commissioner to consider the will of millions of Americans, who were unaware that a highly popular dietary supplement could have been removed from consumer access across the US for containing high-purity omega-3s, and even certain foods (including infant formula), in deciding on this provision that is of great importance to them, and by the same action remove the possibility of a later verdict in favor of Amarin Corp. or another company's monopolizing requests regarding these substances.

C. Environmental Impact

The actions requested herein are subject to categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31.

D. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted only upon the request of the Commissioner.

E. Certification

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information that are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the petitioner on or about the following date: April 15, 2019, during analysis of data concerning the company Amarin Corp. I am not being compensated for the submission of this petition. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

Steven Giardino
President and CEO
Medical Research Collaborative, LLC