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 and 21 C.F.R. § 10.31 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 that the Commissioner have Amarin Corp.'s U.S. Patent No. 8,188,146 (the '146 patent) removed from the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, also known as the *Orange Book*, for being improperly listed therein.

B. Statement of Grounds

Title 21 U.S.C. § 355(c)(3)(D)(ii)(I) (for 505(b)(2) NDAs); id. § 355(j)(5)(C)(ii)(I) (for ANDAs), states that an applicant *"may assert a counterclaim seeking an order requiring the [patent] holder to correct or delete the patent information submitted by the holder . . . on the ground that the patent does not claim either—(aa) the drug for which the application was approved; or (bb) an approved method of using the drug."*

Amarin Corp.'s U.S. Patent No. 8,188,146 (the '146 patent) does not claim an approved method of using the drug, promotes unapproved uses, and in fact eschews the only approved use for icosapent ethyl (aka "Vascepa"), namely, to treat hypertriglyceridemia. Further, its claims describe a product that is impossible to make, relying on the judicial exception of an abstract idea, and is materially different from the manufactured and sold drug, "Vascepa."

Amarin Corp. first appeared as a publicly traded company in 1993, and after divesting its drug delivery business, shifted its focus to that of a drug research and development company, primarily focused on the treatment of psychiatric and neurodegenerative disorders.[1]

From their ca. 2005 Executive Overview:

> "Corporate History
>
> Formerly Ethical Holdings plc, Amarin was incorporated in England as a private limited company on March 1, 1989 and re-registered in England as a public limited company on March 19, 1993. The registered office is currently located at 7 Curzon Street, London W1J 5HG, England. During the period 2003-2004, Amarin completed a significant corporate restructuring that enabled it to focus on developing and commercializing novel drugs for CNS disorders. The key transactions during this period were as follows:
>
> - In October 2003, Amarin divested its drug delivery business, Amarin Development AB, to Watson Pharmaceuticals, Inc.
> - In February 2004, Amarin divested its U.S. neurology sales and marketing operations through the sale of Amarin Pharmaceuticals, Inc (API) to Valeant Pharmaceutical International, Inc ("Valeant") for $38 million in cash. Proceeds contributed toward the settlement of all outstanding debt obligations.
> - In October 2004, Amarin closed the acquisition of Laxdale Limited, Amarin's former research and development partner. This represented an important step toward achieving the Company's newly stated goal of becoming a leader in the research, development, and commercialization of novel drugs for the treatment of CNS disorders. In addition to providing Amarin with control of the clinical development and regulatory processes for Miraxion™ and eliminating a 40-45% royalty to Laxdale, the acquisition broadened its development pipeline to include North American, E.U., and Japanese rights to Miraxion™ for all CNS disorders, including HD and depressive disorders. It also provided Amarin with the LAX-201 and LAX-202 compounds (pages 5 and 31), and an extensive portfolio of intellectual property in the area of CNS…"

Vascepa (active ingredient: ethyl ester EPA, aka "icosapent ethyl," aka "ethyl icosapentate," aka "ethyl-EPA," aka "EPA-EE," aka "EPA-E") is the trademark name for an encapsulation of very high purity (>95%) ethyl ester eicosapentaenoic acid[2] used to treat severe hypertriglyceridemia in the United States. The compound has a long history, however, and was first used in the pharmaceutical setting in Japan ca. 1990 as the active ingredient in "Epadel 300,"[3, 4] being indicated for use in patients with hyperlipidemia (an umbrella heading that includes hypertriglyceridemia[5]).

> "Epadel: The Outcome of Farsighted, Innovative Research

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[1] https://www.sec.gov/Archives/edgar/data/897448/000095016205000950/d65576amrneio.htm
[2] https://www.sciencedirect.com/topics/food-science/eicosapentaenoic-acid
[3] http://www.mochida.co.jp/english/about/history.html
[4] http://www.mochida.co.jp/english/annual/docs/mochida_annual_review2017_full.pdf
[5] https://www.uptodate.com/contents/high-cholesterol-and-lipids-hyperlipidemia-beyond-the-basics

> A drug that epitomizes the unique and innovative strengths of Mochida Pharmaceutical's R&D capabilities is Epadel, a drug for hyperlipidemia and arteriosclerosis obliterans. **Epadel is the world's first high-purity ethyl icosapentate (EPA-E)**. Working in cooperation with Nippon Suisan, Mochida Pharmaceutical made a historic breakthrough by turning purified EPA-E into a pharmaceutical. EPA is a biologically active substance present in fish oil."

This was the same formulation used in the JELIS trial:[6]

> "We use EPADEL Capsule 300TM (Mochida Pharmaceutical Co, Ltd, Tokyo, Japan) containing 300 mg of highly **(98%) purified EPA ethyl ester** (ethyl all-cis-5,8,11,14,17-icosapentaenoate) per capsule. EPA is actually purified from a long-chain polyunsaturated fatty acid present in fish oil (Figure 4). EPADEL Capsule 300 was launched in the Japanese market **in 1990** for the treatment of ASO and **hyperlipidemia**."

The drug name under which Laxdale Ltd. was developing EPA-E for CNS and psychiatric disorders was "LAX-101." Once they submitted a marketing application for LAX-101 for the treatment of Huntington's Disease (a CNS disorder), they did so with the trademark name "Lyxia." And once Amarin acquired Laxdale, they changed these to "AMR-101" and "Miraxion," respectively. But after the failure of multiple trials testing EPA-E in Huntington's Disease,[7] and attempts to garner FDA or EMEA approval on a lark also failed, Amarin suspended its CNS/psychiatric disorder treatment development of AMR-101 and turned its attention to severe hypertriglyceridemia for this compound (>90% EPA-E), assisted in this endeavor by an eventual $70mm private placement.[8] But they had to change the capsule formulation, as FDA does not allow succinylated acid to be present in the gelatin of capsules sold in the US. It seems they also were able to incorporate an even higher purity EPA-E formulation into that capsule at the same time (developed by Nippon Suisan). Hence the change in language from *"over 90% but preferably over 95%"* to *"over 96%"* EPA-E.

After achieving success in a phase 3 trial (MARINE) for this indication, they submitted data to FDA seeking approval of AMR-101 for severe hypertriglyceridemia, and chose the trademark name "Vascepa" to go along with it. Thus, in terms of the active pharmaceutical ingredient (API) itself, a capsule containing a high concentration (>90%) of EPA-E essentially = "Epadel" = "Lyxia" = "Miraxion" = "Vascepa."

Amarin Corp.'s US Patent No. 8,188,146 (the '146 patent),[9] with a priority date of 1999-01-27, originally put together by Laxdale, lists the following as the claimed invention:

> "1. A pharmaceutical composition comprising one or more fatty acids, at least 95% of which are in the form of ethyl-eicosapentaenoic acid, wherein the composition **contains no docosahexaenoic acid** and the composition is present in a capsule.
>
> 2. The composition of claim 1 wherein the composition contains less than 3% of any fatty acid other than eicosapentaenoic acid.

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[6] https://www.sciencedirect.com/science/article/pii/S0002870303003673?via%3Dihub
[7] https://www.reuters.com/article/amarin-drug/update-1-amarins-huntingtons-drug-fails-shares-plunge-idUSN2439824320070424
[8] https://www.sec.gov/Archives/edgar/data/897448/000119312510146186/d424b3.htm
[9] https://patents.google.com/patent/US8188146B2/en

3. The composition of claim 2 wherein the capsule is a gelatin capsule.

4. The composition of any one of claim 1, 2, or 3 wherein the ethyl-eicosapentaenoic acid is present in the composition in an amount of 250 mg to 1000 mg.

5. A pharmaceutical composition comprising 250 mg to 1000 mg of fatty acids at least 95% of which are in the form of ethyl eicosapentaenoic acid, wherein the composition **contains no docosahexaenoic acid**, and the composition is present in a capsule.

6. A pharmaceutical composition comprising 250 mg to 1000 mg of fatty acids at least 95% of which are in the form of ethyl-eicosapentaenoic acid, wherein the composition contains (a) less than 5% in aggregate of arachidonic acid and n-3 docosapentaenoic acid, and (b) **no docosahexaenoic acid**; and wherein the composition is present in a capsule.

7. The pharmaceutical composition of claim 5 wherein the composition contains arachidonic acid in an amount less than 3%, by weight, of said fatty acids.

8. The pharmaceutical composition of claim 6 wherein the composition contains docosapentaenoic acid [DPA] in an amount less than 3%, by weight, of said fatty acids.

9. The pharmaceutical composition of claim 6 wherein the composition contains arachidonic acid and docosapentaenoic acid [DPA] in an aggregate amount of less than 3%, by weight, of said fatty acids.

10. The pharmaceutical composition of claim 6 wherein the capsule comprises about 1000 mg of said composition."

Each of the 10 claims of the '146 patent—the only Vascepa patent listed in the Orange Book with both "DS," or drug substance (active ingredient) and "DP," or drug product (formula and composition) designations—carefully include/are limited by the distinguishing phrase *"contains **no** docosahexaenoic acid"* (DHA), perhaps in an attempt to avoid a rejection for obviousness based on the various patents issued to Nippon Suisan and Mochida Pharmaceuticals, claiming high-purity yields of ethyl ester eicosapentaenoic acid (EPA-E) and various of its uses.[10]

However, it is impossible to remove and/or prove to have removed absolutely all DHA from a batch of crude fish oil by any procedures currently known to man (and especially not ca. 1999—the priority date year of the '146 patent). Methodologies are only so sensitive to detection, and whereas 0.05% of DHA may be detectable, some smaller amount eventually won't be, even though it is still present in the compound. "Containing no DHA" is therefore an abstract idea, and for all intents and purposes, impossible to achieve or prove.

Furthermore, the '146 patent provides no explanation of the processes by which one may magically produce a batch of DHA-less fish oil (that also contains a very high percentage ethyl-EPA) in the specification. In fact, in the specification (description section) of the patent, they go into great detail explaining what CNS/psychiatric disorders that EPA-E might be useful for, but nowhere explain the process for making such high-purity EPA-E, either in a form that does or does not contain DHA. It is not possible to enable one skilled in the art on how to use your invention (contained in the "claims" section

[10] https://patents.google.com/?q=eicosapentaenoic&assignee=nippon+suisan&sort=old

of the patent application) if the claims or a limitation thereof contains an impossible statement. Thus, the '146 claims are all invalid as written for lack of enablement.[11]

> "2164 The Enablement Requirement [R-11.2013]
>
> The enablement requirement refers to the requirement of 35 U.S.C. 112(a) or pre-AIA 35 U.S.C. 112, first paragraph **that the specification describe how to make and how to use the invention**. The invention that one skilled in the art must be enabled to make and use is that defined by the claim(s) of the particular application or patent.
>
> The purpose of the requirement that the specification *[aka "description," "background," or "disclosure"]* describe the invention in such terms that one skilled in the art can make and use the claimed invention is to ensure that the invention is communicated to the interested public in a meaningful way. The information contained in the disclosure of an application must be sufficient to inform those skilled in the relevant art how to **both make and use** the claimed invention…
>
> Detailed procedures for making and using the invention may not be necessary if the description of the invention itself is sufficient to permit those skilled in the art to make and use the invention. A patent claim is invalid if it is not supported by an enabling disclosure.
>
> A conclusion of **lack of enablement** means that… the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)."

If an applicant seeks to claim "high-purity EPA-E" (and especially "as contains **no** DHA"), they must be able to describe a novel, effective method of producing the same, which is not anticipated by prior art. The '146 patent does not do so, neither in its claims nor in its specification.

This is particularly important for so called negative claim limitations. A "negative limitation" refers to a claim recitation which specifically excepts a particular element, composition, structure, sub-assembly, step, or other feature from the claimed invention.[12] There are stricter rules that apply to such limitations:[13]

> "Any claim containing a negative limitation which does not have basis in the original disclosure [specification] should be rejected under 35 U.S.C. 112(a) or pre-AIA 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement…"

The '146 patent specification clearly fails to comply with such a requirement.

As supplemental evidence, here are the results of several more modern purification methods seeking the highest purity of EPA per batch; and although able to achieve over 98% EPA yields, there is always some DHA present:[14]

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[11] https://www.uspto.gov/web/offices/pac/mpep/s2164.html
[12] http://www.hultquistip.com/files/negative_claims.pdf
[13] https://mpep.uspto.gov/RDMS/MPEP/e8r9#/e8r9/d0e218588.html
[14] https://newdrugapprovals.org/2018/10/05/icosapent-ethyl-イコサペント酸エチル/

"As shown in Table 1, this EPA ethyl ester-containing composition contained 98.25% of EPA, 0.43% of ETA, 0.21% of AA, and **0.05% of DHA** in total fatty acids. Also, the trans isomer ratio in EPA was 0.45%.

Example 2 The steps (1), (2) and (3) were carried out in the same manner as in Example 1 except that the step (3) was carried out while maintaining the distillation temperature of 180 to 185 ° C., EPA ethyl ester-containing composition was obtained in a yield of about 58%. As shown in Table 1, this EPA ethyl ester-containing composition contained 98.29% of EPA, 0.40% of ETA, 0.32% of AA, and **0.05% of DHA** in total fatty acids.

The EPA ethyl ester-containing composition was obtained by performing vacuum distillation (step (3)) of ethyl esterified sardine oil and then steps (1) and (2). The conditions of each step were the same as in Example 1. As shown in Table 1, this composition contained 95.05% EPA, 0.72% ETA, 0.50% AA, **0.21% DHA** in total fatty acids."

[0041]

[table 1]

質量%	原料	実施例1		実施例2	比較例1	比較例2
		工程(2)後の生成物	最終生成物	最終生成物	最終生成物	最終生成物
アラキドン酸 (AA)	1.77	0.17	0.21	0.32	0.63	0.50
エイコサテトラエン酸 (ETA)	1.52	0.32	0.43	0.40	0.86	0.72
ドコサヘキサエン酸 (DHA)	6.92	14.87	0.05	0.05	0.22	0.21
エイコサペンタエン酸 (EPA)	44.09	74.54	98.25	98.29	97.44	95.05
エイコサペンタエン酸(シス体比)	98.77	99.81	99.55	99.72	98.63	98.45
エイコサペンタエン酸(トランス体比)	1.23	0.19	0.45	0.28	1.37	1.55
エイコサペンタエン酸の収率	–	–	52.9%	58.1%	51.0%	30.8%

A mix containing 0.05% DHA is about the best possible, based on the above ca. 2012 data.[15] In the year that the '146 patent application was submitted (ca. 1999) the methods were of course also still evolving.

Thus, the claim, "contains no DHA," should be rejected for not qualifying as patent-eligible subject matter, falling under the judicial exception of an "abstract idea."[16]

However, the more significant issue with the patent relative to its being listed in the Orange Book lies in its conflicted nature as an unapproved (by FDA, EMEA, etc.) method of use patent, posing as a composition of matter patent.

The specification of the '146 patent only outlines methods for using ethyl-EPA to treat CNS/psychiatric disorders, even stating explicitly that such a product (high-purity ethyl-EPA) was already available for public use, being manufactured by others well before the application was crafted. It is therefore invalid as a composition of matter patent and can only be considered an irrelevant method of use patent—

[15] https://patents.google.com/patent/WO2014054435A1

[16] https://www.uspto.gov/web/offices/pac/mpep/s2106.html

irrelevant to any FDA-approved indication for icosapent ethyl. It is thus improperly listed in the FDA Orange Book.

As the FDA does not thoroughly analyze the contents of patents submitted to the Orange Book, adopting a ministerial role only,[17] it is not a difficult matter to have a patent listed therein, even if incorrectly. The highly burdened FDA relies on penalty of perjury laws the applicant is bound by, preserving resources for more important matters, such as the review of new drug applications. Allegations of antitrust violations have been made on the basis of improperly listed Orange Book patent information.[18] Those that submitted the '146 patent and signed the declaration could potentially be held liable.

But why did the examiner in making a prima facie case[19] fail to reject the '146 patent for obviousness and lack of novelty (and lack of enabling disclosure) back in ca. 1999? To more fully understand that, one has to look to the "Broadest Reasonable Interpretation" clause, and the differences in how the Patent Trial and Appeal Board (PTAB) in an *inter partes* review or the courts in a patent litigation case versus how a PTO examiner in a *prima facie* case consider patent claims to be valid or invalid.

> "2111 Claim Interpretation; Broadest Reasonable Interpretation [R-07.2015]
>
> CLAIMS MUST BE GIVEN THEIR BROADEST REASONABLE INTERPRETATION **IN LIGHT OF THE SPECIFICATION**
>
> During patent examination, the pending claims must be "given their broadest reasonable interpretation consistent with the specification." The Federal Circuit's en banc decision in Phillips v. AWH Corp., 415 F.3d 1303, 1316, 75 USPQ2d 1321, 1329 (Fed. Cir. 2005) expressly recognized that the USPTO employs the "broadest reasonable interpretation" standard:
>
> *The Patent and Trademark Office ("PTO") determines the scope of claims in patent applications not solely on the basis of the claim language, but upon giving claims their broadest reasonable construction "in light of the specification as it would be interpreted by one of ordinary skill in the art." In re Am. Acad. of Sci. Tech. Ctr., 367 F.3d 1359, 1364[, 70 USPQ2d 1827, 1830] (Fed. Cir. 2004). Indeed, the rules of the PTO require that application claims must "conform to the invention as set forth in the remainder of the specification and the terms and phrases used in the claims must find clear support or antecedent basis in the description so that the meaning of the terms in the claims may be ascertainable by reference to the description." 37 CFR 1.75(d)(1).*
>
> Patented claims **are not** given the broadest reasonable interpretation **during court proceedings** involving infringement and validity, and can be interpreted based on a fully developed prosecution record. In contrast, an examiner must construe claim terms in the broadest reasonable manner during prosecution as is reasonably allowed in an effort to establish a clear record of what applicant intends to claim. Thus, the Office does not interpret claims in the same manner as the courts. In re Morris, 127 F.3d 1048, 1054, 44 USPQ2d 1023, 1028 (Fed. Cir. 1997); In re Zletz, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1321-22 (Fed. Cir. 1989).

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[17] https://www.fda.gov/drugs/developmentapprovalprocess/ucm079031.htm
[18] https://www.govinfo.gov/content/pkg/USCOURTS-njd-2_02-cv-02007/pdf/USCOURTS-njd-2_02-cv-02007-0.pdf
[19] https://www.uspto.gov/web/offices/pac/mpep/s2142.html

> …In re Prater, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-51 (CCPA 1969) (Claim 9 was directed to a process of analyzing data generated by mass spectrographic analysis of a gas. The process comprised selecting the data to be analyzed by subjecting the data to a mathematical manipulation. The examiner made rejections under 35 U.S.C. 101 and 35 U.S.C. 102. In the 35 U.S.C. 102 rejection, the examiner explained that the claim was anticipated by a mental process augmented by pencil and paper markings. The court agreed that the claim was not limited to using a machine to carry out the process since the claim did not explicitly set forth the machine. The court explained that "reading a claim in light of the specification, to thereby interpret limitations explicitly recited in the claim, is a quite different thing from 'reading limitations of the specification into a claim,' to thereby narrow the scope of the claim **by implicitly adding disclosed limitations which have no express basis in the claim**." **The court** found that applicant was advocating the latter, i.e., **the impermissible importation of subject matter from the specification into the claim**.).
>
> …In re Morris, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997) (The court held that the PTO is not required, in the course of prosecution [which involves the initial review of the patent application], to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded **by the written description contained in applicant's specification**.")."

It appears that just as In re Prater, so too were Amarin's '146 patent claims inherently narrowed in scope by implicitly adding disclosed limitations from the specification into the claims, which had no express basis in the claims themselves, during the patent's initial review. As enumerated above, when making a *prima facie* case for an obviousness rejection during the initial round of prosecution of a patent application, the USPTO examiner is required to give patent claims their "broadest reasonable interpretation" (BRI), using the specification of the patent itself also as guidance.[20, 21] The '146 patent spends the entirety of its specification enumerating the ways in which high-purity EPA-E can be used to treat CNS/psychiatric disorders; and that makes sense, as it was Laxdale that originally submitted it. There is also no discussion on the process for creating high-purity EPA-E (especially as "contains no DHA"). In fact, the specification states that the product it is describing to be used for CNS/psychiatric disorders (high-purity EPA-E) was made years before the '146 patent application was submitted, thus relinquishing any rights to priority of the invention in that regard (composition of matter).

From the specification of the '146 patent:

> "In PCT filing WO98/16216 attention was drawn to the value of a particular fatty acid, eicosapentaenoic acid (EPA), and its derivatives, in the treatment of schizophrenia, depression and dementias.
>
> As described in PCT filing WO 98/16216 it was unexpectedly found that an oil enriched in EPA was of value in treating schizophrenia, while an oil enriched in the closely related fatty acid,

[20] https://www.uspto.gov/web/offices/pac/mpep/s2142.html
[21] https://www.uspto.gov/web/offices/pac/mpep/s2111.html

> docosahexaenoic acid (DHA), was not. This was surprising because DHA is found in large amounts in human brain whereas EPA is found only in trace quantities. It was therefore anticipated that DHA would be effective but EPA would not. In fact the opposite was found. WO 98/16216 disclosed the use of EPA and its derivatives for the treatment of psychiatric disorders.
>
> The present invention provides a pharmaceutical preparation comprising EPA in an appropriately assimilable form where of all the fatty acids present in the preparation at least 90%, and preferably at least 95%, is in the form of EPA and where less than 5%, and preferably less than 3%, is in the form of DHA. Such preparations are for the treatment of any disorder **except** peripheral vascular disease and **hyper-triglyceridaemia**."

It is interesting that in the first patent listed for Vascepa in the Orange Book—a drug indicated *solely* to treat hypertriglyceridemia—we have a clear mention the claimed invention is for treating any disorder *except* hypertriglyceridemia (and PVD). Of course, when Laxdale had it written they were likely seeking not to infringe on Mochida's patents, which covered Epadel's approved indication for hyperlipidemia (including hypertriglyceridemia), and so introduced this exception. They had no intention of seeking approval for EPA-E for the treatment of hypertriglyceridemia, as is ironically clearly evidenced by this patent. It was only after Amarin took possession of the asset and its patents, and after it failed in two phase 3 trials in Huntington's Disease, that they decided to advance the compound in trials testing the therapy in subjects with severe hypertriglyceridemia.

Also noticeable is the contradiction in this section of the specification with the claims that all rely upon the limitation "contains no DHA." In the above we have the admission that Vascepa may contain as much as 5% DHA. In *Straight Path IP Group, Inc. v. Sipnet EU S.R.O., Case No. 2015 (Fed. Cir. Nov. 25, 2015)*, the Federal Circuit held that when claim language is unambiguous, the specification plays a more limited role; that is, instead of acting as a guide for resolving "uncertainties on interpretive questions," the specification can only impact claim scope if it clearly disclaims or redefines the unambiguous language (Id. at 8).[22] Thus, although this mention of 5% DHA in the specification may accurately reflect the amount of DHA in Vascepa, the claims contradict it, asserting over and over 0% DHA, and it is the claims that are paramount to what constitutes "the invention." The specification is important to clarify ambiguity and define uses of the invention that are not listed in the claims, and will help inform a claim construction during litigation proceedings—however, as the claims stand, they are a misrepresentation of what Vascepa truly contains.

The '146 patent continues:

> "The application of these **known techniques** has been difficult to apply in practice on a large scale and only recently has pure EPA (more than 90% pure and preferably more than 95% pure) become available for testing in psychiatric and CNS disorders. In one version of the purification process, natural fish oil triglycerides rich in EPA are saponified and the fatty acids converted to the ethyl ester form. A preparation enriched in ethyl EPA is then prepared by molecular distillation with collection of the appropriate fraction. This fraction is then converted to a preparation containing over 80% of ethyl EPA by urea precipitation. The final preparation of

[22] http://www.chsblaw.com/single-post/2015/11/27/CAFC-Overrules-PTAB-Claim-Construction-That-Used-The-Specification-To-Contradict-Unambiguous-Claim-Language

more than 96% pure ethyl EPA is then achieved by either silica gel chromatography or high pressure liquid chromatography."

Using the specification as context (as no doubt the PTO examiner had), the claims of the '146 patent can be understood to apply only to the use of highly purified EPA-E for the treatment of psychiatric and neurodegenerative disorders. This also harmonizes with the drug development history of the sponsor's acquiree, Laxdale Ltd., who had constructed the patent to begin with. In fact, USPTO guidance states that the specification *"…shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention."*[23] And when we look at the concluding remarks of the '146 patent specification we find the following:

> "The present invention has identified ethyl-EPA as being highly effective. However, it is likely that any form of highly purified EPA which is able to raise EPA levels in the blood is of **value in psychiatric disorders**. These EPA compounds will all be of value in the treatment **of psychiatric and neurological disorders when prepared in pure form**. It will always be important to keep to the absolute minimum the presence of related fatty acids, which might interfere with the EPA. The compounds which are known, but which have not previously been prepared or proposed in such pure **forms for use in psychiatric and CNS disorders** are:
>
> 1. Ethyl-EPA which is widely used in Japan for the treatment of cardiovascular disorders.
>
> 2. Lithium-EPA which was previously disclosed in U.S. Pat. No. 5,252,333 but which was not then distinguished from any other lithium HUFA derivative as being of particular value in psychiatric disorders. The value of this derivative lies in the fact that lithium itself is a treatment of choice in bipolar disorder and is also known to have therapeutic effects in schizophrenia, schizoaffective disorder and depression. Recently it has been demonstrated that inhibition of PLA2 and of the PLC inositol phosphate cycle are important actions of lithium. Since EPA has related actions, the lithium derivative of EPA will be of particular value.
>
> 3. Triglycerides, monoglycerides or diglycerides in which more than 90% and preferably more than 95% of the fatty acids present in the molecule consist of EPA.
>
> 4. Other esters and compounds capable of delivering fatty acids to the body in which more than 90% and preferably more than 95% of the fatty acids present are in the form of EPA…
>
> In each of the following examples the product is at least 90% and preferably 95% or more pure. This is very important as other fatty acids will compete with the EPA for the binding sites and reduce its efficacy. In particular, fatty acids such as DHA, AA, DPA-n-3 will, individually, be present in concentrations of less than 5% and preferably less than 3%. The total aggregate of such competing compounds must be less than 10% and preferably less than 5%. This degree of purity is also valuable in minimising the volume of material which must be consumed each day**, a major factor in helping compliance in psychiatric patients where lack of compliance is a serious problem**.

[23] https://www.uspto.gov/web/offices/pac/mpep/mpep-9015-appx-l.html#d0e302824

1. Capsules made of hard or soft gelatin which contain 250 mg, 500 mg, or 1000 mg of ethyl-EPA, triglyceride EPA or other appropriate form of EPA.

2. Tablets containing 250 mg, 500 mg or 1000 mg lithium-EPA or hard gelatin capsules containing similar amounts.

3. Emulsions, solutions or dispersions in which the lithium-EPA, ethyl-EPA, triglyceride EPA or other appropriate form of EPA are prepared in a palatable liquid form for oral administration.

4. Suppositories or pessaries into which 100 mg to 5 g of one of the EPA compounds are formulated.

5. Intravenous solutions or emulsions containing from 10 mg to 500 mg/ml of one of the EPA compounds.

5-10. As examples 1-5, but using 2-substituted derivatives of EPA.

11-20. As in 1-10 but **in which the EPA compound is formulated with the usual dose of any other drug used for the treatment of psychiatric or neurological disorders**.

21-30. As in 1-10 but in which **the EPA compound is formulated with clozapine**."

It seems clear that the above is what guided the PTO examiner's decision to allow the patent. The '146 patent asserts an unapproved, novel method of use for high-purity EPA-E for the treatment of CNS/psychiatric disorders, and that is all that is novel and non-obvious about it. As such, it has no place in the FDA's Orange Book currently. Further, the claimed composition is materially different from icosapent ethyl, marketed as "Vascepa," as the latter contains DHA, whereas the 146' patent claims assert it does not. Lastly, Amarin Corp. is not even asserting the '146 patent claims are infringed by ANDA filers in the ongoing patent infringement proceedings (consolidated Case No. 2:16-cv-02525-MMD-NJK), which is a de facto admission the assignee does not think its claims defensible.

Thus, the '146 patent is (a) by Amarin's omission to include it in current proceedings, not defensible; (b) asserts unapproved methods of use only; (c) states within its specification that EPA-E is not being claimed to be used for hypertriglyceridemia in this patent, even though that is the only FDA-approved use for icosapent ethyl; (d) states in its specification the composition of matter upon which the application relies is known and the intellectual property of another (Mochida); and (e) claims a composition that is impossible to make (>90% EPA with 0% DHA), and is materially different from that which is marketed and sold under the brand name "Vascepa" (which contains low amounts of DHA). For these reasons, we conclude that it has no place in the FDA's Orange Book, and should be removed from being listing therein.

C. Environmental Impact

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

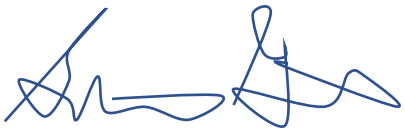
D. Economic Impact

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