CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202057Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2013
See OMB Statement on Page 3.

NDA NUMBER
202-057

NAME OF APPLICANT/NDA HOLDER
Amarin Pharmaceuticals Ireland Limited

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Vascepa

ACTIVE INGREDIENT(S)	STRENGTH(S)
icosapent ethyl	1 gram

DOSAGE FORM
Capsule

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6479544	November 12 2002	June 29 2021

d. Name of Patent Owner		
Amarin Neuroscience Limited	Address *(of Patent Owner)*: c/o Byrne Wallace - Tom Maher; 2 Grand Canal Square	
	City/State: Dublin 2	
	ZIP Code: Ireland	FAX Number *(if available)*:
	Telephone Number: +353 (0)1 6699 020	E-Mail Address *(if available)*:

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		
Amarin Pharma Inc. c/o Peggy Berry	Address *(of agent or representative named in 1.e.)*: 12 Roosevelt Ave.	
	City/State: Mystic, CT	
	ZIP Code: 06355	FAX Number *(if available)*: (860) 572-4940
	Telephone Number: (860) 572-4979	E-Mail Address *(if available)*: peggy.berry@amarincorp.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number(s) *(as listed in the patent)* 14	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)* VASCEPA is indicated as an adjunct to diet to reduce triglyceride (TG) (b) (4) levels in adult patients with very high (≥ 500 mg/dL) triglycerides.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	19 Sept 2011

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Amarin Pharmaceuticals Ireland Limited (John F. Thero, Director)	
Address c/o Amarin Pharma Inc. 12 Roosevelt Ave., 3rd Floor	City/State Mystic, CT
ZIP Code 06355	Telephone Number (860) 572-4979
FAX Number *(if available)* (860) 572-4949	E-Mail Address *(if available)* john.thero@amarincorp.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, Room 400
Rockville, MD 20850

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html.*

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Ave
Building 51
Silver Spring, MD 20993

MAY 31 2016

Robert A. Dormer
Hyman, Phelps & McNamara, P.C.
700 13th Street N.W., Suite 1200
Washington, D.C. 20005-5929

Re: Vascepa (icosapent ethyl) Capsules (NDA 202057) Exclusivity Determination

Dear Mr. Dormer:

This letter concerns the eligibility of Vascepa (icosapent ethyl, new drug application (NDA) 202057) for 5-year new chemical entity (NCE) exclusivity. On February 21, 2014, the U.S. Food and Drug Administration (FDA or Agency) determined that Vascepa was not eligible for NCE exclusivity.[1] Vascepa's sponsor, Amarin Pharmaceuticals Ireland Limited (Amarin), filed suit, challenging FDA's exclusivity determination. In a Memorandum Opinion and Order dated May 28, 2015, the U.S. District Court for the District of Columbia (Court) vacated FDA's February 21, 2014, exclusivity determination, and remanded the matter to FDA for further proceedings consistent with the Court's Opinion. FDA has carefully reconsidered Vascepa's eligibility for NCE exclusivity in light of the Court's Opinion. As explained below, and consistent with the Court's Opinion, FDA now determines that Vascepa is eligible for NCE exclusivity.

I. FACTUAL BACKGROUND

A. Vascepa's Approval and Labeling

On July 26, 2012, FDA approved NDA 202057 for Vascepa. Vascepa's labeling lists a single molecule, icosapent ethyl, as the drug's active ingredient.[2] Icosapent ethyl is the ethyl ester of eicosapentaenoic acid (EPA), an omega-3 fatty acid. Vascepa was approved as "an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 [milligrams (mg)/ deciliter (dL)]) hypertriglyceridemia."[3]

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[1] Letter from Janet Woodcock to Robert A. Dormer, Vascepa (icosapent ethyl) Capsules (NDA 202057) Exclusivity Determination (Feb. 21, 2014) (Vascepa Exclusivity Letter), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202057Orig1s000AdminCorres_edt.pdf, at 86 of the pdf (internal references to this letter reflect the page number of that letter).

[2] Vascepa labeling, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202057S000lbl.pdf, at 1.

[3] Id.

B. Lovaza's Approval and Labeling

On November 10, 2004, more than 7 years prior to FDA's approval of Vascepa, FDA approved NDA 021654 for Lovaza (omega-3-acid ethyl esters) capsules. Lovaza's labeling lists "omega-3-acid ethyl esters" as the active ingredient of that drug product.[4] The relevant United States Pharmacopeia (USP) monograph defines "Omega-3-Acid Ethyl Esters" as a mixture containing, among other things, seven distinct omega-3 fatty acid ethyl esters obtained from fish oil (the Lovaza mixture).[5] Similarly, Lovaza's labeling describes its composition as follows:

> Each 1 gram capsule of LOVAZA contains at least 900 mg of the ethyl esters of omega-3 fatty acids sourced from fish oils. These are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA – approximately 465 mg) and docosahexaenoic acid (DHA – approximately 375 mg).[6]

Thus, two of the seven omega-3-acid ethyl esters, the ethyl esters of EPA and DHA, make up approximately 85 percent of the Lovaza mixture.

Although the established name for Lovaza, "omega-3-acid ethyl esters," could suggest that Lovaza's active ingredient is its omega-3-acid ethyl ester component, the Lovaza labeling and relevant portions of the drug's NDA establish that FDA defined the drug's active ingredient as the entire mixture at the time of approval. Indeed, prior to approval, Lovaza's sponsor (GlaxoSmithKline) suggested that Lovaza's established name should consist of the names for EPA ethyl ester (EPAee) and DHA ethyl ester (DHAee). The Agency rejected the suggestion because Lovaza's active ingredient is "a natural product derived from fish oil, and contains the two major compounds (EPA and DHA ethyl esters) along with several other minor compounds."[7] FDA concluded that the sponsor's proposed name "implies that there are no other components to the drug substance, when, in fact, there are."[8] FDA instead determined that the established name "omega-3-acid ethyl esters" would be suitable because it "was designed to correspond to the mixture (natural product containing EPA and DHA ethyl esters, among other compounds)."[9]

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[4] Lovaza labeling, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021654s041lbl.pdf, at 12.

[5] *Omega-3-Acid Ethyl Esters*, USP, 39 National Formulary 34, 5138 (2016).

[6] Lovaza labeling at 5-6.

[7] Center for Drug Evaluation and Research Approval Package for NDA 21-654: Administrative/Correspondence (Nov. 1, 2004) (CDER Approval Package), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-654_Omacor_AdminCorres_P1.pdf, at 28.

[8] Id. at 29.

[9] Id. at 28.

C. Lovaza Strength Citizen Petition and FDA's Response

On February 6, 2013, FDA received a citizen petition requesting that the Agency amend the strength listing for Lovaza,[10] including the strength listing in the Orange Book.[11] Specifically, the Lovaza Strength Citizen Petition requested that FDA:

(1) Amend its listed strength for Lovaza (omega-3-acid ethyl esters) capsules, including the strength listing in the Orange Book, to 900 mg, so that the strength "appropriately identifies the amount of active ingredient per administration unit without reference to any other capsule properties such as product weight/fill weight, excipients, or other inactive ingredients"; or, alternatively,[12]

(2) Adopt a strength of 840 mg "for Lovaza based upon the fixed amount of major omega-3-acid ethyl esters specified in the Lovaza [NDA] reviews and labeling."[13]

FDA responded to the Lovaza Strength Citizen Petition on February 21, 2014.[14] In its response, FDA explained that its regulatory framework for the definition of "strength" is based on the amount of active ingredient per administration unit.[15] When Lovaza was approved, FDA concluded that the active ingredient of Lovaza was the fish oil mixture in its entirety.[16] That conclusion was consistent with the Agency's approach to naturally derived mixtures that are not fully characterized. FDA explained the reasoning behind the Agency's approach:

> As the Agency has stated in several instances, when naturally derived mixtures are not sufficiently characterized to precisely identify every molecule that meaningfully contributes to the activity of the mixture, it is difficult to define the active ingredient in terms of the specific components of such a mixture. In such cases, the Agency may identify the entire mixture as the active ingredient of the product.[17]

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[10] John H. Fuson, Citizen Petition, Docket No. FDA-2013-P-0148 (Feb. 6, 2013) (Lovaza Strength Citizen Petition), available at https://www.regulations.gov/#!documentDetail;D=FDA-2013-P-0148-0001.

[11] See FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book), at 3-318 (33rd Ed., 2013), available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf.

[12] Lovaza Strength Citizen Petition at 1.

[13] Id. at 6.

[14] Janet Woodcock, Citizen Petition Response, Docket No. FDA-2013-P-0148 (Feb. 21, 2014) (Lovaza Strength Citizen Petition Response), available at https://www.regulations.gov/#!documentDetail;D=FDA-2013-P-0148-0006, at 1.

[15] Id. at 4.

[16] Id. at 6.

[17] Id.

The petitioner had claimed that FDA now possesses data that would demonstrate that certain components of Lovaza are inactive ingredients.[18] FDA disagreed: "We are aware of no new studies that have ruled out the possibility that the non-omega 3 components (or the omega 3 components other than EPAee or DHAee) make a meaningful contribution to Lovaza's activity."[19] The Agency further explained:

> Because the clinical studies to establish Lovaza's safety and efficacy were based on the entire mixture – not just on the omega-3 component or a combination of just EPAee and DHAee – and because FDA does not have a sufficient basis to conclude that the other components of the drug do not meaningfully contribute to Lovaza's pharmacological effect, there is no basis to change the characterization of the entire mixture as the active ingredient in Lovaza.[20]

Turning to the petitioner's specific requests, FDA found that it lacked sufficient evidence to designate the strength of Lovaza as 900 mg because the petitioner had not provided any new information or data that would identify the omega-3-component as being solely responsible for Lovaza's pharmacological effect.[21] Similarly, FDA found that it lacked sufficient evidence to designate the strength of Lovaza as 840 mg because the petitioner had not provided any new information or data to support a conclusion that all components of the Lovaza mixture other than EPA ethyl ester and DHA ethyl ester are inactive ingredients.[22] Accordingly, FDA denied the citizen petition. As a result of the Agency's determination, the strength of Lovaza continued to be described as 1 gram containing at least 900 mg of the ethyl esters of omega-3 fatty acids sourced from fish oils.

II. STATUTORY AND REGULATORY BACKGROUND

Section 505(b-d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(b-d)) establishes the approval requirements for NDAs. To be approved, an application submitted under section 505(b) of the FD&C Act must, among other things, be supported by full investigations showing the drug product to be safe and effective under the conditions of use described in the labeling.[23] The 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments) introduced abbreviated pathways for approval of drug products that allow an applicant to rely to the maximum extent possible on what is already known about a drug. These pathways are described in section 505(b)(2) (which established the 505(b)(2) application pathway) and 505(j) (which established the Abbreviated New Drug Application

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[18] Id. at 7.

[19] Id.

[20] Id.

[21] Id. at 6.

[22] Id.

[23] Section 505(b)(1) of the FD&C Act.

(ANDA) pathway) of the FD&C Act.[24] At the same time, the Hatch-Waxman Amendments provided incentives for pharmaceutical innovation, including exclusivity to delay competition from ANDAs and 505(b)(2) applications when certain conditions are met.

Section 505(j)(5)(F)(ii) and (c)(3)(E)(ii) of the FD&C Act describe a 5-year exclusivity period for certain drugs, during which certain 505(j) and 505(b)(2) applications may not be submitted for review (i.e., 5-year NCE exclusivity). Specifically, section 505(j)(5)(F)(ii) of the FD&C Act provides, in relevant part, as follows:

> If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), is approved after the date of the enactment of this subsection, no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b) of this section . . . .[25]

The FD&C Act also provides for a 3-year period of exclusivity under certain circumstances,[26] but this section is not directly relevant to the discussion in this letter.

FDA's regulations implementing the 5-year NCE exclusivity provision of the Hatch-Waxman Amendments, at 21 CFR 314.108, provide that:

> If a drug product that contains a new chemical entity was approved . . . in an application submitted under section 505(b) of the act, no person may submit a 505(b)(2) application or abbreviated new drug application under section 505(j) of the act for a drug product that contains the same active moiety as in the new chemical entity for a period of 5 years from the date of approval of the first approved new drug application . . . .[27]

The regulations define "new chemical entity" as:

> [A] drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act.[28]

"Active moiety," in turn, is defined as:

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[24] The precise nature of these pathways and their attendant requirements are not relevant to our analysis or the conclusions we reach regarding the issues discussed in this letter.

[25] See also section 505(c)(3)(E)(ii) of the FD&C Act (containing the same language for 505(b)(2) applications).

[26] See section 505(j)(5)(F)(iii)-(iv) and (c)(3)(E)(iii)-(iv) of the FD&C Act.

[27] 21 CFR 314.108(b)(2).

[28] 21 CFR 314.108(a).

> [T]he molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.[29]

In the Agency's regulations governing applications for new drugs, FDA has defined "drug product" as:

> [A] finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.[30]

In the same regulation, "drug substance" is defined as:

> [A]n active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates use [sic] in the synthesis of such ingredient.[31]

III. PROCEDURAL HISTORY

A. FDA's February 21, 2014, NCE Exclusivity Determination for Vascepa

In April 2012, Amarin requested that FDA recognize that Vascepa is eligible for 5-year NCE exclusivity. "The key legal issue," in Amarin's view at that time (and throughout its subsequent submissions), was

> whether the prior approval of a drug product, the active ingredient of which is a complex mixture of constituents, constitutes approval of each constituent as an individual active ingredient so as to preclude NCE exclusivity for a new drug product in which one of those constituents alone is the active ingredient.[32]

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[29] Id.

[30] 21 CFR 314.3(b).

[31] Id.

[32] Letter from Robert A. Dormer to Elizabeth H. Dickinson, Vascepa (icosapent ethyl) Capsules Exclusivity Determination (Apr. 23, 2012) (Dormer Letter I). Amarin submitted numerous other letters to the Agency on this matter. See Letter from Robert A. Dormer to Elizabeth H. Dickinson, Vascepa (icosapent ethyl) Capsules Exclusivity Determination (July 6, 2012) (Dormer Letter II); Letter from Robert A. Dormer to Eric Colman, Vascepa (icosapent ethyl) Capsules Exclusivity Determination; General Advice Response (Aug. 8, 2012) (Dormer Letter III); Letter from Robert A. Dormer to Elizabeth H. Dickinson, Vascepa (icosapent ethyl) Capsules Exclusivity Determination (Apr. 12, 2013) (Dormer Letter IV); Letter from Robert A. Dormer to Elizabeth H. Dickinson, Vascepa (icosapent ethyl) Capsules Exclusivity Determination (Sept. 25, 2013) (Dormer Letter V).

In February 2014, FDA responded to Amarin's request for 5-year NCE exclusivity.[33] In its analysis, the Agency identified the issue as follows: "As a product that contains icosapent ethyl as its active ingredient and EPA as its active moiety, Vascepa's eligibility for 5-year NCE exclusivity depends on whether EPA is an active moiety previously approved in Lovaza."[34] To assess whether EPA is an active moiety previously approved in Lovaza, the Agency first had to identify the applicable framework for analyzing active moieties in the context of naturally derived mixtures. The Agency acknowledged several aspects of the regulatory framework (described briefly above) that made identifying the applicable principle challenging for naturally derived mixtures. First, "neither the statute nor the regulations expressly address 5-year NCE exclusivity in the context of naturally derived mixtures."[35] Second, "the few relevant prior Agency statements and prior actions where FDA considered 5-year NCE exclusivity matters in the context of naturally derived mixtures have not necessarily resulted in consistent outcomes."[36] Third, FDA "has not always used precise terminology in addressing exclusivity for such mixtures."[37]

With regard to precise terminology, the Agency noted that "[t]he difference between 'active ingredient' and 'active moiety' can be difficult to discern, and the two terms are often conflated."[38] The Agency further explained:

> [F]or drugs that are composed of a single, well-characterized molecule, the distinction between "active moiety" and "active ingredient," generally is negligible. In such drugs, the single molecule that comprises the active ingredient typically contains the only active moiety in the drug product, and the two regulatory concepts refer to the same molecule for the purposes of the exclusivity analysis. But where a drug product contains a naturally derived mixture comprising multiple molecules, more than one of which potentially could be responsible for the physiological or pharmacological action of the drug substance, the distinction between active ingredient and active moiety and the relationship between the two become crucial.[39]

The Agency declined to adopt an approach urged by Amarin in which the entire mixture in a drug product containing a naturally derived mixture is considered to constitute both the single active ingredient and the single active moiety of the drug.[40] The Agency recognized that this "one-to-one" relationship between "active ingredient" and "active moiety" generally exists in

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[33] See Vascepa Exclusivity Letter, supra note 1.

[34] Id. at 16.

[35] Id. at 6.

[36] Id.

[37] Id.

[38] Id.

[39] Id. (footnotes omitted).

[40] Id.

drugs with "simple" active ingredients that consist of a single molecule and may be appropriate for poorly characterized naturally derived mixtures.[41] But the Agency found:

> In cases where at least part of the mixture is well characterized and some components of the mixture that are consistently present and active are identifiable or have been identified, an approach in which the mixture is identified as both the active ingredient and the active moiety appears inconsistent with the definition of active moiety as a "molecule or ion . . . responsible for the physiological or pharmacological action of the drug substance."[42]

Moreover, "[t]he approach that is the most consistent with the relevant definitions, facts, and policies present in this case is one in which the entire mixture is the single active ingredient, but that active ingredient may contain more than one component active moiety."[43] Accordingly, FDA set forth a "one-to-many" framework that it believed, at that time, provided "the best approach for identifying the active moiety or moieties of such mixtures."[44] A description of that framework follows:

> Where a drug product contains a naturally derived mixture, the Agency generally will consider certain component molecules of the mixture to be previously approved active moieties for the purpose of determining a subsequent drug's eligibility for 5-year NCE exclusivity when the following three criteria are met:
>
> > **(1) Characterization**: The previously approved mixture has been characterized such that one or more specific molecules in the mixture have been identified;
> >
> > **(2) Consistent Presence**: The evidence demonstrates that one or more specific molecules identified in criterion 1 are consistently present in the mixture; and
> >
> > **(3) Activity**: The evidence demonstrates that the molecule or molecules identified in criteria 1 and 2 are responsible at least in part for the physiological or pharmacological action of the mixture, based on a finding that they make a meaningful contribution to the activity of the mixture.
>
> If these criteria are met, the molecule or molecules would be identified as the active moiety or moieties of a naturally derived mixture. When such a molecule is an active moiety in a subsequently approved drug, it will be considered a

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[41] Id. at 6-7.

[42] Id. at 7.

[43] Id.

[44] Id.

> previously approved active moiety and the drug will not be eligible for 5-year NCE exclusivity.[45]

The Agency devised this framework based on a review of "the relevant authorities and the outcomes of and the bases for FDA's prior actions."[46] That review led the Agency to conclude:

> Although the Agency has not always acted consistently with regard to identification of the 'active ingredient' or 'active moiety' of a naturally derived mixture, it generally has applied the 'one-to-one' approach to poorly characterized mixtures, and often has (although not universally) applied the 'one-to-many' approach to well-characterized mixtures, with the three criteria analysis described above used to determine which molecules are active moieties of such a mixture.[47]

Specifically, in actions relating to products containing pancrealipase and hyaluronidase, the Agency appeared to treat the entire mixture as both the active ingredient and active moiety and therefore recognized their eligibility for 5-year NCE exclusivity.[48] The Agency concluded, however, that the 5-year NCE exclusivity determinations relating to products containing pancrealipase and hyaluronidase are distinguishable from Lovaza because the former are very poorly characterized in comparison to Lovaza (where roughly 90 percent of the mixture has been well characterized and the two main components have been the subject of many clinical studies).[49]

Applying this "one-to-many" framework to Lovaza, FDA determined that EPA is an active moiety previously approved in Lovaza because the EPA in the Lovaza mixture meets three criteria mentioned above in the manner described below:

> **(1) Characterization**: The Lovaza mixture is sufficiently characterized such that EPA has been identified as a specific molecule present in the mixture. Lovaza's labeling describes the composition as containing approximately 465 mg of EPA ethyl ester;
>
> **(2) Consistent Presence**: EPA is consistently present in the Lovaza mixture, and Lovaza meets the product description in the labeling, as well as the standards set forth in the relevant USP drug substance and drug product monographs; and
>
> **(3) Activity**: . . . [T]he available evidence establishes that EPA has meaningful pharmacological activity in lowering serum triglyceride levels, the approved

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[45] Id. at 7-8 (footnotes omitted).

[46] Id. at 6.

[47] Id. at 8.

[48] Id. at 9-10, 13-15.

[49] Id. at 9-10, 13-15, 19-20.

> indication for both Lovaza and Vascepa, and thus EPA contributes meaningfully to the pharmacological action of Lovaza.[50]

Consequently, the Agency determined "that Vascepa is not eligible for 5-year NCE exclusivity, because EPA, the single active moiety in Vascepa, was also an active moiety contained in another, previously approved drug, Lovaza (omega-3-acid ethyl esters) Capsules (Lovaza)."[51]

B. Amarin's Complaint and the Parties' Summary Judgment Motions

On February 27, 2014, Amarin filed a Complaint in the D.C. District Court, challenging FDA's February 2014 exclusivity determination. Amarin alleged:

> The controlling statutes grant 5-year exclusivity to any new drug, no "active ingredient (including any ester or salt of the active ingredient)" of which has been previously approved by FDA. It is undisputed that the "active ingredient" of Lovaza is an undifferentiated fish oil mixture. That mixture is not the same as Vascepa's active ingredient (icosapent ethyl). Nor is the mixture an ester or salt of icosapent ethyl, or vice versa. In refusing to recognize Vascepa's 5-year statutory exclusivity, FDA has improperly substituted the words "active moiety" for the statute's words ("active ingredient").[52]

For relief, Amarin sought an order that would, among other things, vacate FDA's denial of 5-year NCE exclusivity for Vascepa.[53]

The parties filed cross-motions for summary judgment. In its Summary Judgment Motion, Amarin argued, among other things, that "FDA's interpretation of 'active ingredient' not to mean 'active ingredient' fails at *Chevron* Step One."[54] In its Summary Judgment Motion, the Government responded that the statute is ambiguous and that FDA has reasonably interpreted the relevant provision in view of its best judgment as to the scope of exclusivity intended by Congress and in light of applicable judicial precedent.[55]

C. The Court's May 28, 2015, Opinion

The Court granted Amarin's Summary Judgment Motion and denied the Government's. The Court began its discussion by observing that under the applicable statutory text, "a drug manufacturer is entitled to five-year exclusivity if its newly-approved drug does not contain an

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[50] Id.

[51] Id. at 1.

[52] Complaint at ¶ 7.

[53] Id. at Relief Requested, ¶ 1.

[54] Memorandum in Support of Plaintiff's Motion for Summary Judgment at 16.

[55] Memorandum in Support of Defendants' Motion for Summary Judgment at 17.

'active ingredient' that was previously approved in another drug application."[56] The Court further observed that "under the FDA's implementing regulations, in contrast, the drug manufacturer is entitled to exclusivity only if its drug does not contain an 'active moiety' that was previously approved in another drug application."[57] The Court noted that "[i]n most cases, this distinction is inconsequential," but not where "the exclusivity regulations are applied under the FDA's new framework to fully or partially characterized mixtures, like Lovaza."[58] "In that context, the symmetry between the regulatory and statutory language breaks down, because the FDA maintains that the drug may have a single 'active ingredient'—the entire mixture—but multiple 'active moieties.'"[59] The Court found that if the statutory reference to a drug's "active ingredient" is distinct from the regulation's reference to "active moiety," as it was in the Vascepa exclusivity determination, then "the statutory language must control, and the decision must be set aside."[60]

In the Court's view, FDA's interpretation of the statute, as applied in this case, "suffers from at least three difficulties."[61] First, "the contention that 'active ingredient' means 'active moiety' is at odds with the canon against surplusage."[62] In the Court's view, "FDA's contention that 'active ingredient' means 'active moiety' . . . would render the parenthetical clause in the exclusivity provisions either redundant or incomprehensible."[63] Specifically,

> [i]f 'active ingredient' means 'active moiety,' and 'active moiety' is defined as a molecule excluding (among other things) those portions that render the molecule a salt or an ester, 21 C.F.R. § 314.108(a), there are no circumstances in which the parenthetical clause would have any coherent meaning.[64]

Second, FDA's interpretation "requires the Agency to interpret the phrase 'active ingredient' differently for purposes of the ANDA and exclusivity provisions of the Act."[65] The Court found that there were "strong reasons to conclude that the presumption of consistent usage applies."[66] The Court further found that the presumption of consistent usage was not rebutted in this case

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[56] *Amarin Pharms. Ireland Ltd. v. FDA*, 106 F. Supp. 3d 196, 206 (D.D.C. 2015).

[57] Id. (citing 21 CFR 314.108(a)).

[58] Id. at 206-7.

[59] Id. at 207.

[60] Id.

[61] Id. at 209.

[62] Id.

[63] Id.

[64] Id.

[65] Id. at 210.

[66] Id.

because this is "not a circumstance where Congress used the phrase loosely or where a consistent definition is 'incompatible' with the statutory structure or purpose."[67]

The Court observed that FDA's own practices demonstrate that adopting a consistent interpretation of "active ingredient" would not result in any "incompatibility" with the statutory structure or purpose.[68] Specifically, the Court noted that "in other contexts, the FDA has made its exclusivity determination based on an entire mixture, rather than the mixture's 'active moieties' . . . ."[69] The Court further noted:

> Ultimately, the FDA is free to determine whether any particular naturally derived mixture is better understood as containing one or multiple active ingredients. To the extent that the FDA is concerned that granting five-year exclusivity for different mixtures will unduly allow pharmaceutical companies to obtain exclusivity for components of mixtures that were already well-understood, it can take precisely that approach.[70]

The third difficulty the Court had "with the Agency's approach is that its focus on a drug component that was never the subject of the FDA's approval is also inconsistent with the statutory text, which considers whether the new drug contains an 'active ingredient' which has been approved in a prior application."[71] Because "the relevant 'active moieties' are not even identified until the Agency acts on an application for exclusivity," the Court found that "the FDA's approach fails to make temporal or substantive sense of the statutory reference to an 'active ingredient' 'which *has been approved*,' and thus, once again, is at odds with the statute."[72]

Based on this analysis, the Court held that FDA's "ultimate conclusion that Vascepa, a drug 'no active ingredient of which . . . has been approved' in a previous NDA, was not entitled to exclusivity, is contrary to the statute's plain meaning."[73] In its Memorandum Opinion and Order, the Court vacated FDA's February 21, 2014, determination denying Amarin's request for 5-year NCE exclusivity and remanded the matter to FDA for proceedings consistent with its Opinion.[74]

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[67] Id. at 211.

[68] Id. at 212.

[69] Id.

[70] Id.

[71] Id. at 213.

[72] Id. at 214 (citing 21 U.S.C. 355(c)(3)(E)(ii), 355(j)(5)(F)(ii)) (emphasis in original).

[73] Id. at 219.

[74] Id. See also May 28, 2015, Memorandum Opinion and Order, *Amarin Pharms. Ireland Ltd. v. FDA*, 106 F. Supp. 3d 196 (D.D.C. 2015) (No. 1:14-cv-0324).

IV. ANALYSIS

In light of the Court's Opinion, FDA has reconsidered whether Vascepa is eligible for 5-year NCE exclusivity. Because the Court did not invalidate the Agency's 5-year NCE exclusivity regulations, we apply the applicable regulations in a manner consistent with the Court's Opinion – as we must – to decide whether Vascepa contains an NCE, i.e., whether EPA, the sole active moiety in Vascepa after discounting the relevant ester-bonded portion of the drug's active ingredient, is a previously approved active moiety.

In light of the Court's Opinion, we have reevaluated whether the "one-to-many" or the "one-to-one" framework should be applied to Lovaza to determine whether EPA is an active moiety previously approved in Lovaza. For the reasons provided below, and under the narrow circumstances of this case, the Agency has decided to apply the "one-to-one" framework to Lovaza to resolve the exclusivity issue in a manner consistent with the Court's Opinion. Under this approach, the Agency concludes that, in light of both its previous decision that the active ingredient of Lovaza is the entire mixture and the Court's Opinion, FDA now characterizes the active moiety of Lovaza as the entire mixture. As a result, EPA, the single active moiety in Vascepa, is *not* an active moiety contained in any previously approved drug and thus Vascepa contains an NCE and is eligible for 5-year NCE exclusivity under 21 CFR 314.108.

Multiple factors unique to this matter have influenced the Agency's decision to adopt the "one-to-one" framework in this case. First and foremost, the Agency took into consideration the Court's Opinion, and, in particular, the Court's finding that, in light of FDA's previous decision that the entire mixture is the active ingredient of Lovaza, the application of FDA's exclusivity regulations to Lovaza under the "one-to-many" framework was inconsistent with the statutory language.[75]

Second, the Agency considered its prior active ingredient determination for Lovaza and the reasons underlying it. At the time of approval, FDA determined that the active ingredient of Lovaza was the entire mixture. Also at the time of approval, FDA explicitly rejected the suggestion from Lovaza's sponsor that Lovaza's established name should consist of the names "EPAee" and "DHAee," determining instead that the name "omega-3-acid ethyl esters" would be suitable because it "was designed to correspond to the mixture."[76]

In addition, in its Lovaza Strength Citizen Petition Response, FDA reaffirmed its conclusion that Lovaza's active ingredient is the entire fish oil mixture. The Agency explained that its active ingredient determination for Lovaza at the time of approval was consistent with the Agency's approach to naturally derived mixtures that are not fully characterized: "[W]hen naturally derived mixtures are not sufficiently characterized to precisely identify every molecule that meaningfully contributes to the activity of the mixture, it is difficult to define the active

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[75] *Amarin Pharms.*, 106 F. Supp. 3d at 206.

[76] CDER Approval Package, supra note 7, at 28.

ingredient in terms of the specific components of such a mixture."[77] The Agency also rejected the petitioner's claim that FDA possessed new information that would enable FDA to change its active ingredient determination for Lovaza and provided the following explanation:

> Because the clinical studies to establish Lovaza's safety and efficacy were based on the entire mixture – not just on the omega-3 component or a combination of just EPAee and DHAee – and because FDA does not have a sufficient basis to conclude that the other components of the drug do not meaningfully contribute to Lovaza's pharmacological effect, there is no basis to change the characterization of the entire mixture as the active ingredient in Lovaza.[78]

The Court's reminder that the Agency should consider "active ingredient" and "active moiety" as being coextensive, at least with respect to the core parts of the same molecule,[79] allows FDA to apply its regulation in a way that the Court determined was permissible, i.e., that Lovaza's active ingredient and active moiety refer to the same entity. Under the Court's reasoning, the Agency's previous determination that the entire mixture is Lovaza's active ingredient (and the rationale for that determination) becomes highly relevant to the Agency's determination of Lovaza's active moiety.[80] FDA's active ingredient determination at the time of both approval and its re-affirmation of that determination in 2014 demonstrate that the Agency considered and rejected identifying EPA as a separate active ingredient from the Lovaza mixture. Specifically, the facts that the clinical studies establishing Lovaza's safety and efficacy were based on the entire mixture and that FDA did not have a sufficient basis to conclude that the other components of the drug do not meaningfully contribute to Lovaza's pharmacological effect now weigh in favor of finding that the entire fish oil mixture is both the active ingredient and the active moiety in Lovaza.

Third, FDA reviewed previous Agency 5-year NCE exclusivity decisions in the context of naturally derived mixtures and notes again that at least some of those decisions are consistent with the "one-to-one" framework. As the Agency acknowledged in its initial Vascepa exclusivity determination, "the few relevant prior Agency statements and prior actions where FDA considered 5-year NCE exclusivity matters in the context of naturally derived mixtures

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[77] Lovaza Strength Citizen Petition Response, supra note 14, at 6.

[78] Id.

[79] See *Amarin Pharms.*, 106 F. Supp. 3d at 199-200 ("For salts, esters, and noncovalent derivatives, a molecule's 'active moiety' can be thought of as its core; salt, ester and noncovalent derivative versions of the same basic molecule have different appendages, but they share the same active moiety."); id. at 206 ("When dealing with single molecule drugs, the 'active ingredient' and the 'active moiety' refer to the same molecule and thus the distinction typically makes no difference to the Agency's exclusivity analyses.").

[80] We note that, under this approach, there could not be a "salt or ester" of the entire naturally derived mixture (i.e., only individual molecule components of the mixture could have salts or esters). Therefore, even this interpretation is not a perfect fit with the statutory language. Nevertheless, it appears to be consistent with the Court's Memorandum Opinion and Order.

have not necessarily resulted in consistent outcomes."[81] Some of those decisions, however, suggest that the Agency could consider the entire mixture to be both the active ingredient and the active moiety for Lovaza, as it did in the exclusivity determinations for the lung surfactants InfaSurf and Curosurf and for products containing pancrelipase and hyaluronidase.[82]

Fourth, the Agency considered the lack of guidance describing how FDA makes exclusivity determinations for naturally derived mixtures. Prior to the issuance of the Vascepa exclusivity determination, there was no explicitly defined framework for identifying active moieties in the context of naturally derived mixtures for purposes of 5-year NCE exclusivity, nor could one easily be gleaned from the applicable statute, regulations, and precedent. As discussed above, the statute and regulations do not expressly address 5-year NCE exclusivity in the context of naturally derived mixtures. In fact, the prior Agency statements and actions regarding this matter were difficult to reconcile.[83] Although guidance is not required before FDA can act, FDA believes the lack of guidance and diversity of practice also counsels in favor of applying the "one-to-one" framework on remand.

Lastly, the Agency considered whether any of the reasons it had provided for declining to adopt the "one-to-one" framework when it previously considered the active moiety for Lovaza bars adopting the "one-to-one" framework for Lovaza now. In its original Vascepa exclusivity determination, the Agency stated:

> In cases where at least part of the mixture is well characterized and some components of the mixture that are consistently present and active are identifiable or have been identified, an approach in which the mixture is identified as both the active ingredient and the active moiety appears inconsistent with the definition of active moiety as a "molecule or ion . . . responsible for the physiological or pharmacological action of the drug substance."[84]

But just as the Court recognized that FDA is free to determine whether any particular naturally derived mixture is better understood as containing one or multiple active ingredients,[85] so too the Agency believes it has regulatory and scientific discretion to determine whether any particular naturally derived mixture can be described as containing one or multiple active moieties. Accordingly, as explained in this letter, the Agency has determined, in order to bring the

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[81] Vascepa Exclusivity Letter, supra note 1, at 6; see also id. at 8 ("[T]he Agency has not always acted consistently with regard to identification of the 'active ingredient' or 'active moiety' of a naturally derived mixture."); id. at 19 ("[T]he Agency's past actions indicate that FDA has not had a fully consistent practice in this regard . . . .").

[82] Id. at 9-10, 13-15.

[83] Id. at 6.

[84] Id. at 7.

[85] *Amarin Pharms.*, 106 F. Supp. 3d at 212.

Agency's decision in harmony with the Court's Opinion,[86] that the active moiety of Lovaza, a partially characterized mixture, is the entire mixture.

On balance, the unique circumstances described above weigh in favor of applying the "one-to-one" framework to Lovaza on remand. Such an approach is consistent with the Court's Memorandum Opinion and Order as we have interpreted it in this remand decision. Under this approach, the entire fish oil mixture is both the single active ingredient and the single active moiety of Lovaza, and there is symmetry between the statutory reference to "active ingredient" and the regulatory reference to "active moiety." Because EPA, the single active moiety of Vascepa, is not a previously approved active moiety, Vascepa is eligible for 5-year NCE exclusivity, which runs from the date of Vascepa's approval (July 26, 2012).

V. CONCLUSION

For the reasons described above, FDA concludes that Vascepa is eligible for 5-year NCE exclusivity under the Agency's interpretation of the applicable statutory provisions as described in the applicable regulations.[87]

Sincerely,

Janet Woodcock
Director
Center for Drug Evaluation and Research

cc: Benjamin Block
Covington & Burling LLP

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[86] Although we noted in the Vascepa Exclusivity Letter that Lovaza is a well-characterized mixture with respect to its omega-3 components, Vascepa Exclusivity Letter, supra note 1, at 18, we also noted that at the time of approval, the fish oil mixture in Lovaza had not been fully characterized and that the available data did not adequately demonstrate the activity or inactivity of all components in the mixture. See id. at 2.

[87] See 21 CFR 314.108.

EXCLUSIVITY SUMMARY

NDA # 202057 SUPPL # HFD #

Trade Name VASCEPA

Generic Name icosapent ethyl

Applicant Name Amarin Pharmaceuticals Ireland Limited

Approval Date, If Known 7/26/2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

Reference ID: 3165411

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☐

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

Determination of whether this application qualifies for 3 or 5 years of exclusivity was not finalized by the goal date. The final decision will be made post-approval and this form will be completed at that time.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

Reference ID: 3165411

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

Reference ID: 3165411

summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

Reference ID: 3165411

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a

Reference ID: 3165411

similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 ! !

IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 ! !

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 ! !

YES ☐ ! NO ☐

Reference ID: 3165411

Explain:	! Explain:
Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Kati Johnson
Title: Senior Regulatory Project Manager
Date: July 27, 2012

Name of Office/Division Director signing form: Eric Colman, MD
Title: Deputy Division Director, Division of Metabolism and Endocrinology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Reference ID: 3165411

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATI JOHNSON
07/27/2012

ERIC C COLMAN
07/27/2012

1.3.3 Debarment certification

Amarin Pharmaceuticals Ireland Limited hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

John Thero, Director
Amarin Pharmaceuticals Ireland Limited

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 202057 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: VASCEPA Established/Proper Name: icosapent ethyl Dosage Form: capsules		Applicant: Amarin Pharmaceuticals Ireland Limited Agent for Applicant (if applicable): Amarin Pharma Inc.
RPM: Kati Johnson		Division: Metabolism and Endocrinology Products

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☒ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 7/26/2012	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☒ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	**X** Yes No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Reference ID: 3165389

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☐ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

Reference ID: 3165389

• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).	☐ Yes ☐ No
*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?	☐ Yes ☐ No
*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.* *If "**No**," continue with question (3).*	
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).	☐ Yes ☐ No
*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?	☐ Yes ☐ No
*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**No**," continue with question (5).*	

Reference ID: 3165389

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	X
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP 7/26/2012
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	X
• Example of class labeling, if applicable	N/A

[4] Fill in blanks with dates of reviews, letters, etc.

Reference ID: 3165389

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	X
• Example of class labeling, if applicable	N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	X
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	12/19/2011-Initial OK 6/11/2012-Final OK
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 12/12/2011 ☒ DMEPA 12/23/2011 ☒ DMPP/PLT (DRISK) 6/12/2012 ☐ ODPD (DDMAC) ☐ SEALD ☐ CSS ☒ Other reviews PharmTox 7/25/2012
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	RPM Filing Review 7/26/2012 ☐ Not a (b)(2) 6/5/2012 ☐ Not a (b)(2) 6/5/2012
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	X Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes X No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 3/21/2012 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

Reference ID: 3165389

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	X
❖ Internal memoranda, telecons, etc.	X
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 3/16/2011
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 7/14/2008
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☒ None
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 7/26/2012
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	7/26/2012
• Clinical review(s) *(indicate date for each review)*	7/26/2012, 11/15/2011
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See page 16 of 7/26/2012 clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None

[6] Filing reviews should be filed with the discipline reviews.

Reference ID: 3165389

❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 6/5/2012
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None 5/17/2012,
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 6/1/2012, 11/10/2011
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 6/5/2012, 11/18/2011
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc no sep stat review
❖ ECAC/CAC report/memo of meeting	☐ None 4/11/2012 Included in P/T review, page 65
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 7/26/2012, 5/30/2012, 3/19/2012, 11/10/2011
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 5/23/2012, 11/9/2011
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

Reference ID: 3165389

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	page 74 of 3/19/2012 CMC review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 7/26/2012 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Reference ID: 3165389

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/s/

KATI JOHNSON
07/27/2012

From: Johnson, Kati
To: Peggy Berry
Subject: RE: NDA 202057. VASCEPA, revised labeling
Date: Thursday, July 26, 2012 5:54:10 AM

We note your agreement with the labeling sent to you 7/25/2012 at 12:26 pm.
Kati

From: Peggy Berry [mailto:peggy.berry@amarincorp.com]
Sent: Wednesday, July 25, 2012 12:58 PM
To: Johnson, Kati
Subject: RE: NDA 202057. VASCEPA, revised labeling

This looks great.
Do you need me to make this into an official submission or not – sorry I might have asked that before and I can't remember…

From: Johnson, Kati [mailto:Kati.Johnson@fda.hhs.gov]
Sent: Wednesday, July 25, 2012 12:26 PM
To: Peggy Berry
Subject: NDA 202057. VASCEPA, revised labeling
Importance: High

Peggy,
Here is the revised PI/PPI. It is identical to what you sent me, with the following exceptions:
-In the PPI, we have deleted the statement [redacted] (b) (4) under "**What should I tell my doctor before taking VASCEPA?"**
-In the PPI, under "**What are the possible side effects of VASCEPA?"**, we have revised the sentence [redacted] (b) (4) to read "This is not the only side effect of VASCEPA", since there is only a single side effect mentioned.

Please just e-mail me back and say that the labeling is acceptable, if that is the case. I will archive that e-mail and you will not have to submit anything additional.
Thanks, Kati

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
301-796-1234 (Phone)

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12 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) Immediately Following this Page

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/s/

KATI JOHNSON
07/26/2012

From:	Raggio, Miranda
To:	Johnson, Kati; Galliers, Enid M
Cc:	Ripper, Leah W; Bertha, Amy; Duvall, Beth A; Raggio, Miranda
Date:	Monday, June 04, 2012 2:49:39 PM

Hi Kati,
We discussed NDA 202057 at today's 505(b)(2) clearance meeting and you are cleared for action from a 505(b)(2) perspective.

Please make the following changes to your 505(b)(2) assessment before archiving in DARRTS for your approval action:
Revisions needed to (b)(2) assessments:

- *Question 2: Remove Epadel from the table because it is not a listed drug (b/c it is not approved in the U.S.).*
- *Question 3: Elaborate on the nonclinical bridging study, stating, for example, that Amarin conducted a 4-week rat comparative toxicity and toxicokinetics study with Vascepa (AMR101) and Epadel. Additionally, state the reason why the bridging study was needed, for example, note that Epadel was cited in the literature and Amarin is relying on that published literature.*
- *Question 14: Check the first box, "No patent certifications are required…"*

Thanks for a great job on your 505b2 assessment and for your timely responses to our inquiries.
miranda

Miranda Raggio, RN, BSN, MA
Senior Regulatory Project Manager
Regulatory Affairs Team
Immediate Office/Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Building 22, Room 3310
Silver Spring, MD 20993
301-796-2109
Miranda.Raggio@fda.hhs.gov

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/s/

KATI JOHNSON
06/05/2012

Executive CAC
Date of Meeting: April 10, 2012

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Hanan Ghantous, Ph.D., DAVP, Alternate Member
Karen Davis-Bruno, Ph.D., DMEP, Pharm Tox Supervisor
Stephanie Leuenroth-Quinn, Ph.D., DMEP, Presenting Reviewer

Author of Draft: Stephanie Leuenroth-Quinn

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #202057
Drug Name: Vascepa (icosapent ethyl, ethyl-EPA, AMR101)
Sponsor: Amarin Pharma

Background:

Vascepa (ethyl-EPA) is the ethyl ester of eicosapentaenoic acid, a long chain polyunsaturated omega-3 fatty acid (C20:5). The sponsor is developing Vascepa for the treatment of hypertriglyceridemia. Ethyl-EPA is rapidly converted to EPA by pancreatic lipase, is taken up by enterocytes and repackaged into chylomicrons before secretion into the lymph and eventual systemic absorption. Omega-3 fatty acids will compete with other saturated or unsaturated fatty acids for membrane incorporation throughout the body and can influence cellular signaling, reduce inflammation and decrease triglyceride production by the liver.

Tg.rasH2 Mouse Study:

The sponsor conducted a 6-month TgRasH2 mouse study in which ethyl-EPA was administered at doses of 0 (water control), 500, 1000, 2000 and 4600 mg/kg/day ethyl EPA by oral gavage. The ethyl EPA was administered neat, at increasing volumes. The incidence of skin/subcutis squamous cell papillomas of the proximal tail increased with dose in male mice only (0/25-0/25-0/25-1/25-5/25), and was statistically significant (pairwise analysis: P = 0.0248). The sponsor attributed these tumors to local irritation, inflammation and subsequent cellular proliferation from fecal excretion of excess oil. There was an increased incidence of mesenteric lymph node thrombosis of the perimesenteric vein as well as ileum mesenteric vein thrombosis and inflammation.

Similar to males, female mice had histopathology findings of acanthosis/ hyperkeratosis at the proximal tail along with ulcer/ erosion and inflammation. Clinical signs and macroscopic observations also showed females with nodules at the proximal tail, yet these were not papillomas by histopathology. Systemic exposure of EPA in females was slightly higher than in males.

Rat Carcinogenicity Study:

A two-year rat carcinogenicity study was conducted without prior Exec-CAC concurrence. Wistar rats were administered approximately 91, 273 and 911 mg/kg/day ethyl-EPA by oral gavage. The ethyl EPA was administered neat, at increasing volumes. Two controls were used where control 1 was corn oil (1.0 mL/kg) and control 2 was undosed. The HD female group was terminated at week 98 due to an increase in decedents in this group and deteriorating condition. The incidence of combined hemangiomas/ hemangiosarcomas at the mesenteric lymph node in females was considered drug related when compared to the undosed control (0/50-0/50-5/50-6/50) and was statistically significant (pairwise analysis: P = 0.0047). As EPA first passes from the small intestine through the lymph before systemic absorption, the concentration of this fatty acid would be highest at the mesenteric lymph node; therefore this site is considered independently. Additional evidence that the mesenteric lymph node may be physiologically relevant is the increased incidence of thrombosis (perimesenteric vein of mesenteric lymph node) in both sexes of the 6-month Tg.rasH2 mouse study. When hemangiomas/ hemangiosarcomas from all sites were combined, no drug related increase in this tumor in either sex was observed.

No other neoplasms were statistically significant by the criteria used by the Exec-CAC.

Executive CAC Recommendations and Conclusions:

Tg.rasH2 Mouse:

- The Committee agreed that the study was adequate.
- The Committee concurred that there were no drug-related neoplasms in females and that the skin/subcutis papillomas in the tail of males were drug-related but not relevant to humans.

Rat:

- The Committee agreed that the study was adequate.
- The Committee concurred that there were no neoplasms clearly drug-related in male rats. Mesenteric lymph node hemangiomas/ hemangiosarcomas appeared to be drug related in female rats. However the incidences of hemangiomas/ hemangiosarcomas at all sites, combined, were not statistically significantly increased. The Committee noted that the increased incidence of mesenteric lymph node thrombosis of the perimesenteric vein as well as ileum mesenteric vein thrombosis and inflammation, both seen in the TgRasH2 mice and the high drug exposure at the mesenteric lymph nodes in the rats suggest that the mesenteric lymph node hemangiomas/ hemangiosarcomas in rats are drug-related.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DMEP
/K. Davis-Bruno, Team leader, DMEP
/S. Leuenroth-Quinn, Reviewer, DMEP
/K. Johnson, PM, DMEP
/A. Seifried, OND IO

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/s/

ADELE S SEIFRIED
04/11/2012

DAVID JACOBSON KRAM
04/11/2012

Johnson, Kati

From: Greeley, George
Sent: Tuesday, March 27, 2012 2:04 PM
Johnson, Kati
Mathis, Lisa; Addy, Rosemary; Suggs, Courtney; Lee, Catherine S.; Parks, Mary H
Subject: NDA 202-057 Vascepa

Importance: High

Attachments: 1_Pediatric_Record.pdf

Hi Kati,

This email serves as confirmation of the review for Vascepa (Icosapent Ethyl) conducted by the PeRC PREA Subcommittee on March 21, 2012.

The Division presented a full waiver of studies in pediatric patients because there were too few children with disease/condition to study for the indication of hypertriglyceridemia.

The PeRC agreed with the Division to grant a full waiver for this indication.

The pediatric record is attached for Vascepa.

1_Pediatric_Re
ɔrd.pdf (56 KB).

ank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov
Please consider the environment before printing this e-mail.

Reference ID: 3169581

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202057 **DISCIPLINE REVIEW LETTER**

Amarin Pharma Inc.
US Agent for Amarin Pharmaceuticals Ireland Limited
Attention: Peggy Berry
VP, Quality and Regulatory Affairs
1430 Route 206, Suite 200
Bedminster, NJ 07921

Dear Ms. Berry:

Please refer to your September 25, 2011, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vascepa (icosapent ethyl) Capsules, 1 gram.

We also refer to your amendments dated January 30 and February 6, 2012.

Our review of the chemistry, manufacturing and controls section of your submission is complete, and we have identified the following deficiencies:

1. DMF 15062 is inadequate. Comments have been communicated to the DMF holder.

2. Since the maximum daily dose is > 2 g, the ICH Q3A(R2) identification and qualification threshold for related substances for impurities in drug substances is 0.05%. Therefore, submit revised drug substance specifications to tighten the proposed limit for 'related substances, others' [redacted] (b) (4). In addition, provide data identifying and qualifying all impurities present above [redacted] (b) (4). Because of the harsh manufacturing process and the resulting impurity profile of your drug substance, a tighter threshold for qualification of impurities is required.

3. The application includes only 3-months stability data (long-term and accelerated) for one product batch manufactured by Catalent. An expiration dating period cannot be determined based on such limited data. As previously conveyed to you in our December 8, 2011 letter, we again strongly recommend that Catalent be submitted in a postapproval supplement with all the necessary supporting data (i.e., withdrawn from the current NDA submission).

Please respond to the following request at your earliest convenience.

4. Submit revised comparability protocols that have been modified as follows:
   a. For the drug substance process optimization, revise the stability commitment to state that data will be submitted from three batches placed on long-term stability.
   b. For the additional packaging configurations of the drug product, revise the protocol to state that the required labeling changes will be submitted in a Supplement - Changes Being Effected in 0 Days.
   c. For a new manufacturing site of the drug product, revise the protocol to state that data will be submitted from three batches placed on long-term stability.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ENID M GALLIERS
03/26/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202057

ACKNOWLEDGE CORPORATE NAME/ADDRESS CHANGE

Amarin Pharma Inc.
US Agent for Amarin Pharmaceuticals Ireland Limited
Attention: Peggy Berry
VP, Quality and Regulatory Affairs
1430 Route 206, Suite 200
Bedminster, NJ 07921

Dear Ms. Berry:

We acknowledge receipt on December 30, 2011, of your December 30, 2011 correspondence notifying the Food and Drug Administration that the corporate name and/or address has been changed from

Amarin Pharma Inc.
US Agent for Amarin Pharmaceuticals Ireland Limited
Attention: Peggy Berry
VP, Quality and Regulatory Affairs
Mystic Packer Building
12 Roosevelt Avenue, 3rd Floor
Mystic, CT 06355

to

Amarin Pharma Inc.
US Agent for Amarin Pharmaceuticals Ireland Limited
Attention: Peggy Berry
VP, Quality and Regulatory Affairs
1430 Route 206, Suite 200
Bedminster, NJ 07921

for the following new drug application:

NDA 202057 for VASCEPA (icosapent ethyl) Capsules, 1 gram.

We have revised our records to reflect this change.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

KATI JOHNSON
01/03/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202057

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

AmarinPharma Inc.
Mystic Packer Building
12 Roosevelt Ave, 3rd floor
Mystic, Connecticut 06355

Attention: Peggy Berry, MBA
Vice President, Quality & Regulatory Affairs

Dear Ms. Berry:

Please refer to your New Drug Application (NDA) dated September 23, 2011, received on September 26, 2011, submitted under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for Icosapent Ethyl Capsules, 1000 mg.

We also make refer to your September 23, 2011, correspondence, received September 26, 2011, requesting review of your proposed proprietary name Vascepa.

We have completed our review of the proposed proprietary name, Vascepa, and have concluded that it is acceptable.

The proposed proprietary name, Vascepa, will be re-reviewed 90 days prior to approval. If **any** of the proposed product characteristics as stated in your September 23, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manger in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Kati Johnson at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
12/19/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202057

FILING COMMUNICATION

Amarin Pharma Inc.
US Agent for Amarin Pharmaceuticals Ireland Limited
Attention: Peggy Berry
VP, Quality and Regulatory Affairs
Mystic Packer Building
12 Roosevelt Avenue, 3rd Floor
Mystic, CT 06355

Dear Ms. Berry:

Please refer to your New Drug Application (NDA) dated September 25, 2011, received September 26, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for VASCEPA (icosapent ethyl) Capsules, 1 gram.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **July 26, 2012**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by **June 20, 2012**.

During our filing review of your application, we identified the following potential review issues:

Your 505(b)(2) application did not contain a complete nonclinical package. Specifically, you are relying on non-clinical literature references published by Mochida with Epadel (an approved ethyl-EPA approved in Japan). However, you did not provide an appropriate comparative bridge to Epadel to allow reliance on this data. In lieu of a direct side-by-side comparison of Vascepa (AMR101) to Epadel, published PK studies of Epadel were compared to PK data obtained from AMR101 nonclinical studies. Evaluation of these data does not directly compare the two

products as methodologies, radiolabeling, and length of administration are not similar between the products. Additionally, there was no supportive evidence of product comparability (*i.e.* impurity levels) due to the lack of any extensive chemical characterization between Epadel and Vascepa, submitted to NDA 202057.

We are providing the above comment to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

Clinical

1. Please submit a rationale for assuming the applicability of foreign data in the submission to the U.S. population.

Pharmacology/Toxicology

2. As there is no adequate bridging information to Epadel, conduct an appropriate nonclinical study (*e.g.* 28-Day repeat dose toxicology study in the rat) to demonstrate at a minimum, PK comparability between Epadel and Vascepa (AMR101), so that you may rely on published Epadel literature for your 505(b)(2) application.

Chemistry, Manufacturing, and Controls

3. In the NDA, you include the drug substance specifications from the drug substance manufacturer and from the drug product manufacturer Banner. Reference is made to DMF 25289 for the drug substance specification from the drug product manufacturer Catalent. Provide a copy of the Catalent drug substance specification in the NDA. In addition, clarify which drug substance specification will serve as the regulatory specification (i.e., for FDA's method validation and GMP enforcement purposes).

4. A comparability protocol cannot be located in the NDA even though you proposed one at the Pre-NDA meeting. As stated in FDA's 2003 draft guidance "Comparability Protocols – CMC Information", the protocol should be submitted either in the original NDA or in a post-approval supplement (prior-approval) for FDA's approval prior to the applicant's initiation of the protocol studies. Clarify whether you still intend to use a comparability protocol for qualifying a new drug substance manufacturer.

5. Justify the lack of Microbial Limits in the drug substance specifications. The drug substance is naturally derived and such an attribute should be included in the specification.

6. Include in the drug substance specifications tests and acceptance criteria for contaminants commonly found in fish oil [redacted] (b) (4)

[redacted] (b) (4). Provide safety information to support the proposed acceptance criteria.

7. Submit the Catalent product composition to the NDA.

8. The NDA includes only 1-month stability data (long-term and accelerated) for one product batch manufactured by Catalent. An expiration dating period cannot be determined based on such limited data. We strongly recommend that Catalent be submitted in a post-approval supplement (i.e., withdrawn from the current NDA submission) with all the necessary supporting data (comparative in-vitro testing, at minimum 3-month long-term and accelerated stability data for three product batches at no less than 10% commercial scale).

Product Quality Microbiology

9. Submit the test methods and data sets verifying the suitability of the use of the stated microbial limits test with the drug product.

Biopharmaceutics

10. Provide the method development report of the disintegration test including the parameters for the proposed disintegration test: Medium, Volume, Apparatus, Time, Procedure and Tolerances.

11. Submit disintegration results generated on batches used in both clinical and stability studies. The specification will be set after FDA reviews the disintegration results generated from these batches.

12. Submit comparative disintegration test results comparing batches manufactured at Banner and Catalent and specify the manufacturing site to be used to manufacture the commercial product.

13. Submit comparative disintegration test results comparing the pilot scale batches and the intended commercial scale batches

14. Submit information or data to support that the fill material does not change with time.

Office of Scientific Investigations

15. Please identify for Study 01-01-0016:
    a. Location of Trial Master File and Clinical Investigator Master Files [actual physical site(s) where documents are maintained and would be available for inspection].

    b. Current name, address, and contact information of all CROs used in the conduct of the clinical trial.

    c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies.

d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.) if not included with "a" above.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. Under Table of Contents (TOC), if a section of subsection is omitted from the FPI and TOC, the heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."
2. Under Table of Contents, all section headings must be in bold type, and subsection headings must be indented and not bolded.
3. There should be no periods after numbers for sections and subsections in the Full Prescribing Information and the Table of Contents.
4. Regarding Contraindications, the labeling should not include theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
5. In the Highlights section, the following verbatim statement must be included: "See 17 for Patient Counseling Information and FDA-approved patient labeling" (since you are proposing patient information labeling).

We request that you resubmit labeling that addresses these issues by January 1, 2012. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Your application requests a partial waiver of pediatric studies for ages 0 to 10 years, and a deferral request for ages 11 to 18 years. Your application does not address pediatric patients who are 10 years of age. Within 30 days of the date of this letter, please amend your application to fully address PREA across the entire pediatric age range, 0 to 17 years.

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ERIC C COLMAN
12/08/2011
Eric Colman for Mary Parks

Record of 10-05-11 Telecon and 10-06-11 Email communication re NDA 202057

Between Enid Galliers, CPMS, DMEP, CDER, FDA
And
Peggy Berry, Regulatory Contact, Amarin Corporation

BACKGROUND: **NDA 202057 icosapent ethyl capsules** was submitted as a 505(b)(1) application on Sept. 25, 2011, received Sept. 26, 2011. The filing date is Friday, November 25, 2011, and the filing meeting is scheduled for Monday, November 14, 2011.

Apparently, the applicant will rely in part on published preclinical data for another product that is approved in Japan and for which it does not currently have right of reference. Amarin has been concerned about the possibility of receiving a Refusal to File (RTF) action and whether they can amend the application to avoid RTF. Additional questions were raised but the attached email summarizes the essential points of the communications between Ms. Berry and me.

Galliers, Enid M

From: Galliers, Enid M
Sent: Thursday, October 06, 2011 4:26 PM
To: 'Peggy Berry'
Subject: RE: NDA 202057 - additional follow up

Peggy,

I've modified your text a little and added a note reflecting guidance I received today that confirmed that you can switch back to a (b)(1) after filing.

Regards,

Enid

From: Peggy Berry [mailto:peggy.berry@amarincorp.com]
Sent: Thursday, October 06, 2011 1:05 PM
To: Galliers, Enid M
Subject: RE: NDA 202057 - additional follow up

Hi Enid,
Thanks again for your time yesterday. I think that you provided the final clarity that we needed so that we can make a decision going forward. I prepared a brief summary of our call yesterday and I wanted to run it by you quickly to make sure that I got everything right.

The FDA (Enid Galliers) confirmed that if we are relying on literature that we believe is necessary for approval we should switch our submission to be a (b)(2).

The FDA confirmed that being a (b)(1) vs. a (b)(2) does not impact our ability to get exclusivity as an NCE of 5 years because that decision is made completely separately from the type of filing.

The FDA confirmed that it is not the division's policy or practice to contact the sponsor in advance of issuing an RTF to allow them to make the corrections or changes needed to make it fileable. This is generally because there is either not enough time for the applicant to submit an amendment, much less for FDA to review any amendment that might be submitted to ensure that it is appropriate to file the application with the change. Because of the timing of our filing date (right before Thanksgiving), she said the problem is further magnified because people may not be in the office or otherwise available to do the review.

Finally, the FDA further confirmed that if we switch now to a (b)(2) and we later get right of reference to the Mochida data, we can switch back to a (b)(1) if we want to. She said that if this switch is made by month 7, they would NOT extend the timeline for their first response. She also said that if it's done after month 7, and it is not requiring them to review new data that is not already part of the publication, they may not extend the review clock at that time either, but it depends on what's submitted and on discussions with their policy attorneys.
(Additional notes: The only caveat to add is if the literature cites a branded product, then you also need to cite reliance on that listed drug and provide the appropriate patent cert or statement to address reliance on the listed drug cited in literature. And whether you do this before or after filing also has no consequence. A form FDA 356h

should be included in each submission and the 505(b)(1) or 505(b)(2) should be adjusted as needed.

Thanks!
Peggy

From: Peggy Berry
Sent: Tuesday, October 04, 2011 5:55 PM
To: Galliers, Enid M
Subject: RE: NDA 202057 - additional follow up

11 is great. I will call you then.

From: Galliers, Enid M [mailto:Enid.Galliers@fda.hhs.gov]
Sent: Tuesday, October 04, 2011 5:47 PM
To: Peggy Berry
Subject: RE: NDA 202057 - additional follow up

HI Peggy,

Would 11:00 AM be convenient for you? Will you call me at my office number (below)?

Thanks,

Enid

From: Peggy Berry [mailto:peggy.berry@amarincorp.com]
Sent: Tuesday, October 04, 2011 5:44 PM
To: Galliers, Enid M
Subject: RE: NDA 202057 - additional follow up

Hi Enid,
Could we schedule a brief call for tomorrow? The morning works best for me, but any time that works for your schedule will be fine.
Thanks,
Peggy

From: Galliers, Enid M [mailto:Enid.Galliers@fda.hhs.gov]
Sent: Friday, September 30, 2011 3:17 PM
To: Peggy Berry
Subject: FW: NDA 202057 - additional follow up
Importance: High

Hello Peggy,

First, please contact me regarding this NDA during Kati's absence. Second, an application can be amended during the initial 60-day filing review period. However, the review team must have enough time to consider any amendments relevant to a filing decision prior to the filing meeting. Therefore, I recommend that your company carefully consider FDA's 1999 draft guidance for industry *Applications Covered by Section 505(b)(2)*, and if you decide to amend your NDA as a 505(b)(2), to assure delivery of the amendment by the end of October

so that the review team can evaluate fileability accordingly.

I will be available (preferably at a prescheduled time) to discuss the guidance with you next week. Please arrange a teleconference with me by email.

Regards,

Enid

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: 301-796-1211
Fax: 301-796-9712
email: enid.galliers@fda.hhs.gov

Submissions:

FDA, CDER, CDR
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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From: Johnson, Kati
Sent: Friday, September 30, 2011 12:11 PM
To: Galliers, Enid M
Subject: FW: NDA 202057 - additional follow up
Importance: High

From: Peggy Berry [mailto:peggy.berry@amarincorp.com]
Sent: Friday, September 30, 2011 11:26 AM
To: Johnson, Kati
Subject: NDA 202057 - additional follow up
Importance: High

Hi Kati,
I'm sure that you don't want to hear from me today – but, I have been asked to do an additional follow up with you before you go on vacation. We had a call with our Board last night and everyone still believes that we are a 505(b)(1). However, they are a little freaked out about not having the possibility to amend the application to be

a 505(b)(2) in the event that the FDA disagrees with us at day 45. All of the regulatory lawyers and other regulatory advisors who we have consulted with say that the FDA, as a general standard practice, allows the company to amend the NDA prior to issuing a RTF if the change can be made quickly – like 24 hours. As a small company, we can't survive having a RTF because it could put us out of business. So that's what they are having more struggle now than before is that it sounds like we won't have that opportunity here. Can you confirm for me that this is the case? Or, is there someone else that I could or should discuss this with while you're out?
Thanks again for all of your help with this – I really do appreciate it!
Peggy

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/s/

ENID M GALLIERS
10/06/2011

Sharma, Khushboo

From: Sharma, Khushboo
Sent: Wednesday, September 28, 2011 8:45 AM
To: 'peggy.berry@amarincorp.com'
Cc: Johnson, Kati

Dear Ms. Berry,

We are reviewing the Chemistry, Manufacturing and Controls section of your NDA 202-057 received September 26, 2011. We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your submission:

- Please provide a contact name, phone number, fax number for the Drug Substance Manufacturer (Nisshin Pharma Inc, Japan)
- Please provide a statement that all the facilities are ready for GMP inspection.
- Please list all the drug substance manufacturers and drug product manufacturers together as an attachment to the Form 356H.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issues under consideration. Otherwise, please provide the appropriate information as an amendment to the submission. In addition, a copy of your response submitted by e-mail (khushboo.sharma@fda.hhs.gov) will expedite the review of your request. In your cover letter refer to the date on which this information was requested.

Please acknowledge the receipt of this email and provide the time line of the amendment submission.

Thank you

Khushboo Sharma
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment III
Phone (301)796-1270

Reference ID: 3021498

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/s/

KHUSHBOO SHARMA
09/28/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202057

NDA ACKNOWLEDGMENT

Amarin Pharma Inc.
US Agent for Amarin Pharmaceuticals Ireland Limited
Attention: Peggy Berry
VP, Quality and Regulatory Affairs
Mystic Packer Building
12 Roosevelt Avenue, 3rd Floor
Mystic, CT 06355

Dear Ms. Berry:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: VASCEPA™ (icosapent ethyl) Capsules, 1 g

Date of Application: September 25, 2011

Date of Receipt: September 26, 2011

Our Reference Number: NDA 202057

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 25, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:
http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 22057** submitted on September 25, 2011, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight

mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, call me at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATI JOHNSON
09/27/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102457

MEETING MINUTES

Amarin Pharma Inc.
Attention: Peggy Berry
VP, Head of Quality and Regulatory Affairs
Mystic Packer Building
12 Roosevelt Avenue, 3rd Floor
Mystic, CT 06355

Dear Ms. Berry:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AMR101 (ethyl-EPA) Capsules.

We also refer to the meeting between representatives of your firm and the FDA on March 16, 2011. The purpose of the meeting was to discuss issues pertaining to your to-be-submitted NDA.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes
DSI Documents

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: March 16, 2011, 12:30 pm
Meeting Location: FDA White Oak Campus
Building 22, Conference Room 1315

Application Number: IND 102457
Product Name: AMR101 (ethyl-EPA) Capsules, 1 gram
Indication: Adjunct to diet to reduce triglyceride (TG) levels in patients with very high (≥ 500 mg/dL) TG levels.

Sponsor/Applicant Name: Amarin Pharma Inc.
Meeting Chair: Eric Colman, MD
Meeting Recorder: Kati Johnson

FDA ATTENDEES

Division of Metabolism & Endocrinology Products
Eric Colman, MD-Deputy Director, Lipid Team Leader
Iffat Chowdhury, MD-Clinical Reviewer
Stephanie Leuenroth-Quinn, Pharmacology/Toxicology Reviewer
Bola Adeolu-Project Manager
Kati Johnson-Project Manager

Office of Translational Sciences, Office of Clinical Pharmacology
Sally Choe, PhD-Team Leader
Manoj Khurana, PhD-Reviewer

Office of Translational Sciences, Office of Biostatistics
Todd Sahlroot, PhD-Deputy Director, Division of Biometrics II
Japobatra Choudhury, PhD-Statistician

SPONSOR ATTENDEES

Amarin Pharma Inc.
Peggy Berry-VP, Regulatory Affairs and Quality
Rene Braeckman, PhD-Development Operations
Paresh Soni, MD, PhD-Senior VP, Development
William Stirtan, PhD-Sr. Director, Project Management & Nonclinical

BACKGROUND

AMR101 is ethyl EPA and is being investigated for the following indications:

1. As an adjunct to diet to reduce triglyceride (TG) levels in adults with very high (>500 mg/dL) TG levels

(b) (4)

To support the elevated TG indication above, the firm submitted Protocol **AMR-01-0016**, *A Phase 3 Multi-Center Placebo-Controlled, Randomized, Double-Blind, 12-Week Study with an Open-Label Extension to Evaluate the Efficacy and Safety of AMR101 in Patients with Fasting Triglyceride Levels ≥500 mg/dL and ≤1500 mg/dL:* The AMR101 **MARINE** Study. The design and planned analysis was found acceptable in a May 1, 2009 Special Protocol Agreement.

The IND was submitted May 22, 2009.

(b) (4) the firm submitted Protocol **AMR-01-01-0017**, *A Phase 3 Multi-Center Placebo-Controlled, Randomized, Double-Blind, 12-Week Study to Evaluate the Effect of Two Doses of AMR101 on Fasting Serum Triglyceride Levels in Patients with Persistent High Triglyceride Levels (≥200 mg/dL and ≤500 mg/dL) Despite Statin Therapy:* The AMR101 **ANCHOR** Study**.** The design and planned analysis were found acceptable in a July 6, 2009 Special Protocol Agreement. The protocol was later revised, with regard to inclusion/exclusion criteria, on May 12, 2010.

(b) (4)

On August 12, 2010, the sponsor requested a Pre-NDA meeting to discuss chemistry, manufacturing and controls issues. In lieu of a meeting, written responses were provided on January 20, 2011.

The sponsor requested a Pre-NDA meeting on December 14, 2010. The meeting was granted on January 3, 2011.

2. DISCUSSION

Preliminary responses were provided to the sponsor on Tuesday, March 15, 2011.

The sponsor's questions are followed by our **bolded** preliminary responses, which are followed by any meeting discussion in <u>underlined</u> text. Any post-meeting comments are in *italicized* text.

<u>NONCLINICAL (NC)</u>

NC-1 Amarin considers that the new toxicity studies conducted with AMR101 along with the published studies conducted with ethyl-EPA (Epadel®) provide a comprehensive ICH M3 compliant package of preclinical information that can be used to assess the safety and

toxicity of AMR101. The available preclinical studies are summarized in Table 1, Table 2, Table 3, Table 4, and Table 5 and will be provided in the NDA. Amarin will rely on these data for the planned NDA and considers this a stand-alone preclinical package.

Does the FDA agree that the nonclinical information available for ethyl-EPA is sufficient to support a NDA filing?

FDA Preliminary Response:
Ultimately, the acceptability of the toxicology studies to support NDA filing can not be determined until the NDA has been submitted and all study reports have been reviewed. Preliminary review of the combination of submitted literature references and Amarin's nonclinical studies conducted with AMR101, appears sufficient; however the scientific adequacy remains a review issue. Since you plan to rely on nonclinical data which you do not own or have right of reference to, this application will not be considered a stand-alone package.

Genotoxicity experiments have shown that AMR101 is negative in the AMES assay, positive for clastogenicity (±S9), and negative in the mouse micronucleus assay. As final Agency review has not been completed for the 2-year rat or the 6-month transgenic RasH2 mouse carcinogenicity studies, it would be premature to comment on the adequacy and therefore safety assessment of these studies as a whole.

Meeting Discussion: None

NC-2 Amarin will provide electronic datasets for the carcinogenicity studies as SAS transport (Xport) files - version 5 (104-week rat study) and version 6 (26-week mouse study). Does the FDA agree to the proposed electronic data submission for the 2 carcinogenicity studies as described above?

FDA Preliminary Response:
FDA agrees to the proposal to submit the tumor data in SAS transport files. However, it is important to make sure that the data in the SAS transport files are in the FDA data format described in the guidance document entitled "Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications".

Meeting Discussion: None

CLINICAL (CL)

CL-1 Does the FDA agree that at present, a deferral of the pediatric study requirement is acceptable?

FDA Preliminary Response: According to the Pediatric Research and Equity Act (PREA), at the time of the NDA submission, you must either submit a deferral, waiver, or the results of a pediatric study for the proposed indication(s). Since, to our knowledge, Amarin does

not have such a study, submission of a deferral or waiver will be necessary. You must state the specific age groups for which you are seeking a waiver/deferral and provide a justification for the request. The acceptability of the deferral/waiver will be determined during the course of the NDA review.

Meeting Discussion: The agency confirmed that the inclusion of a waiver/deferral request would render the submission a complete application for filing purposes, at least from a PREA perspective. The sponsor was reminded to address the entire pediatric group from 0 to 17 years of age.

CL-2 Does the FDA agree that Amarin, pending approval of AMR101 in adults, may submit to FDA a pediatric written request and be eligible for 6 months additional exclusivity upon completion of an agreed pediatric program?

FDA Preliminary Response: A Proposed Pediatric Study Request (PPSR) may be submitted at any time; whether the written request is issued is a review issue.

Meeting Discussion: None

CL-3 Amarin plans to submit a single study to support the efficacy of AMR101 for patients with very high (≥500 mg/dl) triglycerides. As there are no additional trials to integrate for efficacy, Amarin does not propose to submit an integrated summary of efficacy for AMR101, and will simply refer to the completed study report for MARINE (AMR-01-01-0016). Does the FDA agree with this approach?

FDA Preliminary Response: Under CFR 314.50(d)(5)(v), the Integrated Summary of Effectiveness (ISE) must include:

- **An integrated summary of the data demonstrating substantial evidence of effectiveness for each claimed indication**
- **Evidence that supports the dosage and administration section of the labeling, including support for the recommended dosage and dose interval**
- **Effectiveness data analyzed by sex, age, and racial subgroups**
- **Evidence that is pertinent to individualization of dosing and the need for modifications of dosing for specific subgroups**

Further guidelines of what should be included in the ISE can be found in the *Guidance for Industry: Integrated Summary of Effectiveness*. If you plan to submit the study report for MARINE in lieu of the ISE, please make sure that the study report contains all the necessary elements of an ISE.

Meeting Discussion: The sponsor asked about inclusion of efficacy information from the ANCHOR study, which would add approximately 700 patients to the approximately 250 patients in the MARINE study. According to the firm, the MARINE study demonstrates that AMR101 therapy does not result in an increase in LDL. The study will be completed when the NDA is

submitted, but the final report will not be available at that time. The sponsor was notified that we would discuss this internally and provide a response in the finalized meeting minutes.

Post-Meeting Discussion- The study populations, inclusion and exclusion criteria as well as the different indications of the ANCHOR and the MARINE trials preclude the integration of the efficacy data from the trials. Thus your offer to include efficacy data from the ANCHOR study is not accepted as part of the Integrated Summary of Efficacy for the indication "as an adjunct to diet to reduce triglyceride levels in adult patients with very high ≥ 500 mg/dL triglyceride levels".

CL-3.1 If yes, because this is an eCTD, is it acceptable to provide a link to the clinical study report from section 5.2.5.2? Or should no link be provided?

FDA Preliminary Response: A link to the clinical study report from section 5.2.5.2 is acceptable.

Meeting Discussion: None

CL-3.2 If No, please indicate what additional analyses are required?

CL-4 Amarin proposes that the Clinical Summary of Efficacy within Module 2 will also provide a full summary of the data obtained from the single pivotal efficacy study for patients with very high triglycerides (MARINE; AMR-01-01-0016). The Clinical Overview will take into account published literature as well as the pivotal efficacy study through the discussion. Does the FDA agree with this approach?

FDA Preliminary Response: Yes.

Meeting Discussion: None

CL-5 Four (4) integrated databases will be presented to support the safety of AMR101 use in patients:

- Safety data from 2 multicenter, randomized, double-blind, placebo-controlled, Phase 3 clinical studies in subjects with hypertriglyceridemia
- Safety data from 8 multicenter, randomized, double-blind, placebo-controlled, Phase 2 and Phase 3 clinical studies in subjects with CNS disorders
- Safety data from 3 studies with healthy subjects treated with AMR101
- Safety data from all subjects treated with AMR101, regardless of study phase or indication

Does the Division agree that Amarin's plan for integrating the safety data is acceptable?

FDA Preliminary Response: Yes.

Meeting Discussion: None

CL-6 Amarin proposes to provide narratives for patient cases for deaths, discontinuations due to adverse events and serious adverse events for all AMR101 studies. Does the Division agree with this approach?

FDA Preliminary Response: Yes.

Meeting Discussion: None

CL-7 Amarin proposes to provide case report forms (CRFs) for all deaths, discontinuations due to adverse events (AEs), and serious adverse events (SAEs) across all treatment arms within the hypertriglyceridemia studies with the NDA. CRFs for these types of events in other studies will be provided at Agency request. Does the Division agree with this approach?

FDA Preliminary Response: Yes.

Meeting Discussion: None

CL-8 Within the subject NDA, Amarin plans to include the following information for each of the studies:

Full Study Report Module 5.3.1	Electronic Dataset Module 5.2.2	Summary of Results Module 2.7	Synopsis of Study Module 2.7.6
MARINE (AMR-01-01-0016)	MARINE (AMR-01-01-0016)	MARINE (AMR-01-01-0016)	MARINE (AMR-01-01-0016)
PK study (LA01.01.0009)		PK study (LA01.01.0009)	PK study (LA01.01.0009)
PK study (AMR-01-01-0018)		PK study (AMR-01-01-0018)	PK study (AMR-01-01-0018)
DDI study (AMR-01-01-0020)		DDI study (AMR-01-01-0020)	DDI study (AMR-01-01-0020)
		ANCHOR (AMR-01-01-0017)	ANCHOR (AMR-01-01-0017)
	ISS (includes all studies)		All CNS studies

Does the FDA agree with these contents?

FDA Preliminary Response (Clinical): Yes.

FDA Preliminary Response (Clinical Pharmacology): To enable a comprehensive and timely review, please submit raw concentration and PK parameter data for all applicable analytes (preferably as SAS transport files) for all PK/clinical pharmacology studies (LA01.01.0009, AMR-01-01-0018, and AMR-01-01-0020).

- **The concentration data-set(s) should at least have the following columns: ID, Analyte Name, Nominal Time, Actual Time, Concentration, Unit, Comments (if any), Treatment, Period, and Sequence.**
- **The PK parameter data set(s) should at minimum have the following columns: ID, Trial Number, Parameter Name, Unit, Comments (if any), Treatment, Period, and Sequence.**

In addition, include the electronic data-sets used for exposure-response analysis mentioned on page 34 section 3.2.7.4.4 in your submission. Also, include bioanalytical study reports supporting the concentration data in your submission.

Meeting Discussion: According to the background package, the sponsor has conducted in vitro studies to evaluate metabolic induction and inhibition potential of AMR101 on other drugs. The following CYP450 enzymes indicated a possible drug-drug interaction (in decreasing order of inhibition potential): 2C19, 2C9, 2C8 and 2B6. Based on their interpretation of the FDA Guidance:Drug Interaction Studies-Study Design, Data Analysis, and Implications for Dosing and Labeling (2006), Amarin conducted an in vivo study to test the inhibition of 2C19 and 2C8 (using respective substrates of omeprazole and rosiglitazone).
The agency interprets the guidance document differently. Positive in vitro studies tell you that there is sufficient signal to warrant conducting in vivo study(ies) and the agency would expect in vivo assessment of both 2C9 and 2B6 in the future NDA. In response to a question from the firm, the agency said they would file the NDA with draft report(s) reports of these in vivo studies, and the final reports would follow in 4 to 6 weeks.

During the internal meeting in preparation for this meeting with the sponsor, it was not clear what the proposed dosing regimen will be. The firm will be seeking approval for (b) (4) 4 g daily doses, and said they have information that exposure of 4 g daily dosing is equivalent to that of 2 g twice daily dosing used in the MARINE pivotal study. The agency told the sponsor that a simple pharmacokinetic comparison will not be sufficient to extrapolate twice daily dosing to once daily dosing. A justification is needed to show that the higher Cmax with once daily dosing would not be a safety issue. In addition, information must be provided to demonstrate that efficacy would not be adversely affected with once daily regimen. Agency asked for additional clarification for the intention behind the development of 500 mg capsule used in the PK study; sponsor mentioned that 500 mg capsule is being used in studies conducted under CNS indication and for this submission, they are not proposing 500 mg capsule as part of NDA.

Post-Meeting Discussion:
The firm provided some text from the Drug Interaction guidance to support their position that negative interaction results in vivo for CYP enzymes with the largest [I]/Ki obviates the need to conduct in vivo evaluations of the other CYPs with smaller [I]/Ki . Based on this information,

we have the following comments:

We agree with the sponsor's comments on the draft DDI guidance language. However, the CYP inhibition potential that was identified with CYP2C9 can not be waived based on the guidance language because of the potential use of warfarin, the recommended sensitive CYP2C9 substrate and narrow therapeutic index drug. Therefore, depending on the in vivo DDI study with a sensitive CYP2C19 substrate, waiving the evaluation of in vivo DDI study with CYP2B6 is acceptable. We, however, continue to recommend that the sponsor conduct in vivo DDI studies evaluating the inhibition potential of CYP2C9 and 2C8 in addition to 2C19. These recommendations are based on the sponsor's claimed in vitro study results. If our review of the in vitro results do not agree with the sponsor's conclusions, these comments will not be applicable.

CL-9 Amarin studies were not designed to study withdrawal/rebound effects or abuse potential. Amarin believes that the risk of abuse potential is low. Thus, no withdrawal/rebound effects or abuse potential will be presented in the submission. Does the Division agree with Amarin's plan?

FDA Preliminary Response: Although you have no specific trials to test for drug abuse potential, you should plan to submit documentation stating any prior history of drug abuse potential or withdrawal with other members of AMR101 pharmacological class of drugs. Reports of significant overdose in post-marketing data from other countries should be submitted. You should also submit directives for overdose measures.

Meeting Discussion: In response to a question from the firm, the agency clarified that drug abuse potential or withdrawal documentation should pertain to the pharmacological class of drugs (fish oil products) approved by a regulatory body in Japan, Europe, or the US.

CL-10 Amarin plans to provide analyses on special topics of the FDA requested possible drug related hepatic disorders and severe cutaneous adverse events in the integrated safety summary. Does the Division agree with this approach?

FDA Preliminary Response: Yes.

Meeting Discussion: None

CL-11 Amarin proposes the definitions shown in the following table for potentially clinically significant (PCS) laboratory values. Does the Division agree with the proposed PCS laboratory criteria?

Potentially Clinically Significant Chemistry Values

Parameter	PCS Low	PCS High
Albumin	≤3.3 g/dL	≥5.8 g/dL
Alkaline Phosphatase	NA	>1x ULN to 2x ULN >2x ULN to 3x ULN

Parameter	PCS Low	PCS High
		>3x ULN
ALT	NA	>1x ULN to 2x ULN >2x ULN to 3x ULN >3x ULN
AST	NA	>1x ULN to 2x ULN >2x ULN to 3x ULN >3x ULN
Bilirubin	NA	>1x ULN to 2x ULN >2x ULN to 3x ULN >3x ULN
ALT + Bilirubin	NA	>3x ULN (ALT) + 2 x ULN (Bilirubin)
AST + Bilirubin	NA	>3x ULN (AST) + 2x ULN (Bilirubin)
Calcium	≤7 mg/dL	≥12 mg/dL
Creatinine	<0.5 mg/dL (Female) <0.65 mg/dL (Male)	≥1.6 mg/dL (Female) ≥2.0 mg/dL (Male)
Creatinine Kinase		≥1xULN to 5xULN ≥5xULN to 10xULN ≥10xULN
Glucose (fasting)	≤36 mg/dL	≥130 mg/dL
Magnesium	<1.5 mg/dL	≥2.7 mg/dL
Potassium (K)	≤3.0 mEq/L	≥5.5 mEq/L
Sodium (Na)	≤130 mEq/L	≥150 mEq/L
Total Protein	<5.0 g/dL	≥9.5 g/dL
Urea nitrogen (BUN)	NA	≥31 mg/dL

Note: values are given in terms of Conventional units Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; g/dL = grams per deciliter; Eq/L = milliequivalents per liter; mg/dL = milligrams per deciliter; NA = Not applicable; PCS = potentially clinically significant, ULN = upper limit of normal.

Potentially Clinically Significant Hematology Values

Parameter	PCS Low	PCS High
Hemoglobin (Hb)	≤10.0 g/dL (Female) ≤10.0 g/dL (Male)	≥16.5 g/dL ≥18.0 g/dL
Red Blood Cells (RBC)	≤3.5 X 10^6/µL (Female) ≤3.8 X 10^6/µL (Male)	>5.5 X 10^6/µL (Female) >6.0 X 10^6/µL (Male)
White Blood Cells (WBC)	≤1.5 X 10^3/µL	NA

Parameter	PCS Low	PCS High
Platelet count	≤100 X 10^3/µL	≥500 X 10^3/µL

Note: values are given in terms of SI units
Abbreviations: g/dL = grams per deciliter; NA = Not Applicable; PCS = potentially clinically significant; µL = microliter

FDA Preliminary Response: Yes.

Meeting Discussion: None

CL-12 Amarin proposes the definitions shown in the following tables for change from baseline categories (i.e. shift) and potentially clinically significant (PCS) vital signs values. Does the Division agree with the proposed change from baseline and PCS vital sign criteria? Supine positions if available and alternatively, sitting positions will be used. Does the Division agree with this approach?

FDA Preliminary Response: Yes.

Meeting Discussion: None

Vital Signs Value Categories (Change from Baseline Categories)

Vital Sign	Low	Normal	High
Systolic Blood Pressure	≤90 mmHg	>90 mmHg-<160mmHg	≥160 mmHg
Diastolic Blood Pressure	≤50 mmHg	>50 mmHg-<100mmHg	≥100 mmHg
Pulse	≤50 beats/min	>50 beats/min-<90beat/min	≥90 beats/min

Potentially Clinically Significant Vital Signs Value Definitions

Vital Sign	PCS Low	PCS High
Systolic Blood Pressure	≤90 mmHg AND decrease of ≥20 mmHg	≥160 mmHg AND increase of ≥20 mmHg
Diastolic Blood Pressure	≤50 mmHg AND decrease of >10 mmHg	≥100 mmHg AND increase of >10 mmHg
Pulse	≤50 beats/min AND decrease of ≥15 beats/min	≥90 beats/min AND increase of ≥15 beats/min

CL-13 Amarin proposes that the Clinical Safety Summary in Module 2 will comprise the front matter from the Integrated Summary of Safety contained within 5.2.5.2. Does the FDA agree with this approach?

FDA Preliminary Response: Yes.
Meeting Discussion: None

CL-14 Amarin plans on submitting CDISC SDTM datasets based upon the implementation guide 3.1.2 and ADaM datasets based upon the implementation guide 1.0. These datasets will be submitted as Version 5 SAS transport format (SAS Xport). Does the Division agree with this approach?

FDA Preliminary Response: This appears acceptable.

Meeting Discussion: None

CL-15 Amarin will be using a single version of MedDRA for the Hypertriglyceridemia studies, the ISS data and ISS analysis. Other indications were re-mapped from the raw datasets to the updated MedDRA version. The clinical study reports and individual study datasets for the CNS studies will not be submitted in this submission. Therefore, it is not necessary to provide a list of events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another version. Does the Division agree with this approach?

FDA Preliminary Response: Clarify why the CNS studies will not be submitted.

Meeting Discussion: The following agreements were reached:

- The individual study datasets from the CNS trials would NOT be submitted. However, the sections of the CNS study reports pertaining to safety will be provided in Module 5.
- Safety data from the CNS trials will be provided in the integrated summary of safety database and reports
- Narratives and Case Report Forms from the CNS trials for the appropriate patients will be provided

CL-16 The 120-day safety update will include information regarding any treatment emergent SAEs observed in ongoing studies (MARINE open label and REDUCE-IT). There is no plan to further integrate data or provide additional clinical data at that time. Does the Division agree with this approach?

FDA Preliminary Response: Yes.

Meeting Discussion: None

REGULATORY (RA)

NOTE- We have not responded to most of the labeling questions below. The final label will be negotiated following review of the application.

RA-1 Given the significant improvement demonstrated in the MARINE study, of eliminating the treatment-limiting drug reaction of substantial increases in LDL-C over the approved products, Amarin asserts that on this basis and in accordance with FDA MAPP 6020.3 - PRIORITY REVIEW POLICY, a review classification of P -- Priority review should be assigned to the NDA application. Does the FDA agree that this application will qualify for priority review?

FDA Preliminary Response: A determination as to whether the application will be designated for a Standard or Priority review will be made by the filing date (60 days following receipt of the application).

Meeting Discussion: The firm pressed for a more definitive response given the limited resources of the company. The sponsor was informed that there was a higher probably that the application would be reviewed under a Standard review timeline than under a Priority review timeline.

RA-2 Based upon the results of the MARINE clinical study and the factors set forth in section III.A.1 of the FDA's August 2008 Guidance on Convening Advisory Committee Meetings, AMR101 is not likely to be referred for Advisory Committee review. Does the FDA agree?

FDA Preliminary Response: Under 505(s) of the FD&C Act, all new chemical entities must either be discussed at an Advisory Committee Meeting or a justification provided as to why it will not be discussed. A final decision on whether AMR101 is a new chemical entity has not been made.

Meeting Discussion: The firm pressed for a more definitive response given the limited resources of the company. The sponsor was informed that, based on what is known about the compound at this time, and in our opinion it was less likely that AMR101 would go to an Advisory Committee. Final decision on the question of an Advisory Committee would be made after submission of the NDA.

RA-3 Amarin proposes to display, in tabular format, adverse events from the MARINE study only in the Adverse Event section. Does the FDA agree with this approach?

RA-4 Amarin proposes to display in the table of adverse events, from the MARINE study, all those events that occurred at a rate of >3% (i.e., in more than 2 patients) in any treatment group. Does the FDA agree that this is acceptable?

FDA Preliminary Response: This is acceptable. However, the events must also occur at a rate more often in subject taking drug than in subjects taking placebo.

Meeting Discussion: In response to a question from the firm, the agency clarified that we were asking for adverse events from that single study, not from the integrated report.

Post-Meeting Discussion- We request that you provide the adverse reaction data both from the single MARINE trial and from the pooled integrated summary of safety data (two tables).

RA-5 Amarin proposes to describe the adverse events for the Integrated Dataset, including the ANCHOR study and CNS studies, in paragraph form below the adverse event table. Does the FDA agree with this approach?

RA-6 Amarin proposes to describe adverse events, from the Integrated Dataset in the text, that are >5% in the AMR101 treated patients. Does the FDA agree with this approach?

RA-7 Amarin proposes to describe adverse events from the Integrated Safety Database that occurred in special populations, such as diabetics and patients concomitantly treated with statins, in text below the adverse event table. This information is important for physicians in determining whether or not treatment with AMR101 is appropriate for these patients. Potential text may be as follows. Does the FDA agree with this approach?

> X### patients have received statin treatment concurrent with AMR101 treatment. The incidence of adverse events for patients on statins plus AMR101 was not different from patients treated with AMR101 alone.
>
> X### patients with diabetes mellitus have been treated with AMR101. The safety profile for patients with diabetes mellitus is similar to non-diabetics.

RA-8 Within the package insert where the pivotal clinical study will be described, Amarin proposes to display results in graphical format (see example above) in order to most effectively communicate the effects and differences across dose groups. Does the FDA agree with this approach?

Meeting Discussion: The agency is not opposed to data being presented in graphical format.

RA-9 Amarin proposes that the endpoints displayed in the graphical example will be the endpoint data that are displayed from the MARINE study as it is the most relevant to a physician's prescribing decision for use of the drug. Does the FDA agree with this approach?

RA-10 Additional endpoints that were measured in the clinical study will be briefly described in paragraph format below the efficacy data graph as shown in the sample text below.

> AMR101 4 grams per day significantly reduced LDL particle number (p=0.0042), remnant-like particle cholesterol (p=0.0041), hs-CRP (p=0.0012), Apo A1 (p=0.009), and the AA/EPA ratio from baseline relative to placebo.

Does the FDA agree with this approach?

(b) (4)

RA-12 Does the FDA have any additional comments or guidance regarding the preparation of the draft package insert?

FDA Preliminary Response: No.

Meeting Discussion: None

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None

4.0 ACTION ITEMS

None

5.0 ATTACHMENTS AND HANDOUTS

Division of Scientific Investigations (DSI) documents pertaining to the future NDA submission

DSI Comments for the preNDA meeting IND 102,457
Product: AMR101 Capsules
Sponsor: Amarin Pharma, Inc.
From: Susan Leibenhaut, M.D., GCPB II/DSI/OC

DSI has 2 types of requests for data to be submitted to the NDA; one type addresses the clinical data submitted in the NDA that will be used for the inspection as background materials (Items I and II) and the other type addresses the site selection process (Item III).

I. Request for general study related information and specific Clinical Investigator information

A. Please include the following information in a tabular format in the original NDA for the completed Phase 3 clinical trial MARINE, AMR-01-01-0016:

1. Site number
2. Principle investigator
3. Location: City State, Country, to include contact information (phone, fax, email)

B. Please include the following information in a tabular format by site in the original NDA for the completed Phase 3 clinical trial:

1. Number of subjects screened for each site by site
2. Number of subjects randomized for each site by site
3. Number of subjects treated who prematurely discontinued for each site by site

C. Please include the following information in a tabular format in the NDA for the completed Phase 3 clinical trial:

1. Name, address and contact information of all CROs used in the conduct of the clinical trials
2. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
3. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

II. Request for Site Level Data

1. For each site in the pivotal clinical trial: Name of primary investigator, accurate address and phone number, e-mail contact.
2. For the pivotal trial: Sample blank CRF and case report data tabulations for the site with coding key.
3. For the pivotal trial: Site-specific individual subject data (“line”) listings from the datasets:
    a. Line listings for each site listing the subject/number screened and reason for subjects who did not meet eligibility requirements

b. Line listings by site and subject, of treatment assignment (randomization)
c. Line listings by site and subject, of drop-outs and discontinued subjects with date and reason
d. Line listings by site of evaluable subjects/ non-evaluable subjects and reason not evaluable
e. Line listings by site and subject, of AEs, SAEs, deaths and dates
f. Line listings by site and subject, of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
g. Line listings by site and subject, of the primary and secondary endpoint efficacy parameters or events.
h. Line listings by site and by subject, concomitant medications (as appropriate to the pivotal clinical trials)
i. Line listings by site and by subject, of laboratory tests performed for safety monitoring

III. Request for Individual Patient Data Listings format:

DSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to the attached document, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide datasets, as outlined, for each pivotal study submitted in your application.

Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

I. INTRODUCTION

The purpose of this electronic submission of a single new clinical site dataset is to facilitate the timely evaluation of data integrity and selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

II. DESCRIPTION OF THE SUMMARY LEVEL CLINICAL SITE DATASET

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection and are not intended to support evaluation of efficacy. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Variance (TRTEFFV) – the variance of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Variance (SITEEFFV) – the variance of the site-specific efficacy effect size (SITEEFFE)

- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in theDefine file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, "TRTEFFR".

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the "endpoint" plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1.

III. CREATING AND SUBMITTING THE DATA FILE (SUBMISSION TEMPLATE AND STRUCTURE)

A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt). The file may be submitted electronically through the FDA Electronic Submission Gateway (ESG) referencing the active IND number or via secure CD addressed to the Division of Scientific Investigations point of contact.

Exhibit 1: Summary Level Clinical Site Data Elements

Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
IND	IND Number	Num/Char	6 digit identifier	FDA identification number for investigational new drug	010010
TRIAL	Trial Number	Char	String	Study or Trial identification number	ABC-123
SITEID	Site ID	Num/Char	String	Investigator site identification number	50
ARM	Treatment Arm	Num/Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters)	Active (e.g. 25mg), Comparator drug product name (e.g. Drug x), or Placebo
ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site	20
SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site	100
DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site	5
ENDPOINT	Endpoint	Char	String	Plain text label used to descr be the primary endpoint as described in the Define file included with each application. (limit 200 characters)	Average increase in blood pressure
ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other)	Continuous
TRTEFFR	Treatment Efficacy Result	Num	Floating Point	The efficacy result for each primary endpoint, by treatment arm	0, 0.25, 1, 100
TRTEFFV	Treatment Efficacy Result Variance	Num	Floating Point	The variance of the efficacy result (TRTEFFR) for each primary endpoint, by treatment arm	0, 0.25, 1, 100
SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	The effect size should be the same representation as reported for the primary efficacy analysis	0, 0.25, 1, 100
SITEEFFV	Site-Specific Efficacy Effect Size Variance	Num	Floating Point	The variance of the site-specific efficacy effect size (SITEEFFE)	0.065
CENSOR	Censored Observations	Num	Integer	The number of censored observations for the given site and treatment	5
NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site. This value should include multiple events per subject.	10
SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site. This value should include multiple events per subject.	5
DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site	1

Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
PROTVIOL	Number of Protocol Violations	Num	Integer	Number of deviations from the protocol noted by the sponsor for a given site. This value should include multiple violations per subject.	20
FINLDISC	Financial Disclosure Amount	Num	Integer	Total financial disclosure amount ($USD) by the site investigator	50000.00
LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572	Doe
FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572	John
PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator	555-555-5555, 44-555-555-5555
FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator	555-555-5555, 44-555-555-5555
EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator	john.doe@mail.com
COUNTRY	Country	Char	ISO 3166-1-alpha-2	Country in which the site is located	US
STATE	State	Char	String	Unabbreviated state or province in which the site is located	Maryland
CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located	Silver Spring
POSTAL	Postal Code	Char	String	Postal code for the site	20850
STREET	Street Address	Char	String	Street address and office number at which the site is located	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: General Structure of Data Submission Template

IND	TRIAL	SITEID	ARM	ENROLL	SCREEN	DISCONT	ENDPOINT	ENDTYPE	TRTEFFR
000001	Study 1	001	Active	26	61	3	Percent Responders	Binary	0.48
000001	Study 1	001	Placebo	25	61	4	Percent Responders	Binary	0.14
000001	Study 1	002	Active	23	54	2	Percent Responders	Binary	0.48
000001	Study 1	002	Placebo	25	54	4	Percent Responders	Binary	0.14
000001	Study 1	003	Active	27	62	3	Percent Responders	Binary	0.54
000001	Study 1	003	Placebo	26	62	5	Percent Responders	Binary	0.19
000001	Study 1	004	Active	26	29	2	Percent Responders	Binary	0.46
000001	Study 1	004	Placebo	27	29	1	Percent Responders	Binary	0.12

TRTEFFV	SITEEFFE	SITEEFFV	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLDISC	LASTNAME	FRSTNAME	PHONE
0.0096	0.34	0.0198	NA	0	2	0	1	0.00	Doe	John	555-123-4567
0.0049	NA	NA	NA	2	2	0	1	0.00	Doe	John	555-123-4567
0.0108	0.33	0.0204	NA	3	2	1	0	45000.00	Washington	George	020-3456-7891
0.0049	NA	NA	NA	0	2	0	3	45000.00	Washington	George	020-3456-7891
0.0092	0.35	0.0210	NA	2	2	0	1	0.00	Jefferson	Thomas	01-89-12-34-56
0.0059	NA	NA	NA	3	6	0	0	0.00	Jefferson	Thomas	01-89-12-34-56
0.0095	0.34	0.0161	NA	4	1	0	0	0.00	Lincoln	Abraham	555-987-6543
0.0038	NA	NA	NA	1	2	0	1	0.00	Lincoln	Abraham	555-987-6543

FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

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/s/

KATI JOHNSON
03/23/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202057Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS - PART 2

VASCEPA EXCLUSIVITY DETERMINATION

EXCLUSIVITY SUMMARY

NDA # 202057 SUPPL # HFD # 510

Trade Name Vascepa

Generic Name icosapent ethyl

Applicant Name Amarin Pharmaceuticals Ireland Ltd.

Approval Date, If Known 7/26/2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES X NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES X NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

c) Did the applicant request exclusivity?

YES X NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO X

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO X

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

*** Following the D.C. District Court's Opinion and Order vacating FDA's February 21, 2014, determination that Vascepa was not eligible for 5-year NCE exclusivity and remanding the matter to FDA, FDA concludes that Vascepa is eligible for 5-year NCE exclusivity under the Agency's interpretation of the applicable statutory provisions as described in the applicable regulations. ***

YES ☐ NO X

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed

only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Kati Johnson
Title: Senior Regulatory Project Manager
Date: June 9, 2016

Name of Office/Division Director signing form: James P. Smith, MD, MS
Title: Deputy Director, Division of Metabolism and Endocrinology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATI JOHNSON
06/15/2016

JAMES P SMITH
06/15/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Ave
Building 51
Silver Spring, MD 20993

FEB 21 2014

Robert A. Dormer
Hyman, Phelps & McNamara, P.C.
700 13th Street N.W., Suite 1200
Washington D.C. 20005-5929

Re: Vascepa (icosapent ethyl) Capsules (NDA 202057) Exclusivity Determination

Dear Mr. Dormer:

This letter is in response to your request to the Food and Drug Administration (FDA or the Agency) on behalf of your client, Amarin Pharmaceuticals Ireland Limited and its U.S. affiliate Amarin Pharma Inc. (collectively, Amarin), that FDA recognize the eligibility of Vascepa (icosapent ethyl) Capsules (NDA 202057) for 5-year new chemical entity (NCE) exclusivity.[1] You maintain that eicosapentaenoic acid (EPA), the single active moiety in Vascepa, was not previously approved as an active moiety of any other drug, and thus Vascepa is entitled to 5-year NCE exclusivity.

The Agency has carefully reviewed your submissions, as well as additional relevant materials. For the reasons set forth below, the Agency has determined that Vascepa is not eligible for 5-year NCE exclusivity, because EPA, the single active moiety in Vascepa, was also an active moiety contained in another, previously approved drug, Lovaza (omega-3-acid ethyl esters) Capsules (Lovaza).

I. FACTUAL BACKGROUND

On July 26, 2012, FDA approved NDA 202057 for Vascepa. Vascepa's labeling lists a single molecule, icosapent ethyl, as the drug's active ingredient.[2] Icosapent ethyl is the ethyl ester of EPA, an omega-3 fatty acid. Because the Agency does not consider the ester component of a

[1] Your position is set forth in detail in numerous letters to the Agency. See Letter from Robert A. Dormer to Elizabeth H. Dickinson, Vascepa (icosapent ethyl) Capsules Exclusivity Determination (April 23, 2012) ("Dormer Letter I"); Letter from Robert A. Dormer to Elizabeth H. Dickinson, Vascepa (icosapent ethyl) Capsules Exclusivity Determination (July 6, 2012) ("Dormer Letter II"); Letter from Robert A. Dormer to Eric Colman, Vascepa (icosapent ethyl) Capsules Exclusivity Determination; General Advice Response (August 8, 2012) ("Dormer Letter III"); Letter from Robert A. Dormer to Elizabeth H. Dickinson, Vascepa (icosapent ethyl) Capsules Exclusivity Determination (April 12, 2013) ("Dormer Letter IV"); Letter from Robert A. Dormer to Elizabeth H. Dickinson, Vascepa (icosapent ethyl) Capsules Exclusivity Determination (September 25, 2013) ("Dormer Letter V").

[2] See Vascepa Labeling at 1, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202057S000lbl.pdf.

molecule in determining its active moiety,[3] EPA (the de-esterified portion of the icosapent ethyl molecule) is the sole active moiety in Vascepa. Vascepa was approved as "an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia."[4]

On November 10, 2004, more than 7 years prior to FDA's approval of Vascepa, FDA approved NDA 021654 for Lovaza, which lists "Omega-3 acid ethyl esters" as its active ingredient.[5] The relevant monograph defines "Omega-3 acid ethyl esters" as a mixture containing, among other things, seven distinct omega-3 fatty acid ethyl esters obtained from fish oil (the Lovaza mixture).[6] Two of the seven omega-3 acid ethyl esters, the ethyl esters of EPA and docosahexaenoic acid (DHA),[7] make up approximately 85% of the Lovaza mixture.[8] Similarly, Lovaza's labeling describes its composition as follows: "Each 1 gram capsule of LOVAZA contains at least 900 mg of the ethyl esters of omega 3 fatty acids sourced from fish oils. These are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA – approximately 465 mg) and docosahexaenoic acid (DHA – approximately 375 mg)."[9] The "Description" section of the Lovaza labeling further gives the empirical formulas, molecular weights and structural formulas of EPA ethyl ester and DHA ethyl ester, respectively, without referring to any other component of the Lovaza mixture.

A significant body of evidence supports the conclusion that EPA meaningfully contributes to and at least in part "is responsible for physiological or pharmacological effect"[10] of the Lovaza mixture.[11] First and most significantly, numerous clinical studies predating the approval of either Lovaza or Vascepa, the first of which was published in 1983, suggest that EPA independently lowers serum TG levels. Such studies provide evidence of significant serum TG reduction when subjects are treated individually with EPA or DHA. Specifically, there have been at least five controlled trials, three of which predate Lovaza's approval, that conclude that the administration of EPA alone causes a significant decrease in serum TG levels compared with

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[3] 21 CFR 314.108(a); see section 505(j)(5)(F)(ii) of the FD&C Act.

[4] Vascepa labeling, supra note 2, at 1.

[5] Lovaza labeling at 1, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021654s034lbl.pdf.

[6] See id. at 5-6; *Omega-3-Acid Ethyl Esters*, United States Pharmacopeia 36-National Formulary 31, at 4571 (2013).

[7] For ease of reference, this letter will continue to refer to the ethyl esters of EPA and DHA as simply EPA and DHA.

[8] Supra note 6.

[9] Lovaza labeling, supra note 5, at 5-6.

[10] 21 CFR 314.108(a).

[11] This field appears to be well-studied. See, e.g., Jacobson, T. A., et al., *Effects of Eicosapentaenoic Acid and Docosahexaenoic Acid on Low-density Lipoprotein Cholesterol and Other Lipids: A review*, 6 J. of Clin. Lipidology 5 (2012) (discussing 22 studies with EPA and/or DHA); Wei M. Y. and Jacobson T. A., *Effects of Eicosapentaenoic Acid versus Docosahexaenoic Acid on Serum Lipids: A Systematic Review and Meta-Analysis*, 13 Current Atherosclerosis Reports 474 (2011) (analyzing the results of 33 studies with EPA and/or DHA).

placebo.[12] At least six additional studies comparing EPA with DHA also have indicated that both EPA and DHA have activity in reducing serum TG levels.[13]

In addition, Lovaza's labeling emphasizes the importance of EPA's contribution to the pharmacological effect of the drug. The pharmacokinetics section of the Lovaza labeling discusses the uptake of EPA and DHA, without addressing the uptake of any of the other components of the mixture.[14] The Lovaza labeling thus specifically associates the pharmacological effect of the drug with EPA and DHA.[15] In addition, Lovaza and Vascepa are both indicated "as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia."[16] Finally, according to their labeling, Lovaza and Vascepa also appear to share almost identical mechanisms of action. The Lovaza labeling states that:

> Potential mechanisms of action include inhibition of acyl-CoA:1,2-diacylglycerol acyltransferase, increased mitochondrial and peroxisomal oxidation in the liver, decreased lipogenesis in the liver, and increased plasma lipoprotein lipase activity.[17]

Vascepa's labeling describes its mechanisms of action as follows:

> Potential mechanisms of action include increased β-oxidation; inhibition of acyl-CoA:1,2-diacylglycerol acyltransferase; decreased lipogenesis in the liver; and increased plasma lipoprotein lipase activity.[18]

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[12] Kurabayashi T., et al., *Eicosapentaenoic acid effect on hyperlipidemia in menopausal Japanese women, The Niigata Epadel Study Group*, 96 Obstet. Gynecol. 521 (2000); Satoh N., et al. *Purified eicosapentaenoic acid reduces small dense LDL, remnant lipoprotein particles, and C-reactive protein in metabolic syndrome*, 30 Diabetes Care. 144 (2007); Ando M, et al., *Eicosapentaenoic acid reduces plasma levels of remnant lipoproteins and prevents in vivo peroxidation of LDL in dialysis patients*, 10 J. Am. Soc. Nephrol. 2177 (1999); Nagakawa Y., et al., *Effect of eicosapentaenoic acid on the platelet aggregation and composition of fatty acid in man: A double blind study*, 47 Atherosclerosis 71 (1983).

[13] Grimsgaard S., et al., *Highly purified eicosapentaenoic acid and docosahexaenoic acid in humans have similar triacylglycerol-lowering effects but divergent effects on serum fatty acids*, 66 Am J. Clin. Nutr. 649 (1997); Egert S., et al., *Dietary alphalinolenic acid, EPA, and DHA have differential effects on LDL fatty acid composition but similar effects on serum lipid profiles in normolipidemic humans*, 139 J. Nutr. 861 (2009); Mori T.A. and Woodman R.J., *The independent effects of eicosapentaenoic acid and docosahexaenoic acid on cardiovascular risk factors in humans*, 9 Curr. Opin. Clin. Nutr. Metab. Care. 95 (2006); Woodman R.J., et al., *Effects of purified eicosapentaenoic and docosahexaenoic acids on glycemic control, blood pressure, and serum lipids in type 2 diabetic patients with treated hypertension*, 76 Am. J. Clin. Nutr. 1007 (2002); Nestel P., et al., *The n-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid increase systemic arterial compliance in humans*. 76 Am. J. Clin. Nutr. 326 (2002); Park Y. and Harris W.S., *Omega-3 fatty acid supplementation accelerates chylomicron triglyceride clearance.*, 44 J. Lipid Res. 455 (2003).

[14] Lovaza labeling, supra note 5, at 6 ("In healthy volunteers and in patients with hypertriglyceridemia, EPA and DHA were absorbed when administered as ethyl esters orally. . . . Uptake of EPA and DHA into serum phospholipids in subjects treated with LOVAZA was independent of age (<49 years versus ≥49 years).").

[15] Id. ("Lovaza may reduce the synthesis of triglycerides in the liver because EPA and DHA are poor substrates for the enzymes responsible for TG synthesis, and EPA and DHA inhibit esterification of other fatty acids.").

[16] Id. at 1.

[17] Id.

Thus, the available evidence indicates that EPA makes a meaningful contribution to the TG-lowering activity of Lovaza.

II. STATUTORY AND REGULATORY BACKGROUND

Section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) establishes the approval requirements for NDAs. To be approved, an application submitted under Section 505(b) must, among other things, be supported by investigations showing the drug product to be safe and effective under the conditions of use described in the labeling.[19] The 1984 Drug Price Competition and Patent Term Restoration Act ("Hatch-Waxman Amendments") described abbreviated pathways for approval of drug products that allow an applicant to rely to the maximum extent possible on what is already known about a drug. These are described in sections 505(b)(2) (which established the 505(b)(2) application pathway) and 505(j) (which established the Abbreviated New Drug Application (ANDA) pathway) of the FD&C Act.[20] At the same time, the Hatch-Waxman Amendments provided incentives for pharmaceutical innovation, including exclusivity to protect certain products from generic competition for specified periods of time.

Section 505(j)(5)(F)(ii) and (c)(3)(E)(ii) of the FD&C Act describe a 5-year exclusivity period for certain drugs, during which certain 505(j) and 505(b)(2) applications may not be submitted for review (i.e., 5-year NCE exclusivity). Specifically, Section 505(j)(5)(F)(ii) of the FD&C Act provides, in relevant part, as follows:

> If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section . . . no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b) of this section . . . .[21]

The FD&C Act also provides for a 3-year period of exclusivity under certain circumstances, but these sections are not directly relevant to the discussion in this letter.[22]

FDA's regulations implementing the 5-year NCE provision of the Hatch-Waxman Amendments, at 21 CFR 314.108, provide that:

> If a drug product that contains a new chemical entity was approved . . . in an application submitted under section 505(b) of the act, no person may submit a 505(b)(2) application or abbreviated new drug application under section 505(j) of the act for a drug product that

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[18] Vascepa labeling, supra note 2, at 6.

[19] Section 505(b)(1) of the FD&C Act.

[20] The precise nature of, and requirements established by, these pathways are not relevant to our analysis of and conclusions with regard to the issues discussed in this letter.

[21] See also Section 505(c)(3)(E)(ii) of the FD&C Act (containing the same language for 505(b)(2) applications).

[22] See Section 505(j)(5)(F)(iii) and (c)(3)(E)(iii) of the FD&C Act.

> contains the same active moiety as in the new chemical entity for a period of 5 years from the date of approval of the first approved new drug application . . . .[23]

The regulations define "new chemical entity" as:

> [A] drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act."[24]

"Active moiety," in turn, is defined as:

> [T]he molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.[25]

In the Agency's regulations governing new drug applications, FDA has defined "drug product" as:

> [A] finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.[26]

In the same regulation, "drug substance" is defined as:

> [A]n active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates use [sic] in the synthesis of such ingredient.[27]

These statutory provisions and relevant regulations can reasonably be interpreted such that a drug product may contain one or more active ingredients, each of which may contain more than one active moiety. Thus, in the context of naturally derived mixtures, FDA concludes that a drug product may contain a single active ingredient that may in turn contain multiple active moieties.

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[23] 21 CFR 314.108(b)(2).

[24] 21 CFR 314.108(a).

[25] Id.

[26] 21 CFR 314.3(b).

[27] Id.

III. APPLICABLE FRAMEWORK AND RELEVANT PRIOR ACTIONS

A. Analysis of Active Ingredients and Active Moieties in the Context of Naturally Derived Mixtures

The Agency notes that neither the statute nor the regulations expressly address 5-year NCE exclusivity in the context of naturally derived mixtures.[28] To the contrary, relevant statutory and regulatory authorities on 5-year NCE exclusivity appear to focus principally on single component active ingredients. We acknowledge that the few relevant prior Agency statements and prior actions where FDA considered 5-year NCE exclusivity matters in the context of naturally derived mixtures have not necessarily resulted in consistent outcomes. In addition, the Agency has not always used precise terminology in addressing exclusivity for such mixtures. Nonetheless, having reviewed the relevant authorities and the outcomes of and the bases for FDA's prior actions, the Agency believes that the framework described below provides the best approach for identifying the active moiety or moieties of such mixtures.

As a threshold matter, the meanings of the terms "active ingredient" and "active moiety" must be considered in the context of naturally derived mixtures. The difference between "active ingredient" and "active moiety" can be difficult to discern, and the two terms are often conflated.[29] This is not surprising because for drugs that are composed of a single, well-characterized molecule, the distinction between "active moiety" and "active ingredient," generally is negligible. In such drugs, the single molecule that comprises the active ingredient typically contains the only active moiety in the drug product,[30] and the two regulatory concepts refer to the same molecule for the purposes of the exclusivity analysis.[31] But where a drug product contains a naturally derived mixture comprising multiple molecules, more than one of which potentially could be responsible for the physiological or pharmacological action of the drug substance, the distinction between active ingredient and active moiety and the relationship between the two become crucial.

You urge FDA to adopt an approach in which the entire mixture is considered to constitute both the single active ingredient and the single active moiety of the drug, rather than focusing on the individual component molecules in making either determination. This "one-to-one" relationship between active ingredient and active moiety generally exists in drugs with "simple" active ingredients that consist of a single molecule and thus can be applied without difficulty in that

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[28] Naturally derived mixtures also have been referred to as "complex" mixtures. "Complex" implies that such mixtures contain many components and are difficult to characterize. This is not always the case, however. Some naturally derived mixtures, such as the Lovaza mixture, may be amenable to characterization and may in fact be well characterized, at least with respect to their major components that are potentially responsible for the therapeutic effect of the mixture.

[29] As you do here. See Dormer Letter I, supra note 1, at 2 n.3 ("For ease of reference in this letter, we use the term active ingredient to encompass both active ingredient and active moiety.").

[30] After the exclusion of certain portions of the active ingredient for the determination of the active moiety. See 21 CFR 314.108(a) (defining "active moiety").

[31] *See* FDA, Final Rule, Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 FR 50338, 50358 (October 3, 1994) ("The agency has concluded that the term 'active ingredient,' as used in the phrase 'active ingredient (including any salt or ester of the active ingredient),' means active moiety.").

context. In addition, for some naturally derived mixtures which are so poorly characterized that it is difficult to determine with any certainty as to which molecules in the mixture are consistently present or potentially are responsible for the physiological or pharmacological activity of the drug, or where there is no precise way of identifying the molecules or ions that are consistently present and active in the mixture, identifying the entire mixture as the active moiety of the drug may be appropriate. In such cases, each new version of such a naturally derived mixture would be eligible for 5-year NCE exclusivity; that exclusivity, however, typically would not block submission or approval of an application for any subsequent drug product that contains a similar active ingredient (exhibiting a similar lack of characterization), because FDA cannot determine whether the subsequent drug product contains the same active moiety as in the previously approved drug.

While this approach is born of necessity for some poorly characterized mixtures, nothing in the statute or regulations requires that this approach be maintained for all naturally derived mixtures. In cases where at least part of the mixture is well characterized and some components of the mixture that are consistently present and active are identifiable or have been identified, an approach in which the mixture is identified as both the active ingredient and the active moiety appears inconsistent with the definition of active moiety as a "molecule or ion . . . responsible for the physiological or pharmacological action of the drug substance."[32] The approach that is the most consistent with the relevant definitions, facts, and policies present in this case is one in which the entire mixture is the single active ingredient, but that active ingredient may contain more than one component active moiety.[33] This approach recognizes that there can be a "one-to-many" relationship between the active ingredient and its component active moieties.

In the case of Lovaza, both FDA and the U.S. Pharmacopeial Convention (USP) have identified the product as having a single active ingredient. However, as noted above, that active ingredient (the Lovaza mixture) is a naturally derived mixture that contains more than one component molecule potentially responsible for its physiological or pharmacological action, indicating that it could contain more than one active moiety. Where a drug product contains a naturally derived mixture, the Agency generally will consider certain component molecules of the mixture to be previously approved active moieties[34] for the purpose of determining a subsequent drug's eligibility for 5-year NCE exclusivity when the following three criteria are met:

> **(1) Characterization**: The previously approved mixture has been characterized such that one or more specific molecules in the mixture have been identified;
>
> **(2) Consistent Presence**: The evidence demonstrates that one or more specific molecules identified in criterion 1 are consistently present in the mixture; and

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[32] 21 CFR 314.108(a).

[33] Under this approach, a naturally derived mixture would not be subject to the fixed-combination drug policy as a multiple active ingredient product generally would be. 21 CFR 300.50.

[34] Excluding portions of such molecules that cause them to be esters, salts, and other noncovalent derivatives. 21 CFR 314.108(a).

(3) Activity: The evidence demonstrates that the molecule or molecules identified in criteria 1 and 2 are responsible at least in part for the physiological or pharmacological action of the mixture, based on a finding that they make a meaningful contribution to the activity of the mixture.[35]

If these criteria are met,[36] the molecule or molecules would be identified as the active moiety or moieties of a naturally derived mixture. When such a molecule is an active moiety in a subsequently approved drug, it will be considered a previously approved active moiety and the drug will not be eligible for 5-year NCE exclusivity.[37]

B. Discussion of Relevant Prior Actions

Although the Agency has not always acted consistently with regard to identification of the "active ingredient" or "active moiety" of a naturally derived mixture, it generally has applied the "one-to-one" approach to poorly characterized mixtures, and often has (although not universally) applied the "one-to-many" approach to well-characterized mixtures, with the three criteria analysis described above used to determine which molecules are active moieties of such a mixture.

1. Racemates (racemic mixtures) and Enantiomers

FDA's approach to enantiomers and racemates is consistent with the "one-to-many" approach for naturally derived mixtures described above. Racemates are "equimolar mixture[s] of enantiomers of the same molecule" where such enantiomers have "the same molecular formula and chemical connectivity" but "differ in the spatial orientation of the[ir] atoms."[38] In layman's terms, racemates are mixtures that contain equal quantities of two or more molecules that are mirror images of one another. In the context of exclusivity determinations, FDA has taken the position that although a product containing a single enantiomer has a different active ingredient (the enantiomer) than a product containing the racemic mixture as its active ingredient, "a single enantiomer of a previously approved racemate contains a previously approved active moiety, and therefore, is not considered a new chemical entity."[39] Thus, the Agency has treated later

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[35] See, e.g., FDA, Conjugated Estrogens Tablets; Proposal to Refuse to Approve Two Abbreviated New Drug Applications, 62 FR 42562, 42565 (Aug. 7, 1997) ("Premarin FR Notice") ("[N]ot all components that furnish pharmacological activity or other direct effect meet the definition of an active ingredient. A component may be considered an active ingredient only if it provides a clinically meaningful contribution to the therapeutic effect of the drug.") (internal quotation marks omitted).

[36] Though not at issue here, the Agency would make this determination at the time it determines whether a particular molecule is an active moiety of a previously approved mixture, using the technological tools and scientific concepts available at that time.

[37] If these criteria are not satisfied, FDA will not assume that a given molecule that is present in a naturally derived mixture is an active moiety of that mixture. If a subsequently approved drug consistently includes such a molecule and the evidence indicates that the molecule makes a meaningful contribution to the activity of that subsequently approved drug, it may be eligible for 5-year NCE exclusivity.

[38] FDA, Policy on Period of Marketing Exclusivity for Newly Approved Drug Products with Enantiomer Active Ingredients; Request for Comments, 62 FR 2167, 2167 (Jan. 15, 1997).

[39] Id. at 2168 (citing the preamble to FDA's final rule defining "active moiety" for NCE purposes at 59 FR 50338, 50359).

approved single enantiomers as previously approved active moieties if the racemic mixture containing that enantiomer was previously approved.[40] The Agency's historic treatment of racemic mixtures and their enantiomers is consistent with the framework described above for naturally derived mixtures that have been at least partially characterized. Because a racemate can be considered to be a mixture of its component enantiomers, and because the racemic mixture is usually a synthetic product, there usually is no question that a particular enantiomer is consistently present in the racemic mixture. Also, the subsequent approval of a particular enantiomer for the same or similar indication generally indicates that it contributes meaningfully to the pharmacological activity of the racemate.

Thus, a subsequently approved single enantiomer product will not be considered to contain a new chemical entity and will not be eligible for 5-year NCE exclusivity because its active moiety will have been approved in the racemic mixture.[41]

2. *Products Containing Pancrelipase and Hyaluronidase*

Products containing pancrelipase have been commercially available in the United States since before 1938. These products have as their active ingredient pancrelipase, a naturally derived mixture that includes a complex combination of a variety of enzymes, which fall generally into three classes: lipases, amylases, and proteases.[42] However, to date, no sponsor has identified a particular lipase, amylase, or protease that is present consistently or active in every lot of any particular pancrelipase mixture, nor has any pancrelipase mixture been characterized adequately to allow the Agency to identify which molecule or molecules in a particular pancrelipase product, among the possibly hundreds of different enzyme variants present, is responsible for that pancrelipase's physiological or pharmacological action. Therefore, the Agency has recognized the eligibility of each pancrelipase product for 5-year NCE exclusivity.

For hyaluronidase products, too, FDA has never identified which molecules are present and active in any particular hyaluronidase product. For hyaluronidases, the Agency explained that:

> Although the Agency can determine whether a naturally sourced hyaluronidase product contains a member of a class of pharmacologically active enzymes (i.e., of a category of hyaluronidases), the Agency cannot determine the specific enzyme or enzymes contained in any naturally sourced hyaluronidase product (i.e., the structure of the precise molecule or molecules responsible for the pharmacological activity of the drug).[43]

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[40] In 2007, Congress acknowledged this longstanding practice and amended the FD&C Act by adding Section 505(u), which permits a sponsor, under limited circumstances, to elect to have a later-approved single enantiomer not be considered the same active moiety as in the previously approved racemic mixture for 5-year NCE exclusivity purposes.

[41] But see id.

[42] FDA, guidance for industry, *Exocrine Pancreatic Insufficiency Drug Products*, at 1 (Apr. 2006), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071651.pdf.

[43] Steven K. Galson, Citizen Petition Response, Docket No. 2005P-0134 at 5 (Oct. 25, 2005) ("Hyaluronidase Response").

As with pancrelipase products, in the absence of more information about which precise molecules or ions are consistently present and at least partially responsible for its pharmacological action, FDA has determined that each hyaluronidase product is eligible for 5-year NCE exclusivity.

Thus, for products containing pancrelipases and hyaluronidases, the available information has not been sufficient to permit the identification of any of the particular molecule(s) that potentially could be an active moiety in either of these naturally derived mixtures. This lack of knowledge about the chemical identities of the molecules in the mixture led FDA to conclude that none of the potential active moieties in these mixtures could be identified with any precision.[44] In the face of this information gap, the Agency has considered the entire mixture to be both the active ingredient and the active moiety, and has subsequently considered each such product to be eligible for 5-year NCE exclusivity that does not block any other similarly poorly characterized mixture.

3. *Podofilox*

In 1993, Condylox was determined to be eligible for 5-year NCE exclusivity. The single molecule active ingredient in Condylox is podofilox (also referred to as podophyllotoxin). FDA previously had approved several drug products containing podophyllum resin, a naturally derived mixture, as their active ingredient. The NDAs for the older drugs containing podophyllum resin had become effective between 1938 and 1945 and had been withdrawn by the time Condylox was approved.

Condylox's exclusivity determination was made after its sponsor, Oclassen, submitted a citizen petition stating that Condylox should be eligible for 5-year NCE exclusivity in spite of the previous approvals of podophyllum resin products. In its petition, Oclassen asserted that:

> prior approvals of drugs which *might or might not* have contained podophyllotoxin cannot properly form a basis for denying the status of that ingredient as a new chemical entity for purposes of the five-year exclusivity provisions. . . . [I]t is not only unclear but

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[44] Cf. Dormer Letter I, supra note 1, at 12-13. You contend that the Agency's grant of 5-year NCE exclusivity for the later-approved versions of these naturally derived mixtures, despite the approval of older versions, was the result of "a policy of presumption in favor of NCE status." You also assert that "the presumption . . . is not only appropriate in situations where there is a lack of sufficient information to identify the chemical structure of [sic] active ingredient, but also where the inability to identify an active ingredient is the result of a lack of appropriate testing and, therefore, data demonstrating whether a constituent of an identified active ingredient mixture is itself active." You have not cited any support for this contention, and we are unaware of any relevant authority or previous Agency action that would lead to this result. To the extent that the Agency has articulated any presumption in favor of recognizing 5-year NCE exclusivity to drug products that contain naturally derived mixtures, it was carefully limited only to "a novel regulatory question that arose in an unusual factual context," that is, where the naturally derived mixture is uncharacterized to the extent that none of the molecules potentially responsible for the physiological or pharmacological action of the mixture have been precisely identified, and therefore have not been shown to be consistently present. Hyaluronidase Response, supra note 43, at 2. The Agency declines to extend the "presumption" to all naturally derived mixtures, as you seem to be suggesting.

> also completely undocumented that any previously approved product included podophyllotoxin as an "ingredient" or that, if present, the ingredient was "active."[45]

The petition also stated that "processing techniques for podophyllum resin are known to be capable of eliminating or deactivating any podophyllotoxin present."[46] Oclassen stated in the alternative that "to the extent that any of the thirteen products had any activity (a proposition not required to be proven at the time their NDAs became effective), it could have been attributable solely to the numerous other constituents of podophyllum resin."[47]

Although the record is not entirely clear on this point, it appears that FDA's determination that Condylox was eligible for 5-year NCE exclusivity was based, at least in part, on the uncertainty regarding whether podofilox was actually present or active in the finished dosage forms of the previously approved products.[48] Although the fact that podofilox was a component of unprocessed podophyllum resin does not appear to have been in dispute, there appears to have been some uncertainty regarding whether podofilox in the older drugs may have been eliminated or inactivated during processing. The Agency's exclusivity decision thus was informed by the lack of sufficient characterization of the previously approved naturally derived mixtures, i.e., the absence of any reliable evidence regarding whether podofilox was present or active in these previously approved products.

4. *Premarin and Cenestin*

Premarin (conjugated estrogens, USP) contains as its active ingredient a naturally derived mixture of conjugated esters extracted from the urine of pregnant mares. Its NDA was originally allowed to become effective in 1942. At the time, the product was known to contain estrone and equilin, and it was known that additional estrogens were present in smaller amounts. FDA's understanding of the components of the active ingredient in Premarin evolved over time, leading to the drug's labeling being revised to include three additional conjugated estrogens as "concomitant components" that were "required to be in the product."[49] In the context of refusing to approve generic versions of Premarin, FDA acknowledged that "Premarin is not sufficiently characterized at this time to determine all of its active ingredients,"[50] and stated that "the quantitative composition of Premarin with respect to potentially pharmacologically active

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[45] Peter R. Mathers and Daniel R. Dwyer, Citizen Petition, Docket No. 92-P-0051, at 4 (January 30, 1991) ("Condylox Petition") (emphasis in original).

[46] Id. at 8.

[47] Id. at 8-9.

[48] See Carl C. Peck, Citizen Petition Response, Docket No. 92-P-0051, at 1 (July 21, 1993) ("[A]lthough . . . several previously approved NDA's [sic] contained podophyllum or podophyllum resin, the agency has determined that these previously approved NDA's did not characterize podofilox as an active ingredient").

[49] Premarin FR Notice, supra note 35, at 42564. *See* Premarin labeling, available at http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=72825.

[50] Premarin FR Notice, supra note 35, at 42565.

components has not been defined. Without this information it is not possible to define the active ingredients of Premarin."[51]

After the Agency refused to file applications for generic versions of Premarin in 1997 (because the active ingredient of Premarin had not been adequately characterized to permit sameness of active ingredient to be demonstrated), FDA approved Cenestin (synthetic conjugated estrogens, A) in 1999, as a 505(b)(2) application that referenced Premarin as its listed drug. Cenestin is a fixed-combination of synthetic components, not a naturally derived mixture.[52] It contains nine conjugated estrogens, each of which is a synthetic version of a conjugated estrogen that has been shown to be consistently present and active in Premarin. Because Cenestin is a synthetic fixed-combination, each of the conjugated estrogen components in Cenestin can be characterized as a single component active ingredient that contains a single active moiety. FDA determined that Cenestin was not eligible for 5-year NCE exclusivity because it was considered to be "a fixed-combination prescription drug" subject to 21 CFR 300.50,[53] and the presence of at least one previously approved active moiety in such a drug rendered the combination ineligible for 5-year NCE exclusivity. The Agency concluded that one or more of the estrogens contained in Cenestin was a previously approved active moiety in Premarin despite the fact that the active ingredient of Premarin was acknowledged to be the mixture, and despite the lack of precise quantitation of the activities of all of the estrogens that were also shown to be present in the Premarin mixture. Cenestin contained at least one active moiety that had been previously approved in Premarin (for example, Sodium Estrone Sulfate, which had been known to be consistently present and active in Premarin since its approval in 1942), which meant that Cenestin was ineligible for 5-year NCE exclusivity.[54]

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[51] Id. at 42572.

[52] See Cenestin labeling, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/1999/20992lbl.pdf. See also, Administrative Documents Part 3, NDA 20-992, at 14-15 available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20992_admindocs_P3.pdf (Minutes of a Teleconference dated June 16, 1998).

[53] Administrative Documents Part 1, NDA 20-992, at 5, 11-12 available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20992_admindocs_P1.pdf.

[54] You assert that the Cenestin decision supports your claim that Lovaza contains a single active moiety, maintaining that the Agency cited to Premarin (and not to the previously approved single component conjugated estrogen products) in its analysis and that FDA must have determined that "the whole of each of the Cenestin and Premarin mixtures were sufficiently similar as to constitute the same active moiety." Dormer Letter III, supra note 1, at 3-4. The Agency does not agree with your assumptions and does not find these assertions persuasive. FDA considered Cenestin "to be in compliance with the requirements of the fixed-combination drug policy" and characterized the drug as a "combination product" in the exclusivity summary instead of a "single active ingredient product." Moreover, FDA rejected the sponsor's claim that only three of the estrogens in Cenestin should be designated as active ingredients. Instead, the Agency stated that "all components should be designated as active because [Cenestin] is a synthetic product; therefore specifications should be considered for each component." Administrative Documents Part 1, NDA 20-992, at 5, 11-12, 14-15, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20992_admindocs_P1.pdf ("Cenestin Administrative Document").

5. *Infasurf*

Survanta (beractant) was approved in 1991 as a lung surfactant. Its active ingredient, beractant, is a naturally derived "bovine lung extract containing phospholipids, neutral lipids, fatty acids, and surfactant-associated proteins to which colfosceril palmitate, palmitic acid, and tripalmitin are added to standardize the composition and to mimic surface-tension lowering properties of natural lung surfactant."[55] Survanta was eligible for 7 years of orphan drug exclusivity, during which time FDA would "not approve another sponsor's marketing application for the same drug . . . for treatment of the rare disease or condition concerning which orphan drug designation was granted [to Survanta]."[56]

In 1995, FDA refused to file a marketing application submitted by ONY for Infasurf (calfactant), another orphan-designated lung surfactant intended for the same indication as Survanta, based on the Agency's determination that "Infasurf and Survanta are the 'same drug,'" as defined by the Agency's orphan drug regulations.[57] The applicable regulation provides that two "[c]losely related, complex, partly definable drugs with similar therapeutic intent" are considered to be the "same drug," unless the sponsor of the subsequent drug can demonstrate that it is clinically superior to the previously approved drug.[58] Thus, because Infasurf and Survanta were considered to be the "same drug" under this regulation, FDA determined that Survanta's orphan drug exclusivity blocked the approval of ONY's marketing application for Infasurf.

A lengthy, several year-long discussion between ONY and FDA ensued, during which ONY attempted to demonstrate that Infasurf was not the "same drug" as Survanta within the meaning of the orphan drug regulations.[59] The Agency initially applied a "same drug" analysis under which two drugs are the same for orphan drug purposes if they are "[c]losely related, complex, partly definable drugs with similar therapeutic intent."[60] FDA justified this approach by stating that "in contrast to drugs composed of small molecules . . . surfactants are a complex mixture of both large and small molecules, many of which have poorly defined specific or unique physiologic functions."[61]

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[55] Survanta labeling, in Memorandum from John K. Jenkins to Janet Woodcock, NDA 20-521 Request for Dispute Resolution under 21 CFR 314.103, at 1 n.1 (Apr. 22, 1997) ("April 1997 Infasurf Memo"), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20521_Infasurf.cfm (Infasurf NDA 20-521, Drug Approval Package, Correspondence, Part 2).

[56] 21 CFR 316.31.

[57] FDA, Refuse to File Letter from Dr. Hioberg to ONY (May 10, 1995), in Memorandum from John K. Jenkins to Janet Woodcock, regarding the request by ONY for dispute resolution under 21 CFR 314.103 related to NDA 20-521 (July 2, 1997) ("July 1997 Infasurf Memo") *in* Appendix, Administrative Review of IND 27,169 and NDA 20-521: INFASURF (calf lung surfactant) as of March 31, 1997, at 2 ("Infasurf Review"). The Agency later determined that an RTF action is not appropriate in such situations. April 1997 Infasurf Memo, supra note 55, at 3 n.3.

[58] 21 CFR 316.3(b)(13)(ii)(D).

[59] See generally April 1997 Infasurf Memo, supra note 55, at 1-8. See also Infasurf Review, supra note 57.

[60] 21 CFR 316.3(b)(13)(ii)(D).

[61] April 1997 Infasurf Memo, supra note 55, at 5 n.6.

ONY maintained that the "same drug" definition at 21 CFR 316.3(b)(13)(i), which provides that two drugs are the same if they contain the same active moiety, governed the analysis[62] and that under "the active moiety approach," Survanta and Infasurf were not the "same drug," because they do not contain the same active moiety. In considering this claim, FDA advised ONY that, to demonstrate that Infasurf does not contain the same active moiety as Survanta, it would need to demonstrate that a particular active moiety of the Infasurf mixture is both present and active in Infasurf and that it is either not present or present at levels that are inactive in the previously approved product, Survanta.[63]

ONY asserted that SP-B, a protein component present in both Infasurf and Survanta, was present in much lower levels in, and had not been shown to be active in, Survanta, and, therefore, that SP-B was not an active moiety of Survanta. As support, ONY pointed out that Survanta's sponsor had never demonstrated that SP-B contributed to Survanta's activity and that the levels of SP-B in Survanta were "very low and sub-threshold for activity," while SP-B was present at a level "20-40 times higher and necessary for activity" in Infasurf.[64] In addition, ONY noted that the two products had different established names and exhibited differences in their physiologic, pharmacologic, and clinical effects.[65]

With respect to ONY's claim that the clinical differences between the two drugs meant that the active moieties were not the same and that, therefore, the drugs were not the same drug under the active moiety test, FDA stated:

> [T]wo drug products with the same active moiety may also have different physiologic/pharmacologic properties; i.e., as might occur with two drug products that contain the same active moiety in a different dose or in formulations with different bioavailabilities. The physiologic/pharmacologic properties of a drug product are not adequate surrogates for the active moiety of the drug product, a point the sponsor repeatedly appears to fail to recognize in their arguments as to why Infasurf and Survanta should not be considered the 'same' drug.[66]

FDA ultimately determined that Infasurf and Survanta were the same drug for orphan drug purposes under the active moiety approach because they contain the same active moieties. The Agency noted that "simply establishing quantitative differences in the levels of SP-B between the two surfactants would not be adequate to demonstrate that they were 'different,' rather it would be necessary to demonstrate the significance of any observed quantitative differences."[67]

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[62] The definition of "active moiety" in the orphan drug context is identical to the definition in the NCE context. Compare 21 CFR 316.3(b)(13)(i) with 21 CFR 314.108(a).

[63] See Letter from Division to ONY (May 24, 1996) in 20512_INFASURF INTRACHEAL SUSPENSION_corres_P1.pdf at 19-20 available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20521_INFASURF%20INTRACHEAL%20SUSPENSION_corres_P1.pdf.

[64] April 1997 Infasurf Memo, supra note 55, at 2.

[65] These are similar to certain assertions you make in this case. See Dormer Letter I, supra note 1, at 5-6. FDA dismissed these assertions. July 1997 Infasurf Memo, supra note 57, at 7, 15.

[66] July 1997 Infasurf Memo, supra note 57, at 15.

[67] Id. at 16.

FDA found that ONY had not done so. The Agency recognized that although beractant and calfactant were different active ingredients, they both contained SP-B, the same active moiety, and therefore Infasurf and Survanta were considered the same drug for orphan drug purposes.

Subsequently, despite having determined that Infasurf has the same active moiety as a previously approved drug, Survanta, under a definition of active moiety that is identical to that in the NCE context, FDA nevertheless recognized Infasurf's eligibility for 5-year NCE exclusivity. Unlike the extensive record of the Agency's decision-making process in the orphan drug context, there does not appear to be a record documenting the reasons for the decision to recognize Infasurf's eligibility for 5-year NCE exclusivity. Furthermore, there does not appear to have been an attempt to meaningfully distinguish that decision from the decision made regarding the active moieties of Infasurf and Survanta in the orphan exclusivity context.

Additionally, in 1999, FDA recognized that Curosurf, another lung surfactant from a different sponsor, was eligible for 5-year NCE exclusivity, despite the fact that it contains both SP-B and colfosceril palmitate, which had been previously approved in Exosurf in 1990 and Survanta in 1991. The exclusivity decisions for Infasurf and Curosurf directly contradict the determination made in the orphan exclusivity context that SP-B is a previously approved active moiety. Because the records for these determinations are sparse, it is not clear whether the Agency has attempted to resolve or address this contradiction.

6. *Menotropins*

The Agency has also taken a different approach to identifying the active ingredient and active moiety of a naturally derived mixture in multiple drug products. Menotropins are naturally derived and partially characterized mixtures that are contained in Pergonal (menotropins for injection, USP), Repronex (menotropins for injection, USP), and Menopur (menotropins for injection, USP). Pergonal is a drug extracted from human urine that was first approved in 1975. The two main characterized components of Pergonal are the hormones follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and the product labeling identified FSH and LH as active ingredients. In addition to FSH and LH, Pergonal contains various urinary proteins that had never been shown to contribute to the physiological or pharmacological action of Pergonal.

In considering what constituted the active ingredient of Pergonal in the context of whether a generic version contained the same active ingredient, the Agency appears to have considered and rejected a "one-to-one" approach, i.e., the assertion that the entire mixture was the active ingredient (and the active moiety) of the drug. In 1992, Pergonal's sponsor asked the Agency, among other things, to recognize the menotropins mixture as a single active ingredient.[68] FDA refused,[69] stating that:

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[68] See Janet Woodcock, Citizen Petition Response, Docket No. 92P-0487, at 14 (June 17, 1997) ("Pergonal Response") ("The agency does not agree with your argument that the urinary proteins are, essentially, a part of one active ingredient. . . . The urinary proteins, other than FSH and LH, do not provide a clinically meaningful contribution to the therapeutic effect of menotropins, and thus are not 'active ingredients.'").

[69] FDA later litigated this issue in the context of approval of an ANDA referencing Pergonal and received a favorable decision from the D.C. Circuit. See *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313 (1998).

> FDA is not aware of any evidence that the nonactive urinary proteins make any contribution to the therapeutic effect of the drug product. [S]uch urinary proteins [cannot be considered] active ingredients in the absence of objective evidence of a clinically meaningful contribution to the therapeutic effect of the drug product.[70]

Subsequently, Repronex and Menopur were approved as mixtures derived from urine of pregnant women, which differed from the mixture in Pergonal, but with their active ingredients being listed as FSH and LH. Repronex was approved as a "single active ingredient product" that was ineligible for 5-year NCE exclusivity because it contained the same active moiety as in Pergonal.[71] Similarly, Menopur was approved as a "single active ingredient product" that was also ineligible for 5-year NCE exclusivity because it contained the same active moiety as Repronex.[72] Therefore, these menotropins products provide an example where the Agency has refused to consider a naturally derived mixture in its entirety as either the active ingredient or the active moiety of a drug.

IV. VASCEPA ANALYSIS

A. EPA is a Previously Approved Active Moiety

As a product that contains icosapent ethyl as its active ingredient and EPA as its active moiety, Vascepa's eligibility for 5-year NCE exclusivity depends on whether EPA is an active moiety previously approved in Lovaza. Because Lovaza is a well-characterized mixture with respect to its omega-3 acid components, the Agency believes that the "one-to-many" framework described above should apply. Applying this framework to Lovaza, the Agency has concluded that EPA is an active moiety in Lovaza.

The EPA in the Lovaza mixture meets the three criteria described above.

> **(1) Characterization**: The Lovaza mixture is sufficiently characterized such that EPA has been identified as a specific molecule present in the mixture. Lovaza's labeling describes the composition as containing approximately 465 mg of EPA ethyl ester;
>
> **(2) Consistent Presence**: EPA is consistently present in the Lovaza mixture, and Lovaza meets the product description in the labeling, as well as the standards set forth in the relevant USP drug substance and drug product monographs; and
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> **(3) Activity**: As described fully in Section I, supra, the available evidence establishes that EPA has meaningful pharmacological activity in lowering serum triglyceride levels, the approved indication for both Lovaza and Vascepa, and thus EPA contributes meaningfully to the pharmacological action of Lovaza.

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[70] Pergonal Response, supra note 68, at 9.

[71] Repronex, NDA 21-047, Exclusivity Summary at 2-3 in Administrative Documents at 9-10, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/21-047_Repronex_Admindocs.pdf.

[72] Menopur, NDA 21-663, Exclusivity Summary at 2 in Administrative/Correspondence Reviews at 6, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-663_Menopur%20For%20Injection_admincorres.PDF.

Accordingly, the Agency concludes that EPA is an active moiety in Lovaza, and, as a later approved application that includes EPA as its sole active moiety, Vascepa does not qualify for 5-year NCE exclusivity.

B. Your Assertions in Support of 5-Year NCE Exclusivity are Not Persuasive

1. The Activity of EPA

You assert that EPA should not be considered an active moiety that was previously approved in Lovaza because the approved active moiety in Lovaza is the same as its active ingredient: the Lovaza mixture.[73] In your view, the applicable statutory and regulatory authorities and relevant prior Agency actions demonstrate that "the active moiety of a drug product approved as a complex mixture is the mixture taken as a whole, and not the individual constituents taken separately."[74] Under your view, a "complex mixture" "should [never] be broken down into its possibly-active constituents" for evaluating whether any such "constituent" is itself an active moiety.[75] In this regard, you seem to be asserting both that there is no evidence that supports a conclusion that EPA is an active moiety of Lovaza,[76] and that, in any event, in identifying the active moiety or moieties of Lovaza, FDA should not consider evidence regarding whether EPA (or any other component of the Lovaza mixture) is a "molecule or ion . . . responsible for the physiological or pharmacological action"[77] of the Lovaza mixture. The Agency disagrees with both contentions.

You claim that EPA cannot be the active moiety of Lovaza because "FDA did not determine (and the clinical data do not support a conclusion) that EPA is, in fact, responsible for the physiological or pharmacological action of [Lovaza's] drug substance, or even that it plays an active role in that action within [the mixture]."[78] You assert that:

> It was not the individual constituents, but the complex mixture of omega-3-acid ethyl esters that was demonstrated to be responsible for the pharmacology of Lovaza and determined by FDA to be the single active ingredient in Lovaza. The presence of EPA among the constituents in the complex mixture of omega-3-acid ethyl esters in Lovaza does not render EPA an active moiety or active ingredient in Lovaza as described in 21 C.F.R. § 210.3(b)(7) and 21 C.F.R. § 314.108(a).[79]

You similarly assert that the presence of components other than EPA in Lovaza "raises significant questions regarding whether any single constituent, or combination thereof, is

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[73] E.g., Dormer Letter III, supra note 1, at 15 ("The active moiety of Lovaza is a complex mixture of omega-3 acid ethyl esters.").

[74] Id. at 1.

[75] Dormer Letter I, supra note 1, at 16.

[76] See, e.g., id. at 2 ("EPA has not been demonstrated to be responsible for the physiological or pharmacological action of Lovaza despite its presence in that mixture"); Dormer Letter II, supra note 1, at 4 (same).

[77] 21 CFR 314.108(a).

[78] Dormer Letter II, supra note 1, at 4.

[79] Id. at 7.

responsible for the drug's physiological and pharmacological effects" and that EPA's precise contribution to Lovaza's pharmacological activity has not been measured relative to the other components of Lovaza's active ingredient.[80] You further contend that FDA cannot consider EPA to be an active moiety in the absence of "direct evidence" in the form of "a factorial design trial of many . . . randomized arms to demonstrate the contribution, if any, of each of the seven constituents, to the efficacy of Lovaza."[81] The Agency disagrees.

First, there is, in fact, substantial evidence that EPA contributes meaningfully to the activity of the Lovaza mixture. EPA is the most prominent component of the Lovaza mixture, it is controlled for in the mixture, and the effects and pharmacokinetics of Lovaza are described in terms of the uptake and activity of EPA. In addition, studies predating and postdating approval of Lovaza indicate that EPA has activity in lowering triglycerides – the pharmacological effect of the Lovaza mixture.[82]

Second, the mere fact that the Lovaza mixture includes components (including omega-3 acid ethyl esters) other than EPA does not affect the outcome in this case. It is not necessary to determine the precise level of activity of EPA in Lovaza or to find that EPA contributes to the activity of both Lovaza and Vascepa in precisely the same way to conclude that EPA in Vascepa is a previously approved active moiety. Rather, the findings that (1) the Lovaza mixture in Lovaza is sufficiently characterized to identify EPA as a specific component; (2) EPA is required to be consistently present in the mixture (at ~465 mg per 1-gram capsule); and (3) EPA is pharmacologically active in lowering serum triglyceride levels, support the conclusion that EPA is an active moiety in Lovaza.[83]

Finally, the use of factorial designs to isolate and demonstrate the individual activity of multiple components generally is employed in the context of fixed-combinations when two or more active components are intentionally combined into a single product or are copackaged together. In that setting, FDA's "fixed-combination policy" applies, and factorial studies generally are used to ensure that "each component makes a contribution to the claimed effects and the dosage of each component . . . is such that the combination is safe and effective . . . ."[84] The fixed-combination policy generally is not applicable to drugs containing naturally derived mixtures, which typically are not amenable to a factorial analysis because of the difficulties in characterizing and isolating all potentially active components. In the case of such mixtures, therefore, often it is necessary to look to other methods of establishing the contribution of individual components. Therefore, for naturally derived mixtures, the precise contribution of every component need not be established to determine that one or more of these components is an active moiety of the drug.

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[80] Dormer Letter I, supra note 1, at 9.

[81] Dormer Letter II, supra note 1, at 7 n.19.

[82] See, e.g., Jacobson, et al., supra note 11; Wei & Jacobson, supra note 11. See also notes 12 and 13, supra.

[83] You also point to clinical differences between Lovaza and EPA, such as the finding that there may be a synergistic effect between Vascepa and statins, which is lacking for Lovaza. For the reasons described in the text, these issues are not relevant to the question whether EPA is a previously approved active moiety.

[84] See 21 CFR 300.50.

In light of the above, the Agency has concluded that EPA is an active moiety of the Lovaza mixture, despite the fact that the relative contribution of all of its various components has not been precisely determined or quantified. As the party asserting that Vascepa is eligible for 5-year NCE exclusivity, it is incumbent upon Amarin to demonstrate that EPA was not an active moiety in any previously approved product, including Lovaza. Amarin has not met its burden in this case.

2. *Prior Agency Actions*

Although FDA generally considers the active ingredient of a naturally derived mixture to be the mixture itself, you oversimplify the analysis by asserting that this is always true for the active moiety or moieties of every such mixture. You assert that the Agency's prior practices establish that the "prior approval of a mixture as a single-ingredient drug product will not preclude NCE exclusivity for later drug product containing a constituent of the mixture."[85] Similarly, you allege that "the active ingredient of a drug product comprised of a mixture is the mixture as a whole and not the individual constituents."[86] Though the Agency agrees that the active ingredient of Lovaza is the Lovaza mixture as a whole, it disagrees that this leads to the conclusion that the Lovaza mixture is also Lovaza's only active moiety. As discussed above, a drug product with a single active ingredient may contain multiple active moieties. The identification of the active moieties of a naturally derived mixture depends on how well the mixture can be characterized, whether the component in question is consistently present in the mixture, and whether there is evidence that the component is clinically active.

The prior actions that you cite do not counsel a different outcome. Though the Agency's past actions indicate that FDA has not had a fully consistent practice in this regard, this is not by itself sufficient reason to conclude that your selective reading of these actions should be accorded conclusive weight. To support your assertion that "the prior approval of a mixture as a single-ingredient drug product does not preclude NCE exclusivity for a later drug product containing a constituent of the mixture," you heavily rely on the fact (among others) that the lung surfactants Infasurf and Curosurf were determined to be eligible for 5-year NCE exclusivity.[87] As discussed in Section III.B.5., supra, despite its determination that Infasurf was eligible for 5-year NCE exclusivity, FDA also determined that Infasurf and a previously approved drug, Survanta, contained the same active moiety (the protein SP-B) in the orphan drug context. This decision was based on a definition of active moiety in the orphan drug context that is identical to the definition of active moiety in the 5-year NCE exclusivity context. The determination that Survanta and Curosurf were eligible for NCE exclusivity despite the presence of colfosceril palmitate in these drugs, which was also present in Exosurf, another, previously approved surfactant, much like the Infasurf NCE exclusivity determination, also does not appear to be consistent with the determination that the active moieties of Infasurf and Survanta were the same in the orphan drug context.

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[85] Dormer Letter I, supra note 1, at 9.

[86] Id. at 10.

[87] Dormer Letter I, supra note 1, at 3.

The Agency concludes that it is not possible to reconcile the contradictory Agency determinations regarding the active moieties of lung surfactants in the 5-year NCE exclusivity and orphan drug contexts. Some of these NCE determinations were made before the relevant regulations were finalized.[88] Additionally, these exclusivity determinations also appear to be inconsistent among themselves,[89] which decreases their value as reliable, relevant prior Agency action. These exclusivity determinations also do not appear to be supported by a detailed record, unlike the extensive record underlying the Agency's decision in the orphan drug exclusivity context. Based on that record, as well as FDA's detailed discussion and explanation for the basis for its conclusion that the SP-B in Infasurf was a previously approved active moiety in Survanta for purposes of orphan drug exclusivity, where the definition of active moiety is identical to that for 5-year NCE exclusivity, the Agency concludes that the 5-year NCE exclusivity decisions for Survanta, Infasurf, and Curosurf were incorrect. Survanta, Infasurf, and Curosurf should all have been ineligible for 5-year NCE exclusivity because each contains at least one previously approved active moiety.

As you acknowledge, FDA concluded that Cenestin was ineligible for 5-year NCE exclusivity in light of the prior approval of Premarin.[90] You try to distinguish this outcome by asserting that the Agency must have concluded that "the whole of each of the Cenestin and Premarin mixtures were sufficiently similar as to constitute the same active moiety"[91] because the Agency cited to Premarin (and not to any other previously approved single component conjugated estrogen products) in its exclusivity analysis.[92] You also point to comments in the record emphasizing the similarity of all short-acting conjugated estrogens (including Premarin and Cenestin) to justify the applicability of the relevant Drug Efficacy Study Implementation (DESI) findings for such compounds for the purposes of the Agency's fixed-combination policy.[93]

The Agency does not agree with your assumptions and does not find your claims persuasive. There is no specific significance associated with a reference to Premarin in the exclusivity summary for Cenestin. As explained above, that reference is consistent with the conclusion that Premarin contains multiple active moieties, at least one of which also exists in Cenestin. In addition, your statements regarding the similarity of short-acting conjugated estrogens do not support your conclusions. First, referring to two drugs as being "similar" does not mean that they contain the same active moiety. Second, taking your assertion to its natural conclusion would mean that the Agency considers all conjugated estrogen mixtures to contain the same

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[88] Exosurf was approved in 1990 and Survanta was approved in 1991. The relevant regulations were finalized in 1994.

[89] Exosurf was determined to be eligible for 3-year exclusivity, even though the exclusivity summary recommends 5-year NCE exclusivity. It appears that Exosurf's exclusivity status was changed in a later edition of the Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book"), and there does not appear to be an explanation for the change. At the same time, other products containing the same active moiety in Exosurf, colfosceril palmitate, and approved after Exosurf, e.g., Survanta, were determined to be eligible for 5 years of exclusivity.

[90] See Section III.B.4., supra.

[91] Dormer Letter III, supra note 1, at 3.

[92] Id. at 4.

[93] Id.

active moiety, which would be a very broad reading of these statements. Instead, FDA considered Cenestin "to be in compliance with the requirements of the fixed-combination drug policy"[94] and characterized the drug as a "combination product" in the exclusivity summary instead of a "single active ingredient product."[95] Moreover, FDA rejected the sponsor's claim that only three of the estrogens in Cenestin should be designated as active ingredients. Instead, the Agency stated that "all components should be designated as active because [Cenestin] is a synthetic product; therefore, specifications should be considered for each component."[96] These statements, along with the classification of Cenestin as a "combination product," are more consistent with a conclusion that FDA considered each component of Cenestin as a separate active ingredient, each containing a single active moiety.

In addition, you have recently claimed that the Agency's determination that Qutenza was eligible for 5-year NCE exclusivity supports your contentions because the Agency also determined that Qutenza was ineligible for a patent term extension (PTE) due to the prior approval of Relevo Liniment in 1938.[97] The Agency does not believe it is necessary to address your contentions on this point in detail. FDA's PTE determination regarding Qutenza — that the active ingredient in Qutenza had been previously approved due to the approval of the older mixture[98] — does not necessarily support your premise because it does not address the identity of any active moiety in Qutenza.

Finally, you assert that the Agency's "structure-centric" approach, where the Agency will not inquire into the relative contributions of the portions of a molecule bonded by an ester bond,[99] "supports a determination that Vascepa is an NCE entitled to" 5-year NCE exclusivity.[100] As you acknowledge, however, "[s]alts, esters, and non-covalent derivatives are all specific substances of fixed structure, and their deconvolution to the active moiety requires simply the identification of specific bonds within the structure. . . . The same cannot be said of complex mixtures."[101] The Agency agrees that the approach it has taken to determine which portions of a specific molecule constitute its active moiety is meant to address a different question than that

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[94] Cenestin Administrative Document, supra note 54, at 6.

[95] Id. at 11-12.

[96] Administrative Documents Part 1, NDA 20-992, at 5, 11-12, 14-15, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20992_admindocs_P1.pdf.

[97] Dormer Letter V, supra note 1.

[98] See May 2, 2011, letter from Jane A. Axelrad, CDER, to David J. Kappos, PTO, Docket No. FDA-2010-E-0406 ("The active ingredient in QUTENZA (capsaicin) was previously approved for commercial marketing or use, in Relevo Liniment (Modern Drugs).").

[99] See, e.g., Letter from Gary Buehler to Chad A. Landmon, 5-year NCE exclusivity for Vyvanse, at 7, 9, 11-12 (Oct. 23, 2009), available at http://www.regulations.gov/contentStreamer?objectId=0900006480e6cd97&disposition=attachment&contentType=pdf.

[100] Dormer Letter II, supra note 1, at 11. You repeat this assertion in slightly different forms in your later communications. See Dormer Letter IV and Dormer Letter V, supra note 1.

[101] Dormer Letter II, supra note 1, at 12.

presented here,[102] and therefore, the structure-centric approach is not applicable when determining which components of a naturally derived mixture potentially are its active moiety or moieties.

In summary, the Agency's review of its practice regarding naturally derived mixtures and 5-year NCE exclusivity reveals that the Agency has not always clearly set out its rationale for its determinations in the past, neither the Agency nor regulated industry have used consistent terminology in this context,[103] and, as a result, past exclusivity determinations have not always been consistent. In the face of an inconsistent practice, the Agency is not bound to follow a particular past decision. Instead, in light of the relevant authorities, applicable scientific principles and past Agency action, the framework described in this letter best harmonizes the relevant authorities and the outcomes of relevant prior Agency actions. Specifically, where a specific molecule in a previously approved, naturally derived mixture has been characterized, is consistently present, and meaningfully contributes to the pharmacological activity of the drug for its intended use, it generally will be considered to be a previously active moiety in the absence of evidence to the contrary.

3. *Non-Proprietary Name, Labeling, and Orange Book[104] Listing*

You also claim that the following facts support your assertion that Vascepa is eligible for 5 years of exclusivity:[105]

- Lovaza's labeling lists the active ingredient as the mixture;
- EPA is not an "ingredient" of Lovaza, because it is not listed on the labeling;
- FDA's "Orange Book" lists Lovaza's active ingredient as the mixture; and
- Vascepa's established name is icosapent ethyl, and FDA rejected a name that consisted of the International Non-proprietary Names for EPA and DHA.

The Agency disagrees. Because eligibility for 5-year NCE exclusivity is determined solely by reference to whether a drug contains no active moiety that has been previously approved, neither the non-proprietary name of the product nor the listing of active ingredients in the labeling or the Orange Book is dispositive of the NCE exclusivity determination. Differences between the names or active ingredients listed in the Orange Book or labeling for Lovaza and Vascepa do not answer whether EPA is an active moiety in Lovaza.

Your assertion that EPA cannot be an active moiety of Lovaza because it "is not an ingredient . . . listed in the Lovaza label"[106] is unavailing. The fact that the Lovaza labeling refers only to

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[102] See id. ("[A] constituent has no structural relationship to a mixture and hence a structure-centric approach does not equate a mixture to its constituents.").

[103] Of course, the structure-centric approach would apply after such a molecule has been identified, as it does here. The Lovaza mixture includes the ethyl ester of EPA, and we discount the ester-bonded portion in determining the active moiety.

[104] Orange Book, at 3-294 (30th Ed., 2010).

[105] See Dormer Letter I, supra note 1, passim.

[106] Id. at 5.

the Lovaza mixture as its active ingredient does not answer whether EPA is an active moiety of Lovaza.[107] Moreover, the Agency has never taken the position (and neither the statute nor the regulations require) that each active moiety of a naturally derived mixture must be separately listed in the labeling. As explained above, under FDA's regulations, a drug's active ingredient is distinct from its active moiety, and, at least in the case of a naturally derived mixture, a single active ingredient can have multiple active moieties. If a molecule or ion is consistently present and responsible for the pharmacological action of a mixture, it should be considered an active moiety of the mixture under applicable definitions, regardless of whether it is listed separately in the labeling.

Your claims that depend on the differences between the established names of these two drugs also are unconvincing.[108] FDA already has rejected a similar claim that "[b]y reason of having different established names, [two different drugs] have been officially recognized as different entities, scientifically and legally, and cannot be the same drug."[109] Furthermore, because a drug's active moiety cannot be determined with reference to its established name, the fact that the Agency rejected a particular name suggested by the sponsor has no specific relevance for the determination of that drug's active moiety.

4. Policy Argument

You assert that Amarin undertook a development program to gain marketing approval for Vascepa and, as a policy matter, it deserves the benefits of 5-year NCE exclusivity. The Agency disagrees with this rationale. The amount of research that a sponsor invests in a drug is not determinative of that drug's eligibility for 5-year NCE exclusivity. The Hatch-Waxman Amendments do not recognize the amount of data generated by the sponsor as a factor in the 5-year NCE exclusivity analysis. The consideration of whether a sponsor conducted studies that were necessary for approval is, however, a central factor in whether a drug is eligible for 3-year exclusivity.[110] Congress explicitly chose to award sponsors for conducting new studies that were essential to the approval of their drugs with 3-year exclusivity and new chemical entities with 5-year exclusivity.

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[107] For that matter, Vascepa's labeling does not list EPA as an "ingredient" either; rather, it lists the ethyl ester of EPA, i.e. icosapent ethyl. Accordingly, if the Agency were to take your assertion literally, then EPA could not be the active moiety in Vascepa.

[108] Your assertion that EPA was not selected as the established name of Vascepa "to avoid confusion with dietary supplement products" has no regulatory significance. In any event, the same could easily be true for Lovaza's labeling.

[109] ONY, Inc., Letter to James Bilstad, MD, at 2 (May 13, 1997), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20521_INFASURF%20INTRACHEAL%20SUSPENSION_corres_P1.pdf. As noted above, in that case, FDA rejected the assertion that the two drugs must be different because they had different established names. The Agency ultimately decided that the two drugs at issue were the same drug (i.e., contained the same active moiety) for the purposes of orphan drug "sameness" analysis.

[110] Compare section 505(j)(5)(F)(ii) of the FD&C Act with section 505(j)(5)(F)(iii) of the FD&C Act.

V. CONCLUSION

For the reasons described above, the Agency concludes that Vascepa does not qualify for 5-year NCE exclusivity. Vascepa is instead eligible for 3 years of exclusivity, based on the new clinical studies that Amarin conducted and that were essential to the approval of the marketing application for Vascepa.

Sincerely,

Janet Woodcock
Director
Center for Drug Evaluation and Research