DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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MAY 31 2016

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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:
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> > **(1) Characterization**: The previously approved mixture has been characterized such that one or more specific molecules in the mixture have been identified;
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> > **(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.
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> 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;
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> **(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**: . . . [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.