IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

AMARIN PHARMACEUTICALS IRELAND LIMITED, Plaintiff, v. FOOD AND DRUG ADMINISTRATION, *et al.*, Defendants.	)	No. 1:14-cv-00324-BAH

DEFENDANTS' MOTION FOR SUMMARY JUDGMENT

Pursuant to Rule 56 of the Federal Rules of Civil Procedure, defendants move the court to grant summary judgment in their favor on the grounds that there is no genuine dispute as to any material fact and defendants are entitled to judgment as a matter of law.

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MEMORANDUM IN SUPPORT OF DEFENDANTS' MOTION FOR SUMMARY JUDGMENT AND IN OPPOSITION TO PLAINTIFF'S MOTION FOR SUMMARY JUDGMENT

Plaintiff Amarin Pharmaceuticals Ireland Limited ("Amarin") is challenging the Food and Drug Administration's ("FDA" or "agency") long-standing framework for evaluating "new chemical entity" or "NCE" exclusivity, simply because Amarin is unhappy with FDA's exclusivity determination regarding Amarin's fish oil product in this case. Notably, the regulations that Amarin is now challenging were promulgated nearly 20 years ago and have played a central role in hundreds of NCE exclusivity determinations. Moreover, FDA properly interpreted and applied the relevant statutory and regulatory provisions to determine that Amarin's product Vascepa, indicated as an adjunct to diet to reduce triglyceride levels in certain adults, is not entitled to five years of NCE exclusivity. As evidenced by the Administrative Record, the available science, viewed in light of relevant past agency decisions, demonstrates that FDA correctly concluded that Vascepa contains a single active moiety, namely eicosapentaenoic acid ("EPA"), an omega-3 fatty acid, that is also an active moiety in a

previously-approved product, Lovaza Capsules ("Lovaza"). Vascepa, therefore, does not qualify for five years of NCE exclusivity.

FDA's decision that Vascepa is not a new chemical entity means FDA can immediately accept for filing an application seeking to market a generic version of Vascepa, should such an application be submitted to the agency. No generic version of Vascepa can be approved before July 26, 2015, however, because Amarin was granted three years of exclusivity based on new clinical trials it conducted that were essential to the approval of Vascepa. *See* 21 U.S.C. § 355(j)(5)(F)(iii); Letter from J. Woodcock to R. Dormer (Feb. 21, 2014) ("FDA Letter") at 24.[1]

Amarin contends that FDA's determination that Vascepa is not eligible for five-year NCE exclusivity because it contains a previously-approved active moiety was arbitrary and capricious. Amarin, in essence, disagrees with FDA's conclusion that a single "active ingredient" can contain more than one "active moiety." Unable to offer any challenge to the scientific conclusions on which FDA's decision rests, Amarin also points to no statutory or regulatory basis for its assertion and instead accuses FDA of rewriting the Federal Food, Drug, and Cosmetic Act ("FDCA"). As the D.C. Circuit made clear, *see Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 764 (D.C. Cir. 2010), *Abbott Labs. v. Young*, 920 F.2d 984, 987-88 (D.C. Cir. 1990), the term "active ingredient" in section 355(j)(5)(F) is ambiguous. FDA's regulations give meaning to the statutory language and, in doing so, introduce and define additional terms including "active moiety" and "new chemical entity." FDA's decision here regarding Vascepa is consistent with the FDCA, the agency's implementing regulations, and available scientific information, and should thus be upheld by this Court.

[1] For ease of reference in this brief, FDA will refer to the page number of the letter itself, attached hereto as Exhibit A, rather than the administrative record page number.

I. STATUTORY AND REGULATORY BACKGROUND

A. New Drug Applications and Abbreviated New Drug Applications

A new drug application ("NDA") must be supported by clinical investigations showing the drug product to be safe and effective. 21 U.S.C. § 355(b). The 1984 Drug Price Competition and Patent Term Restoration Act ("Hatch-Waxman Amendments") provided an alternate pathway for submission of abbreviated new drug applications ("ANDAs") for generic versions of listed drugs. 21 U.S.C. § 355(j).[2] The ANDA process shortens the time and effort needed for approval by, among other things, allowing an ANDA applicant to rely on FDA's previous finding of safety and effectiveness for a listed drug rather than requiring the ANDA applicant to repeat the clinical studies conducted to support approval of the listed drug. To rely on such a finding, the ANDA applicant must show, among other things, that its proposed drug product is the same as the listed drug with respect to active ingredient, dosage form, strength, route of administration, and, with certain narrow exceptions, labeling, and that its product is bioequivalent to the listed drug. 21 U.S.C. § 355(j)(2).

B. Five-Year NCE Exclusivity

The Hatch-Waxman Amendments provide incentives for pharmaceutical innovation by conferring various periods of exclusivity to protect qualified drug products approved under 21 U.S.C. § 355(b) from competition. Under the statute, drugs that do not contain a previously approved active ingredient (including any ester or salt of the active ingredient) may obtain a five-year exclusivity period. As interpreted by FDA, this exclusivity generally prevents FDA from accepting an ANDA or § 355(b)(2) application that contains the active moiety in the protected drug for a five-year period from the date of approval of the protected drug. 21 U.S.C.

[2] A "listed" drug is a drug product with an effective approval under 21 U.S.C. § 355(c). *See* 21 C.F.R § 314.3(b).

§ 355(j)(5)(F)(ii).[3]

The statute provides in relevant part:

> 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, is approved after September 24, 1984, 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 . . . .

Id.

The statute provides an exception allowing an applicant to submit an ANDA four years following the date of approval if it contains a patent challenge described in 21 U.S.C. § 355(j)(2)(A)(vii)(IV). *Id*.

C. FDA's Regulations Governing Five-Year NCE Exclusivity

21 C.F.R. § 314.108 implements the FDCA's NCE exclusivity provisions. FDA interprets the statutory language in 21 U.S.C. § 355(j)(5)(F)(ii), which awards five years of exclusivity to drugs "no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application," to preclude the agency from accepting ANDAs (and new drug applications submitted under 21 U.S.C. § 355(b)(2)) for drugs that contain the same active moiety as in a previously approved new chemical entity. The regulation provides:

> If a drug product that contains a new chemical entity was approved. . . in an application submitted under section [21 U.S.C. § 355(b)], no person may submit a[n] . . . abbreviated new drug application under [21 U.S.C. § 355(j)] for a drug product that contains the same active moiety as in the new chemical entity for a

[3] FDA is similarly precluded from accepting an application filed under 21 U.S.C. § 355(b)(2) by the parallel provision relating to such applications, 21 U.S.C. § 355(c)(3)(E)(ii).

> period of 5 years from the date of approval of the first approved new drug application . . . .

21 C.F.R. § 314.108(b)(2). Thus, under FDA's interpretation of the statute (embodied in the regulations), a drug that is a new chemical entity will receive five years of exclusivity. If a drug is not a new chemical entity (*i.e.*, it contains any previously approved active moiety), it may be eligible for three years of exclusivity, but will not be eligible for five years of exclusivity.

FDA has defined "new chemical entity" to mean "a drug that contains no active moiety that has been approved by FDA in any other application submitted under [21 U.S.C. § 355(b)]." 21 C.F.R. § 314.108(a). "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.

Id. This regulation was finalized in 1994. *See* 59 Fed. Reg. 50338 (Oct. 3, 1994). In that Federal Register notice, FDA explained that, "[t]he 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." *Id*. at 50358.

II. FACTUAL BACKGROUND

A. Approval of Lovaza

On November 10, 2004, FDA approved NDA 21654 for Lovaza, as "an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia." Lovaza labeling at 1 (AR 000143). Lovaza lists "Omega-3 acid ethyl esters" as its active ingredient. *Id*. 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"). *Omega-3-Acid Ethyl Esters*, United States Pharmacopeia 36-National Formulary 31, at 4571 (2013) (AR 000157). Two of the seven omega-3 acid ethyl esters, the ethyl esters of EPA and docosahexaenoic acid ("DHA"),[4] make up approximately 85% of Lovaza. *See* Lovaza labeling at 6 (AR 000148). Icosapent ethyl (the ethyl ester of EPA) alone comprises almost half of Lovaza. *See Omega-3-Acid Ethyl Esters*, United States Pharmacopeia 36-National Formulary 31, at 4571 (2013) (AR 000157).

B. Approval of Vascepa

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. *See* Vascepa Labeling at 1 (AR 000097). Icosapent ethyl is the ethyl ester of EPA, and, as noted above, is the single most abundant omega-3 acid ethyl ester present in Lovaza. Because FDA does not consider the ester component of a molecule in determining its active moiety, 21 C.F.R. § 314.108(a); *see also* 21 U.S.C. § 355(j)(5)(F)(ii), EPA (the de-esterified portion of the icosapent ethyl molecule) is the sole active moiety in Vascepa. Like Lovaza, Vascepa was approved as "an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia." Vascepa Labeling at 1 (AR 000097).

C. FDA's Decision

By letter dated February 21, 2014, FDA determined that Vascepa is not eligible for five-year NCE exclusivity because EPA, the active moiety in Vascepa, is also an active moiety contained in another, previously approved drug (i.e., Lovaza). FDA Letter at 1. After outlining the statutory and regulatory provisions governing NCE-exclusivity, FDA noted that that neither

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

the FDCA nor its implementing regulations expressly address five-year NCE exclusivity in the context of naturally derived mixtures. *Id*. at 6. Based on the relevant authorities and prior agency decisions, FDA explained that it generally considers certain component molecules of a drug product's naturally derived mixture to be previously approved active moieties for the purpose of determining a subsequent drug's eligibility for five-year NCE exclusivity when the following 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.

FDA Letter at 6-8.

FDA explained that although the agency "has not always acted consistently" when identifying the active ingredient and/or active moiety of naturally derived mixtures, the agency has generally reached results in accordance with the above three-step analysis. FDA Letter at 8. FDA's letter contains a lengthy and detailed discussion of prior agency actions concerning naturally derived mixtures that, for the most part, are consistent with this framework and support FDA's conclusion that Vascepa is not eligible for five-year NCE exclusivity. *See id*. at 8-16.[5]

[5] FDA acknowledged that not all of its past actions were consistent with the outcome here, but also acknowledged: "[T]he 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." FDA Letter at 20; *see also id*. at 15.

FDA determined that EPA satisfied all three of the criteria outlined above, and concluded that EPA is an active moiety in Lovaza. *See* FDA Letter at 16. In responding to Amarin's challenges to FDA's view that EPA, rather than the Lovaza mixture as a whole, is an active moiety in Lovaza, FDA noted that 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" of the Lovaza mixture. *Id*. at 2, 18-19. In addition, Lovaza's labeling emphasizes the importance of EPA's contribution to the pharmacological effect of the drug. The "Description" section of the Lovaza labeling 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. *See id*. at 2. 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. *See id*. at 3. The Lovaza labeling thus specifically associates the pharmacological effect of the drug with EPA and DHA.

FDA also rejected Amarin's arguments that previous agency decisions mandated a grant of five-year NCE exclusivity for Vascepa. FDA explained:

> the Agency's review of its practice regarding naturally derived mixtures and five-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, 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.

FDA Letter at 22. FDA therefore concluded that Vascepa was not eligible for five-year NCE exclusivity, but concluded that Vascepa was eligible for three years of exclusivity based on the new clinical trials that Amarin conducted that were essential to approval of Vascepa. *See id*. at 24.

III. ARGUMENT

A. Legal Standard

A party is entitled to a summary judgment "if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). FDA has produced an administrative record in this case, and the parties do not dispute the contents of that record. Because the issues for resolution in this case are purely legal in nature, entry of summary judgment for the party entitled to prevail as a matter of law is appropriate. *Bayer v. United States Dep't of Treasury*, 956 F.2d 330, 333-34 (D.C. Cir. 1992).[6]

FDA's administrative decisions are subject to review under the Administrative Procedure Act ("APA"), and may be disturbed only if "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). This standard is highly deferential to the agency. *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971). The agency's administrative decision is entitled to a presumption of validity. *Am. Wildlands v. Kempthorne*, 530 F.3d 991, 997 (D.C. Cir. 2008); *AT&T Corp. v. FCC*, 349

[6] Indeed, this Court has recognized that "[s]ummary judgment is an appropriate procedure for resolving a challenge to a federal agency's administrative decision when review is based upon the administrative record . . . even though the Court does not employ the standard of review set forth in Rule 56, Fed. R. Civ. P." *Fund for Animals v. Babbitt*, 903 F. Supp. 96, 105 (D.D.C. 1995) (citation omitted). An agency is "entitled to summary judgment if the path of its reasoning is sufficiently discernable in light of the record." *Settles v. United States Parole Comm'n*, 429 F.3d 1098, 1108 (D.C. Cir. 2005).

F.3d 692, 698 (D.C. Cir. 2003). In addition, "the party challenging an agency's action as arbitrary and capricious bears the burden of proof." *San Luis Obispo Mothers for Peace v. NRC*, 789 F.2d 26, 37 (D.C. Cir. 1986); *see also City of Olmsted Falls v. FAA*, 292 F.3d 261, 271 (D.C. Cir. 2002).

In reviewing FDA's interpretation of the FDCA, the Court is governed by the familiar two-step analysis of *Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837 (1984). The first question under *Chevron* is "whether Congress has directly spoken to the precise question at issue." *Id*. at 842. "If the intent of Congress is clear, that is the end of the matter." *Id*. at 842-43. Put another way, the Court must initially decide "whether the statute unambiguously forbids the Agency's interpretation." *Barnhart v. Walton*, 535 U.S. 212, 218 (2002).

If, however, the statute "is silent or ambiguous with respect to the specific issue," the Court proceeds to the second prong of *Chevron*, under which "the question for the court is whether the agency's answer is based on a permissible construction of the statute." *Chevron*, 467 U.S. at 843; *Cnty. of L. A. v. Shalala*, 192 F.3d 1005, 1012-13 (D.C. Cir. 1999). The court need not find that the agency construction was the only one it permissibly could have adopted or even the reading the court would have reached; so long as the agency's reading is permissible, it must be sustained. *See Chevron*, 467 U.S. at 843-44 & n.11; *Cnty. of L. A.*, 192 F.3d at 1012-13. The Supreme Court has "long recognized that considerable weight should be accorded to an executive department's construction of a statutory scheme it is entrusted to administer." *United States v. Mead Corp.*, 533 U.S. 218, 227-28 (2001), quoting *Chevron*, 467 U.S. at 844; *see also Udall v. Tallman*, 380 U.S. 1, 16 (1965); *Cnty. of L. A.*, 192 F.3d at 1013; *Orengo Caraballo v. Reich*, 11 F.3d 186, 192-93 (D.C. Cir. 1993).

The measure of deference is at its height when, as here, there are "express congressional authorizations to engage in the process of rulemaking or adjudication that produces regulations or rulings for which deference is claimed," and when it is clear that "Congress actually intended to delegate particular interpretive authority to an agency." *Mead*, 533 U.S. at 229-30; *see also Trans Union LLC v. FTC*, 295 F.3d 42, 50 (D.C. Cir. 2002). Further, deference is appropriate when "the interstitial nature of the legal question, the related expertise of the Agency, the importance of the question to administration of the statute, the complexity of that administration, and the careful consideration the Agency has given the question over a long period of time all indicate that *Chevron* provides the appropriate legal lens through which to view the legality of the Agency interpretation here at issue." *Barnhart*, 535 U.S. at 222.

In addition, when an agency's decision is based on evaluation of scientific information within the agency's area of technical expertise, its decisions are traditionally accorded great deference. *See Am. Wildlands v. Kempthorne*, 530 F.3d 991, 1000 (D.C. Cir. 2008) ("The rationale for deference is particularly strong when the [agency] is evaluating scientific data within its technical expertise") (quoting *Int'l Fabricare Inst. v. EPA*, 972 F.2d 384, 389 (D.C. Cir. 1992)); *Troy Corp. v. Browner*, 120 F.3d 277, 283 (D.C. Cir. 1997) (courts "review scientific judgments of the agency 'not as the chemist, biologist, or statistician that [they] are qualified neither by training nor experience to be, but as a reviewing court exercising [its] narrowly defined duty of holding agencies to certain minimal standards of rationality.'") (quoting *Ethyl Corp. v. EPA*, 541 F.2d 1, 36 (D.C. Cir. 1976)); *Sw. Pa. Growth Alliance v. Browner*, 121 F.3d 106, 117 (3d Cir. 1997) (reviewing court must generally be "at its most deferential" when reviewing factual determinations within an agency's area of special expertise; it is not the role of a reviewing court to second-guess agency's scientific judgments). Such

deference has repeatedly been applied in cases under the FDCA. *See, e.g.*, *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1320 (D.C. Cir. 1998) ("FDA's determination of what is required to establish 'sameness' for purposes of the Act rests on the 'agency's evaluations of scientific data within its area of expertise,' and hence is entitled to a 'high level of deference' from this court.") (quoting *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1490 (D.C. Cir. 1995)); *Henley v. FDA*, 77 F.3d 616, 621 (2d Cir. 1996) ("FDA possesses the requisite know-how to conduct such [scientific] analyses, by sifting through the scientific evidence to determine the most accurate and up-to-date information regarding a particular drug . . . . We therefore defer to its reasonable findings."); *Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995) (FDA's "judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference from us."); *Tri-Bio Labs., Inc. v. United States*, 836 F.2d 135, 142 (3d Cir. 1987) ("We are mindful that in evaluating scientific evidence in the drug field, the FDA possesses an expertise entitled to respectful consideration by this court."), *cert. denied*, 488 U.S. 818 (1988).

B. FDA's Decision was Proper and Should be Upheld as a Matter of Law

1. The Term "Active Ingredient" is Ambiguous

At *Chevron* step one, this Court's review is limited to determining whether the statute "unambiguously forecloses the agency's interpretation, and therefore contains no gap for the agency to fill." *Nat'l Cable & Telecomms. Ass'n v. Brand X Internet Servs.*, 545 U.S. 967, 982-83 (2005). Here, the phrase "active ingredient (including any ester or salt of the active ingredient)," 21 U.S.C. § 355(j)(5)(F)(ii), is, contrary to Amarin's contentions, ambiguous, and FDA's interpretation of that provision is not foreclosed by the statute.

The FDCA provides that a drug that does not contain any previously approved "active

ingredient (including any ester or salt of the active ingredient)" is eligible for a five-year exclusivity period. 21 U.S.C. § 355(j)(5)(F)(ii). Such a drug is referred to as a "new chemical entity" or "NCE," which FDA regulations define as "a drug that contains no active moiety that has been approved by FDA in any other application submitted under [21 U.S.C. § 355(b)]." 21 C.F.R. § 314.108(a); *see also* 21 C.F.R. § 314.108(b)(2). These regulations reflect FDA's interpretation of the phrase "active ingredient" in the relevant statutory provision. *See* 59 Fed. Reg. 50338, 50358 (Oct. 3, 1994).

Under this framework, competition for unique, new drugs (*i.e.*, new chemical entities) is delayed to reward the innovation that went into those products. Thus, the issue in this case centers on whether a drug product (*i.e.*, Vascepa) qualifies for five-year NCE exclusivity because its active ingredient does not contain a previously approved "active moiety." FDA defines "active moiety" 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.

21 C.F.R. § 314.108(a).

The D.C. Circuit first addressed the relevant statutory provision in *Abbott*, and found the language ambiguous as it relates to the meaning of "active ingredient (including any ester or salt of the active ingredient)," noting that it could refer "to either the active ingredient of the original approved drug or the active ingredient in the new drug, depending on how 'the' in the parenthetical and the words surrounding the parenthetical -- 'no active ingredient . . . of which has been approved' -- is interpreted." *Abbott*, 920 F.2d at 987 (emphasis omitted). FDA had argued that the "including" clause covered all forms of the active ingredient and was not limited

to ester(s) or salt(s) of the active ingredient. *See id*. at 988.[7] The court, however, rejected both FDA and Abbotts' proposed interpretations of that expression, and "h[e]ld only that the statute is ambiguous . . . we may not proceed since we have no authority to place a construction on the statute that the agency has not offered." *Id*. at 989-90.

Subsequently, when FDA issued its final rule in 1994, it explained its interpretation of 21 U.S.C. § 355(j)(5)(F)(ii) in light of the *Abbott* decision:

> Although the court of appeals appeared to agree with the agency's conclusion that exclusivity should be limited to the first approved product containing the active moiety, the court found the agency's parsing of the operative statutory phrase "active ingredient (including any salt or ester of the active ingredient)" to be linguistically impermissible as set forth in the agency's administrative decision denying 10-year exclusivity to Abbott. Rather than interpret the term "active ingredient" broadly to include the concept of active moiety, the agency interpreted the term narrowly to refer to the form of the moiety in the product, but interpreted the parenthetical phrase "(including any salt or ester of the active ingredient)" broadly to include all active ingredients that are different but contain the same active moiety. Although the court noted that the agency had, subsequent to the administrative decision, voiced the more linguistically permissible construction (interpreting the term "active ingredient" to refer to active moiety), the court found that it could not consider this construction because it was not relied upon in the administrative decision.

59 Fed. Reg. at 50358. FDA went on to conclude that "active ingredient," as used in the phrase "active ingredient (including any salt or ester of the active ingredient)," means "active moiety," as defined in 21 C.F.R. § 314.108. *Id*.[8]

Twenty years after *Abbott*, the D.C. Circuit, in *Actavis Elizabeth LLC v. FDA*, 625 F.3d

[7] Amarin's statement that FDA "attempted to interpret the phrase 'active ingredient (including any salt or ester of the active ingredient)' to mean 'active moiety'" in *Abbott*, *see* Amarin Br. at 17, shows an incomplete understanding of the FDA decision that led to the *Abbott* litigation.

[8] Amarin's claim that FDA adopted "the very interpretation of the statute that Judge Edwards found impermissible and directly contrary to the statutory language," Amarin Br. at 7, is a red herring. Judge Edwards wrote the dissent in *Abbott*, not the majority opinion. *See Abbott*, 920 F.2d at 990-96 (J. Edwards dissenting).

760 (D.C. Cir. 2010), once again found the term "active ingredient" to be ambiguous. *See Actavis*, 625 F.3d at 764 ("Actavis spends the bulk of its briefs arguing that the FDA's interpretation is inconsistent with the clear meaning of the statute. Where Actavis sees clarity we see ambiguity."); *see also id*. ("The Hatch-Waxman Amendments do not define active ingredient. The legislative history established only that Congress was concerned with providing incentives for innovation by granting five-year exclusivity to 'new chemical entities' and is silent on what determines novelty."). The specific issue in *Actavis* (whether a drug product containing a non-ester covalent derivative of a previously approved active moiety is entitled to five-year NCE exclusivity, s*ee id*. at 763) is not relevant here, but *Actavis* confirms that the relevant statutory language is not, as Amarin argues, "plain and unambiguous." Amarin Br. at 16. Indeed, the D.C. Circuit appears to have accepted without discussion that "to qualify for five-year exclusivity under § 355(j)(5)(F)(ii), an approved drug must contain no previously approved active moieties." *Actavis*, 625 F.3d at 762.

Despite the complex regulatory background surrounding FDA's interpretation of the five-year NCE exclusivity provision, and in the face of two D.C. Circuit opinions finding "active ingredient" to be ambiguous in the NCE context, Amarin nonetheless contends that the statutory language is clear on its face and that FDA's interpretation is contrary to that plain meaning. Amarin Br. at 16-21. Amarin once again misplaces reliance on Judge Edward's dissent in *Abbott*, s*ee, e.g.*, *id*. at 17, 21, ignoring controlling D.C. Circuit law.

As FDA explained in its letter to Amarin:

> 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, 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.

FDA Letter at 6. In other words, the fact that Lovaza and Vascepa are made up of a naturally derived mixture offers another reason to reject Amarin's suggested interpretation of "active ingredient" here.

FDA did not publicly identify EPA as an active moiety in Lovaza at the time of approval because until Amarin requested NCE exclusivity for Vascepa, there was no need to identify the active moiety of a previously-approved drug. Drug approvals are based on, among other things, the demonstrated safety and effectiveness of the drug product. *See* 21 U.S.C. § 355(b). NCE exclusivity determinations, on the other hand, involve, by definition, a comparison between the active ingredients of a newer drug product and a previously-approved drug product. *See* 21 U.S.C. § 355(j)(5)(F). It is thus unsurprising, and entirely appropriate, that FDA "did not purport to identify [Lovaza's] active moiety until ten years later [after approval] in connection with its exclusivity determination for Vascepa." Amarin Br. at 18. This timing does not show that "active ingredient" has a plain and unambiguous meaning.

Amarin's argument that FDA's interpretation of the term "active ingredient" in the statutory provisions governing ANDA approval renders FDA's interpretation in the NCE context unreasonable, *see* Amarin Br. at 19, was expressly rejected by the D.C. Circuit. *See Abbott*, 920 F.2d at 987 (observing that FDA construes "active ingredient" in the ANDA approval provisions narrowly and stating: "We note that it is not impermissible under *Chevron* for an agency to interpret an imprecise term differently in two separate sections of a statute which have different purposes."). Amarin's contention that the definition of "bioavailability" and "bioequivalent" in 21 U.S.C. § 355(j)(8) (governing ANDA approval) shows that FDA's

interpretation of "active ingredient" here violates a basic canon of statutory construction, *see* Amarin Br. at 20, fares no better. Indeed, the fact that Amarin resorts to citing a Federal Register notice for a proposed rule to support its "plain meaning" argument is telling because it shows that the statutory language is far from "plain." Moreover, rather than attempt to demonstrate the supposedly unambiguous meaning of "active ingredient," Amarin instead focuses on canons of statutory interpretation that it claims FDA's interpretation violates. *See* Amarin Br. at 18-21. But the reasonableness of an agency interpretation is the focus of *Chevron* step two, not step one, and Amarin's failure to address how this case could be decided at *Chevron* step one further demonstrates the weakness of its argument.

2. FDA's Interpretation is Reasonable and Entitled to Deference

As described above, the statute is ambiguous with respect to the meaning of "active ingredient (including any ester or salt of the active ingredient)," and FDA has reasonably interpreted that specific phrase in view of its best judgment as to the scope of exclusivity intended by Congress, and in light of applicable judicial precedent. Under *Chevron* step two, this Court must "uphold the agency's interpretation of the ambiguous statute if that interpretation is 'permissible,' that is, if it is 'reasonable.'" *Am. Bar Ass'n v. FTC*, 430 F.3d 457, 468 (D.C. Cir. 2005) (quoting *Chevron*, 467 U.S. at 845). FDA's interpretation of "active ingredient" in terms of "active moiety" reflects a permissible reading of the statute. Accordingly, the agency's interpretation is entitled to *Chevron* deference and should be upheld.

FDA's regulation introducing the terms "new chemical entity" and "active moiety" was proposed in 1989 and finalized in 1994. 59 Fed. Reg. 50338 (Oct. 3, 1994). As FDA explained in the proposed rule:

> FDA interprets the statutory requirement that a drug (new chemical entity) contain "no [previously approved] active ingredient (including any ester or

> salt of the active ingredient)" to mean that the drug must not contain any previously approved active moiety. FDA bases this interpretation on the statutory language and on the definition of a "new molecular entity" or "Type 1" drug in FDA's IND/NDA classification scheme (which is used to classify new drugs by chemical type and therapeutic significance), which was in effect at the time the 1984 Amendments were under consideration in Congress. FDA's longstanding interpretation of the term "new molecular entity" is that it is a compound containing an entirely new active moiety. FDA's interpretation of the scope of the 5-year exclusivity provision is also consistent with the legislative history, which reveals that Congress was aware of FDA's classification scheme and did not intend to confer significant periods of exclusivity on minor variations of previously approved chemical compounds. (*See, e.g.*, Cong. Rec. H9124 (September 6, 1984) (statement of Representative Waxman); H. Rept. 857, Part I, 98th Cong., 2d Sess. 38 (1984).)

54 Fed. Reg. 28872, 28897-98 (July 10, 1989). The focus on active moiety in the NCE exclusivity context ensures that an applicant will be rewarded with exclusivity for truly innovative developments but will not be permitted to block subsequent competition based on only minor changes to an approved product. FDA's interpretation thus implements the over-arching congressional intent behind the Hatch-Waxman Amendments, which was to balance encouraging innovation in the development of new drugs with accelerating the availability to consumers of lower cost alternatives to such drugs. *See* H.R. Rep. No. 98-857 (Part I), 98th Cong., 2d Sess. at 14-15 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647-48; *see also*, *e.g.*, *Tri-Bio Labs., Inc. v. United States*, 836 F.2d at 139.

As FDA noted in its letter to Amarin, the agency's analysis of "active ingredient" and "active moiety" in this case is different from many situations where the drug at issue is comprised of a single, well-characterized molecule. *See* FDA Letter at 6. For products that contain single-molecule active ingredients, FDA employs a "structure-centric" approach to evaluating NCE exclusivity. *Id*. Under this approach, FDA evaluates the molecular structure of the single-molecule active ingredient, such as bonds (*i.e.*, covalent vs. noncovalent), to determine

which portion of the molecule constitutes its active moiety. *See, e.g., Actavis* 625 F.3d at 765-66. With respect to naturally derived mixtures, FDA must first determine which of the constituent molecule(s) of a mixture are consistently present and active, before applying a structure-centric approach and determining which portion of those particular molecule(s) is responsible for the physiological or pharmacological action of the drug substance. *See* FDA Letter at 6-7, 22.[9]

Contrary to Amarin's assertions, *see* Amarin Br. at 24, FDA is not adopting a "new policy" regarding eligibility for five-year NCE exclusivity for naturally derived mixtures, but rather has spelled out the agency's framework for evaluating the issue more clearly than it has in the past. *See* FDA Letter at 7-8.[10] FDA has clarified for applicants, and potential applicants, what criteria apply to eligibility for five-year NCE exclusivity (specifically, (1) characterization, (2) consistent presence, and (3) activity) when a drug product contains a naturally derived

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[9] FDA explained to Amarin that the structure-centric approach was inapplicable in the context of "determining which components of a naturally derived mixture potentially are its active moiety or moieties," FDA Letter at 22, but did not concede, as Amarin claims, either that applying the structure-centric approach "would compel the conclusion that a drug whose active ingredient is a naturally derived mixture must also have that mixture as its active moiety," Amarin Br. at 23, or that the agency "interprets the same statutory provisions and regulations differently for drugs whose active ingredient is a single molecule than for drugs whose active ingredient is a naturally derived mixture." *Id*. at 25. The interpretation is the same for both (*i.e.*, 21 C.F.R. § 314.108); it is the order of analyses that necessarily differs due to the different types of products at issue.

[10] Because FDA is not applying a new policy to Vascepa, Amarin's claim that FDA cannot retroactively apply this purported "new" policy to Vascepa, *see* Amarin Br. at 25-27, is irrelevant and FDA will not address it in this brief. FDA agrees with Amarin that on the same day FDA issued its decision regarding Vascepa, FDA announced that it was reconsidering its approach to exclusivity for fixed-combination drug products and would apply its new policy, once finalized, prospectively only. *See id*. at 2, 14. FDA noted that the approach proposed in that context was a change in interpretation from the interpretation that FDA had applied consistently since 1984 in the fixed-combination drug product context. The difference between the fixed combination drug product context and FDA's decision regarding NCE exclusivity for Vascepa illustrates the agency's awareness of the need to give regulated industry notice before adopting certain changes in interpretation. Where, as here, there is no change in interpretation or policy, there is no need to limit said policy to apply prospectively only.

mixture. *Id*. This clarification of FDA's interpretation provides more certainty to the regulated industry.

FDA's decision on Vascepa is largely consistent with the outcomes of, and/or bases for, relevant prior agency decisions on well-characterized mixtures. In the case of poorly characterized mixtures, where it is difficult to discern which molecule(s) in the mixture are potentially responsible for the physiological or pharmacological activity of the drug or where there is no precise way of identifying the molecules that are consistently present and active in the mixture, identifying the entire mixture as the active moiety may be appropriate. *See* FDA Letter at 7. For example, both pancrelipase and hyaluronidase are naturally derived mixtures comprised of enzymes. Neither FDA nor any applicant has, to date, been able to identify which molecule(s) are consistently present and active, and thus the agency considers the entire mixture to be the active moiety. *Id*. at 9-10 ("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."). Similarly, in the case of Condylox, FDA's exclusivity decision was "informed by the lack of sufficient characterization of the previously approved naturally derived mixtures." *Id* at 11.

In situations where the naturally derived mixture is sufficiently characterized, such as conjugated estrogens (Premarin and Cenestin) and menotropins (Pergonal, Repronex, and Menopur), FDA denied five-year NCE exclusivity to the later-approved applicants. *See* FDA Letter at 11-12, 15-16. Because the later-approved product contained at least one active moiety that was known to be consistently present and active in the naturally derived mixture that was the active ingredient of the earlier-approved product, the later product was not eligible for five-year NCE exclusivity. *See id*.

As noted previously, prior FDA decisions regarding five-year NCE exclusivity for several lung surfactant products cannot be reconciled with FDA's otherwise generally consistent interpretation. In the case of Infasurf, FDA determined that it was the same drug as a previously-approved drug, Survanta, for orphan drug purposes because although the products contained different active ingredients, they both contained the same active moiety. FDA Letter at 15. Despite concluding that Infasurf contained the same previously-approved active moiety as Survanta, FDA nonetheless determined that Infasurf was eligible for five-year NCE exclusivity. *Id*. FDA cannot explain this deviation because there is no satisfactory explanatory record in the agency's files. A similar result occurred in the case of Curosurf, another lung surfactant that contained the same active moiety as Survanta but was nonetheless determined to be eligible for five-year NCE exclusivity. *Id*. FDA notes that Infasurf was approved in 1998 and Curosurf in 1999 (Survanta in 1991), so there is little the agency can add at this time by way of explanation to the sparse records underlying those earlier five-year NCE exclusivity decisions. As stated in its letter, FDA has now concluded that those decisions were incorrect. *See* FDA Letter at 20. Amarin has not cited any authority, and indeed cannot, for the notion that FDA is bound by these two erroneous decisions, rather than the prior (numerous) decisions that are consistent with FDA's interpretation.[11] Amarin relies solely on the lung surfactant decisions that FDA now acknowledges were incorrect and fails to discuss the other agency decisions mentioned in FDA's letter, all of which serve to demonstrate that FDA's decision in Vascepa, based on an interpretation of "active ingredient" that easily passes muster under *Chevron* step two, was

[11] FDA's decision on a request for a patent term extension for Qutenza is not relevant to FDA's decision regarding Vascepa's eligibility for NCE exclusivity because FDA did not have to identify an active moiety in the case of Qutenza. *See* FDA Letter at 21. Indeed, Amarin can cite only to its own letter to FDA in a failed attempt to make the Qutenza decision appear relevant to this case. *See* Amarin Br. at 13.

proper.

3. FDA Correctly Determined that Vascepa Contains a Previously Approved Active Moiety

Based on all currently available scientific data, FDA concluded that EPA is an active moiety in Lovaza.[12] Specifically, FDA concluded that (1) the Lovaza mixture is sufficiently characterized such that EPA has been identified as a molecule in the mixture; (2) EPA must be consistently present in the Lovaza mixture to meet the product's labeling description as well as the relevant USP drug substance and drug product monographs; and (3) EPA meaningfully contributes to the pharmacological action of Lovaza (*i.e.*, lowering triglycerides), which conclusion is supported by the over two dozen scientific articles reviewed by the agency. *See* FDA Letter at 17. Indeed, Amarin does not dispute that EPA is the active moiety in Vascepa. FDA's well-reasoned conclusions that EPA contributes meaningfully to the pharmacological effect of the Lovaza mixture and is an active moiety in both Lovaza and Vascepa are entitled to deference and should be upheld by this Court.

CONCLUSION

For the foregoing reasons, judgment should be entered in favor of defendants.

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Respectfully submitted,

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/s/
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[12] Notably, Amarin does not challenge FDA's scientific determination regarding EPA in its brief, despite doing so in letters to FDA, s*ee*, *e.g.*, AR 00059, 00071, 74, so FDA is not addressing the issue in detail here.

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EXHIBIT A

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FEB 21 2014

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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

[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.

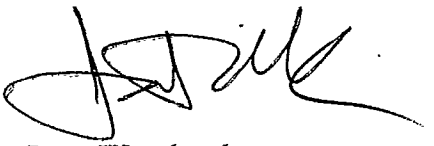
[109] ONY, Inc., Letter to James Bilstad, MD, at 2 (May 13, 1997), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20521_INFASURF%20INTRACHEAL%20SUSPENSION_corres_P1.pdf. As noted above, in that case, FDA rejected the assertion that the two drugs must be different because they had different 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

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

AMARIN PHARMACEUTICALS IRELAND LIMITED,	)	
Plaintiff,	)	
v.	)	No. 1:14-cv-00324-BAH
FOOD AND DRUG ADMINISTRATION, *et al.*,	)	
Defendants.	)	

ORDER GRANTING DEFENDANTS' MOTION FOR SUMMARY JUDGMENT AND DENYING PLAINTIFF'S MOTION FOR SUMMARY JUDGMENT

Having considered the parties' respective motions for summary judgment, the memoranda in support of and in opposition thereto, and the whole record in this case, the Court hereby **ORDERS** that

1. Defendants' motion for summary judgment is **GRANTED**;
2. Plaintiff's motion for summary judgment is **DENIED**;
3. This case is **DISMISSED** with prejudice.

Entered this ____ day of _____ 2014.

_____
HONORABLE BERYL A. HOWELL
United States District Judge