IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

AMARIN PHARMACEUTICALS IRELAND LIMITED, Plaintiff, v. FOOD AND DRUG ADMINISTRATION, MARGARET A. HAMBURG, M.D., Commissioner of Food and Drugs, and KATHLEEN SEBELIUS, Secretary of Health and Human Services, Defendants.	Civ. No. 1:14-cv-0324-BAH

MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF PLAINTIFF'S MOTION FOR SUMMARY JUDGMENT

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INTRODUCTION

Amarin challenges as unlawful, arbitrary, and capricious FDA's decision that Amarin's new drug, Vascepa® (icosapent ethyl) Capsules ("Vascepa"), is not entitled to a 5-year period of market exclusivity under the Federal Food, Drug, and Cosmetic Act ("FDCA").

Congress provided 5-year exclusivity for approved new drugs, "no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application." 21 U.S.C. §§ 355(c)(3)(E)(ii), 355(j)(5)(F)(ii). The purpose of that exclusivity is to incentivize pioneer drug manufacturers to fund research to demonstrate the safety and effectiveness of new active ingredients.

Vascepa's active ingredient is icosapent ethyl. At the time FDA approved Amarin's new drug application for Vascepa, the agency had never before approved an application for a drug with icosapent ethyl as its active ingredient. In meeting with FDA regarding its planned application, Amarin asked FDA to confirm that Vascepa would be eligible for 5-year exclusivity; FDA told Amarin that it would, but that Amarin would need to conduct and submit additional studies to support the application because Vascepa contained a new, never-before approved chemical entity.

Amarin did the additional studies required by FDA, but FDA took back its initial acknowledgment of eligibility for 5-year exclusivity. Instead, in refusing to adhere to the plain language of the statute, FDA read the statutory term "active ingredient" in the phrase "active ingredient (including any ester or salt of the active ingredient)" to mean not "active ingredient," but rather "active moiety." FDA then concluded that its prior approval of Lovaza—an undifferentiated mixture naturally derived from fish oils, whose "active ingredient" FDA concedes is the mixture as a whole—prevented 5-year exclusivity for Vascepa, because icosapent ethyl is one of the many constituents of Lovaza's undifferentiated mixture.

The agency's position should fail at *Chevron* Step One. FDA's attempt to replace the language that Congress used, "active ingredient," with a term that Congress did not, "active moiety," violates basic principles of statutory construction. In fact, the D.C. Circuit and this Court have previously rejected FDA's efforts to rewrite these same statutory provisions to reach the same result FDA seeks again here.

Even if "active ingredient" did not unambiguously mean "active ingredient," FDA's interpretation would be unreasonable at *Chevron* Step Two. Until Vascepa, FDA gave both the statute and its regulations a "structure-centric" interpretation, focusing on the chemical structure of each drug's active ingredient. If a drug's active ingredient was a naturally derived mixture, FDA would treat that mixture *as a whole* as the drug's single active ingredient and single active moiety. But here, FDA announced that it would no longer adhere to its structure-centric interpretation, instead introducing out of whole cloth a new framework unique to naturally derived mixtures that lacks any support in the statutory text or the justifications advanced by the agency for its regulations. FDA's new position also requires reading the same statutory and regulatory text to mean different things in different factual contexts, which is inherently unreasonable.

Finally, FDA acted arbitrarily in applying its new policy retroactively to Amarin. FDA failed entirely to consider the factors relevant to whether a new rule announced in an adjudication should apply retroactively. That failure is all the more egregious because on the same day, in a different proceeding, FDA announced another new position on 5-year exclusivity, yet determined *not* to apply that new policy retroactively. All of the relevant factors weigh against applying FDA's new policy to Amarin, which relied on FDA's prior policy—and indeed representations from FDA officials—in undertaking a more extensive development program for Vascepa than would have been required for a drug that is not eligible for 5-year exclusivity.

STATEMENT OF FACTS

A. Legal Background

1. Statutory Grant of 5-year Exclusivity

In the Hatch-Waxman Act, Congress amended the FDCA to authorize FDA approval of generic drugs based at least in part on safety or efficacy studies performed by pioneer drug manufacturers. *See* Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984). To ensure that generic competition did not nullify the incentives for pioneer manufacturers to invest in the research and development of new drugs, Congress enacted several "exclusivity provisions" that provide pioneer manufacturers with periods of marketing exclusivity (in addition to any applicable periods of patent protection) vis-à-vis generic or other manufacturers who would seek to rely on the results of the pioneer's research to support approval of an application for a competitor product. *See, e.g.*, 21 U.S.C. §§ 355(c)(3)(E), (j)(5)(F); *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 764 (D.C. Cir. 2010) ("Congress was concerned with providing incentives for innovation … ."); *Abbott Labs. v. Young*, 920 F.2d 984, 985 (D.C. Cir. 1990) ("Congress struck a balance between expediting generic drug applications and protecting the interests of the original drug manufacturers.").

Sections 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the Act grant 5-year exclusivity to "drug[s], no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under [Section 505(b)]." 21 U.S.C. §§ 355(c)(3)(E)(ii) & 355(j)(5)(F)(ii).[1]

[1] Esters and salts are chemical compounds formed by reactions between a "parent" substance and another chemical. A salt is formed when the hydrogen of an acid is replaced by a metal or its equivalent. *See Hawley's Condensed Chemical Dictionary* 1020 (Richard J. Lewis, Sr., rev., 12th ed. 1993). An ester typically is formed by the reaction of an acid with an alcohol, resulting in the replacement of the hydrogen of the acid by an organic radical. *See id.* at 473.

2. FDA's Proposed Regulations on 5-year Exclusivity

In 1989, FDA proposed regulations to implement the exclusivity provisions of the Hatch-Waxman Act. *See Abbreviated New Drug Application Regulations*, 54 Fed. Reg. 28,872 (July 10, 1989). In doing so, FDA introduced and defined several terms that do not appear in the statute, including "active moiety" and "new chemical entity," which FDA defined as follows:

> "Active moiety" means the 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.
>
> "New chemical entity" means a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) … .

Id. at 28,930 (codified at 21 C.F.R. § 314.108(a)).[2]

FDA stated that it "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." *Id.* at 28,897. Thus, FDA's proposed regulation provided that a "drug product" will be eligible for 5-year exclusivity only if it "contains a new chemical entity." *Id.* at 28,930 (codified at 21 C.F.R. § 314.108(b)(2)). As a result, 5-year exclusivity is often called "new chemical entity (NCE) exclusivity."

[2] The proposed regulations defined "[d]rug product" to mean "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." *Id.* at 28,915 (codified at 21 C.F.R. § 314.3(b)). The proposed regulations defined "[d]rug substance" to mean "an 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 used in the synthesis of such ingredient." *Id.*

3. Abbott Laboratories v. Young

In *Abbott Laboratories v. Young*, 920 F.2d 984 (D.C. Cir. 1990) ("*Abbott II*"), the D.C. Circuit considered "the meaning of the phrase 'active ingredient (including any ester or salt of the active ingredient).'" *Id.* at 985.

Abbott II concerned whether the drug Depakote was eligible for 10-year exclusivity[3] in light of FDA's prior approval of Depakene. *See Abbott II*, 920 F.2d at 986; *see also Abbott Labs. v. Young*, 691 F. Supp. 462, 463–64 (D.D.C. 1988) ("*Abbott I*"). In Depakene, valproic acid was both the "active ingredient" and the "active moiety." *Abbott II*, 920 F.2d at 986. The later-approved drug, Depakote, had the same "active moiety" (valproic acid) but a different "active ingredient" (divalproex sodium, a salt of valproic acid). *See id.* at 986.

FDA denied Abbott Laboratories' request for 10-year exclusivity based on the agency's interpretation of the entire phrase "active ingredient (including any ester or salt of the active ingredient)" to refer to the "active moiety" of the later-approved drug. FDA specifically interpreted Congress's use of the word "including" to indicate that the parenthetical portion of the phrase was not an exhaustive list of the additional substances that were comprehended by the phrase as a whole, but rather a list of examples of the types of minor variations in chemical structure that Congress did not intend to reward with exclusivity. *See id.* at 987–88. Accordingly, FDA concluded that because Depakote had the same "active moiety" as the previously approved Depakene, Depakote was not entitled to 10-year exclusivity.

[3] *Abbott* dealt with an exclusivity provision, then codified at 21 U.S.C. § 355(j)(4)(D)(i) and now codified at 21 U.S.C. § 355(j)(5)(F)(i), that governs drugs approved between January 1, 1982, and September 24, 1984. *See Abbott II*, 920 F.2d at 985–86. Other than substituting 10-year for 5-year exclusivity, the relevant language is identical to that in current 21 U.S.C. §§ 355(c)(3)(E)(ii) and 355(j)(5)(F)(ii), which govern this case. *See Actavis*, 625 F.3d at 764 n.7.

A unanimous panel of the D.C. Circuit rejected FDA's interpretation of the phrase "active ingredient (including any ester or salt of the active ingredient)" to mean "active moiety." *See id.* at 988 ("We cannot agree with the government's unconvincing attempts to employ the 'including' clause to cover all possible permutations of active ingredient. … It is simply not plausible to read 'including any salt or ester' as merely illustrative, to mean including *any* form that eventually produces the same active moiety."); *id.* at 992 (Edwards, J., dissenting) ("I agree with the ma-majority that the FDA's reading of the statute, which turns entirely on a purported ambiguity or implied delegation in the word 'including,' is implausible and must be rejected.").

The majority, however, ordered the matter remanded to FDA because "the language [of the exclusivity provisions] is ambiguous as it relates to the issue before us." *Abbott II*, 920 F.2d at 987. That issue was whether "the statute precludes the FDA from treating the two chemicals as the same active ingredient because of the sequence of applications." *Id.* at 988–89. The ambiguity existed because:

> The parenthetical phrase ("including any ester or salt of the active ingredient") can refer to *either* the active ingredient of the original approved drug *or* to 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. In other words, the definition of an active ingredient as including both the active ingredient and an ester or salt of *the* active ingredient can refer *both* to the active ingredient in the earlier and the later drug application, which would be the proper reading if Congress had in mind, as it seems to have had, that an active ingredient was to be regarded for purpose of this portion of the statute as equivalent to an ester or salt of itself.

Id. at 987–88.

The majority also noted that between FDA's denial of Abbott's exclusivity request and the D.C. Circuit's decision, FDA had suggested the possibility of yet another interpretation of the statute. Under that interpretation, "the phrase 'active ingredient' itself, even without the parenthetical, could be interpreted to include active moiety." *Id.* at 987. The *Abbott II* majority expressly

declined to consider this interpretation "because the agency did not in its decision on Abbott's application employ this theory." *Id.*

Judge Edwards, however, found that FDA's alternate interpretation of "active ingredient" to mean "active moiety" was also inconsistent with the plain language of the statute, because "'[a]ctive ingredient' is an unambiguous term of art and it does not include 'active moiety.' The agency's suggestion to the contrary flies in the face of the clear terms of the Act." *Id.* at 995 (Edwards, J., dissenting); *see also id.* at 991 ("FDA ignored the literal terms of the statute (focusing on 'active moiety' in place of 'active ingredient'). … The agency concedes that 'active ingredient' and 'active moiety' are not the same; and the agency can point to no statutory provision supporting the gloss that it has placed on [the statute].").

4. FDA's Final Regulations on 5-year Exclusivity

After the D.C. Circuit's decision in *Abbott II*, FDA promulgated final regulations to implement the exclusivity provisions of the Hatch-Waxman Act. *See Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions*, 59 Fed. Reg. 50,338 (Oct. 3, 1994).

FDA finalized its proposed 5-year exclusivity regulation notwithstanding its recognition that in *Abbott II* "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." *Id.* at 50,358. FDA asserted that, in light of *Abbott II*, "[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.* FDA thus adopted the very interpretation of the statute that Judge Edwards found impermissible and directly contrary to the statutory language.

FDA has explained that its "regulation … relies on a relatively straightforward analysis of the chemical structure of a drug" and is "based upon certain reasonable assumptions regarding the activity of different types of molecules." AR000698. Under the agency's structure-based in-

terpretation of the statute, a drug's "active ingredient" is the drug substance prior to its introduction into the human body. *See Abbott II*, 920 F.2d at 986; 54 Fed. Reg. at 28,881. The "active moiety" is identified by disregarding portions of the active ingredient (such as those that cause the active ingredient to be an ester or salt) that are generally separated from the drug substance before or immediately after a drug is absorbed into circulation. *See* AR000704 (quoting Citizen Petition Response, Docket No. 1987P-0339, at 12 n.5 (July 26, 1989)).

Until Vascepa, FDA has consistently maintained that the regulation codifies this structure-based interpretation of the 5-year exclusivity provisions. *See, e.g.*, Brief for the Federal Appellees, *Actavis Elizabeth LLC v. Sebelius*, 625 F.3d 760 (D.C. Cir. 2010) (No. 10-5066), 2010 WL 3207405, at 8 ("FDA *Actavis* Brief") ("FDA has consistently interpreted and applied this regulation to focus only on the chemical structure of any modifications of a previously approved molecule … ."); AR000696 ("FDA's interpretation of the NCE exclusivity provisions has consistently focused on the specific chemical structure of the drug under consideration.").

B. Factual Background

1. Lovaza

On November 10, 2004, FDA approved Lovaza® (omega-3-acid ethyl esters) Capsules ("Lovaza") for use as an adjunct to diet to reduce triglyceride levels in adult patients with severe hypertriglyceridemia. *See* AR000002–3; AR000144.

Lovaza is a "complex mixture," AR000087, that "contain[s] … seven distinct omega-3 fatty acid ethyl esters obtained from fish oil," AR000002, along with "omega-6 fatty acid ethyl esters and other components, some of which have not been characterized," FDA, Citizen Petition Response, Docket No. FDA-2013-P-0148, at 2 (Feb. 21, 2014) ("Lovaza Citizen Petition Response"), *available at* http://www.regulations.gov/#!documentDetail;D=FDA-2013-P-0148-0006; *see also* AR000087. The seven omega-3 esters are the ethyl esters of eicosapentaenoic acid

(EPA), docosahexaenoic acid (DHA), docosapentaenoic acid, stearidonic acid, heneicosapentaenoic acid, eicosatetraenoic acid, and alpha-linolenic acid. *See* AR000054.[4] Lovaza also includes α-tocopherol (in a carrier of soybean oil), gelatin, glycerol, and purified water. AR000148.

FDA determined that the single "active ingredient" of Lovaza is the mixture *as a whole*. AR000007 ("In the case of Lovaza, both FDA and the U.S. Pharmacopeial Convention (USP) have identified the product as having a single active ingredient. … [T]hat active ingredient (the Lovaza mixture) is a naturally derived mixture … ."); *see also* AR000019 ("[T]he Agency agrees that the active ingredient of Lovaza is the Lovaza mixture as a whole … ."); Lovaza Citizen Petition Response at 3 n.4 ("[T]he Lovaza labeling and relevant files in the drug's NDA establish that FDA defined the drug's active ingredient as the entire mixture at the time of approval"); *id.* at 1 ("The clinical studies that supported the approval of Lovaza tested the fish oil *as a whole* to establish the safety and effectiveness of the product." (emphasis added)).

FDA did not purport to identify any "active moiety" of Lovaza, other than the undifferentiated single-active-ingredient mixture as a whole, until the agency issued its decision denying Vascepa's eligibility for 5-year exclusivity.

2. Amarin and Vascepa

Amarin is a biopharmaceutical company focused on the commercialization and development of therapeutics to improve cardiovascular health. On July 26, 2012, FDA approved Amarin's NDA for Vascepa® (icosapent ethyl) Capsules—Amarin's first product to have FDA approval. AR000001. Vascepa is approved for use as an adjunct to diet to reduce triglyceride levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia. AR000003; AR000097.

[4] The amount of each ethyl ester varies within specified limits from capsule to capsule. *See* AR000002; AR000758.

The "active ingredient" in Vascepa is icosapent ethyl. AR000001; AR000016. Icosapent ethyl is a single molecule; it is the ethyl ester of eicosapentaenoic acid (EPA), one of at least seven omega-3 fatty acids that are among the many constituents of Lovaza. Because FDA "exclud[es] those appended portions of the molecule that cause the drug to be an ester" when identifying a drug's "active moiety," 21 C.F.R. § 314.108(a), FDA considers Vascepa's active moiety to be eicosapentaenoic acid (EPA). *See* AR000001–2.

Prior to submitting its NDA for Vascepa and developing the clinical research program to support that application, Amarin consulted with FDA about the studies that would be needed to obtain approval. On July 14, 2008, representatives of Amarin and FDA attended a pre-investigational new drug application meeting. FDA's minutes state that FDA informed Amarin that Vascepa would be entitled to 5-year exclusivity. *See* AR001044. In addition, FDA instructed Amarin that its NDA would be "required" to report the results of carcinogenicity studies in two rodent species, AR001041, AR001042, because "it is generally expected that a carcinogenicity study be conducted in two rodent species to support the marketing approval *of a new chemical entity* for a chronic use indication." AR001042 (emphasis added).

Nearly a year later, on May 20, 2009, an FDA official e-mailed Amarin to state that FDA's initial representation "was not correct." AR001039. The e-mail stated, "Since [ethyl EPA] is a component of an approved product (Lovaza), it would not qualify as a [new chemical entity]." AR001039. Amarin immediately disputed FDA's new position and inquired what procedures were available for asking FDA to reconsider. AR001039. The FDA official then replied that "nothing by e-mail is official. so if you don't want an official answer, then feel free to e-mail." AR001038. The next day, Amarin sent a letter to FDA requesting the agency's "official position." AR001046–1049.

On September 21, 2009, FDA responded that the agency "does not make final exclusivity determinations … until approval of a new drug application (NDA). As described in 21 C.F.R. § 314.108, an applicant should include in its NDA a description of the exclusivity to which the applicant believes it is entitled. FDA will consider Amarin's assertions regarding exclusivity for its proposed product in the review of the New Drug Application." AR0010150.

Amarin submitted its new drug application in September 2011. *See* AR001032–1037. In accordance with 21 C.F.R. § 314.50(j), the NDA included a statement that Amarin was claiming 5-year exclusivity. *See* AR001032–1037. Among other things, the NDA explained that Amarin had completed the additional studies that FDA indicated were necessary for a new chemical entity eligible for 5-year exclusivity. *See* AR001034.

Amarin and FDA subsequently exchanged several letters and had one meeting about Vascepa's eligibility for 5-year exclusivity. *See* AR000068–96; AR001029–1031. Amarin explained that Vascepa's eligibility for 5-year exclusivity would be consistent with the applicable authorities and FDA precedent and with the policies underlying the Hatch-Waxman Act.

When FDA approved Vascepa on July 26, 2012, the agency did not make a determination regarding the drug's eligibility for 5-year exclusivity. Instead, FDA informed Amarin that the agency had not yet made a final decision on Vascepa's exclusivity. *See* AR001029–1031.

3. FDA's Departure from Past Precedent, Announcement of a New Policy for Naturally Derived Mixtures, and Denial of Amarin's Request for 5-year Exclusivity for Vascepa

Eighteen months later, on February 21, 2014, FDA issued a letter in which the agency concluded 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." AR000001; *see* AR000001–24.

In its letter, FDA announced for the first time a new "framework" that, according to the agency, "provides the best approach for identifying the active moiety or moieties" of naturally derived mixtures. AR000006. Under this never-before announced framework:

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

AR000007–8 (footnotes omitted). FDA acknowledged that this framework was not an application of the structure-based interpretation of 5-year exclusivity that FDA has applied previously. *See* AR000021–22.

FDA also acknowledged that its new framework was inconsistent with the results reached in prior 5-year exclusivity decisions involving Survanta, Infasurf, and Curosurf. *See* AR000020 ("[T]he 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.").

All three of these decisions involved mixtures approved as lung surfactants after FDA approved another lung surfactant mixture, Exosurf, in 1990. Each drug had a different mixture as its active ingredient—Survanta (beractant), Infasurf (calfactant), and Curosurf (poractant alfa)—but each contained at least one constituent also found in a previously approved drug.

Addressing Survanta and Infasurf, Dr. John Jenkins, the then-Director of FDA's Division of Pulmonary Drug Products who has now served as the Director of FDA's Office of New Drugs for more than a decade, determined that a drug whose active ingredient is a naturally derived mixture should also have the mixture itself treated as its active moiety:

> Due to the complex nature of the physical interaction of the components that results in the pharmacological activity of naturally derived surfactants, the Division considers the entire mixture to be the active moiety.

AR000071 (citing Memorandum: Addendum to April 22, 1997, memorandum regarding the request by [FDA's Office of New Drugs] for dispute resolution under 21 CFR 314.103 related to NDA 20-521 (July 2, 1997) at 18). In other words, when a drug's active ingredient is a naturally derived mixture as a whole, FDA deemed the entire mixture to be the drug's active moiety as well. Thus, FDA determined that the prior approval of a mixture containing a constituent in a later-approved mixture would not preclude 5-year exclusivity for the later-approved drug. This determination is the case even under an "active moiety" interpretation of the statute because the active moiety is the entire mixture and the mixtures are different.

FDA's 2009 decision recognizing 5-year exclusivity for Qutenza likewise reflects the agency's established rule that a drug whose active ingredient is a naturally derived mixture also has that mixture as its active moiety. Qutenza has as its single active ingredient capsaicin, "a synthetic equivalent of the naturally occurring compound found in chili peppers." AR000094. FDA recognized that Qutenza was eligible for 5-year exclusivity despite the agency's prior approval of Relevo Liniment, a drug product containing capsicum—a mixture naturally derived from cayenne peppers—which FDA has determined includes capsaicin as a constituent. AR0000095. The Qutenza decision thus also confirms that FDA's decision that Vascepa is ineligible for 5-year exclusivity marks an abrupt break from agency precedent.

FDA declined to address how the Qutenza precedent bears on Vascepa's eligibility for 5-year exclusivity. *See* AR000021. Instead, FDA stated that its patent term exclusivity decision for Qutenza did "not address the identity of the active moiety in Qutenza." AR000021. But regardless whether FDA identified Qutenza's active moiety in evaluating the drug's eligibility for a patent term extension, FDA *must* (under FDA's interpretation of the statute) have identified the active moieties of both Qutenza and Relevo in evaluating Qutenza's eligibility for 5-year exclusivity. Indeed, FDA does not dispute that FDA found the active moiety of each drug to be the same as its active ingredient. AR000021.

4. FDA's Failure To Consider Whether To Apply the Agency's New Approach Retroactively to Amarin and Vascepa

Although, as described above, FDA announced a new approach to identifying the active moieties of naturally derived mixtures in its denial of 5-year exclusivity to Vascepa, the agency did not analyze or address whether or why it would be appropriate to apply its new framework retroactively to the Vascepa application. Yet, *on the very same day* that FDA denied 5-year exclusivity to Vascepa, FDA announced that the agency intended to reconsider its approach to 5-year exclusivity for fixed-combination drugs, but that it would apply that new policy only *prospectively*. *See* FDA, Citizen Petition Response, Docket Nos. FDA-2013-P-0058, FDA-2013-P-0119 & FDA-2013-P-0471, at 17 (Feb. 21, 2014) ("Fixed-Combination Drug Citizen Petition Response"), *available at* http://www.regulations.gov/#!documentDetail;D=FDA-2013-P-0058-0006 ("At the time of approval of the drug products at issue here …, our existing interpretation of the relevant statutory and regulatory provisions was in effect. We have decided not to recognize 5-year exclusivity based on our new interpretation of these provisions, which we had not announced prior to the approval of these products.").

Amarin timely filed suit on February 27, 2014. *See* ECF No. 1.

STANDARD OF REVIEW

In cases arising under the APA, "[s]ummary judgment … serves as the mechanism for deciding, as a matter of law, whether the agency action is supported by the administrative record and otherwise consistent with the APA standard of review." *Sierra Club v. Mainella*, 459 F. Supp. 2d 76, 90 (D.D.C. 2006). In relevant part, the APA requires courts to "hold unlawful and set aside agency action, findings, and conclusions found to be," 5 U.S.C. § 706(2), "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law," *id.* § 706(2)(A).

This Court reviews FDA's interpretation of the governing statute under the two-step framework of *Chevron, U.S.A., Inc. v. NRDC*, 467 U.S. 837 (1984). The Court "examines the statute *de novo*," *Int'l Union, United Mine Workers v. Mine Safety & Health Admin.*, 626 F.3d 84, 90 (D.C. Cir. 2010), and "employ[s] traditional tools of statutory construction" to determine whether Congress unambiguously expressed its intent on "the precise question at issue," *Chevron*, 467 U.S. at 843 & n.9. If the statute is ambiguous, the Court then considers "whether the agency's answer is based on a permissible construction of the statute." *Id.* at 843.

The analysis at *Chevron* Step Two may overlap with the arbitrary-and-capricious inquiry. *See, e.g.*, *Arent v. Shalala*, 70 F.3d 610, 616 n.6 (D.C. Cir. 1995). This standard "requires that agency decisionmaking be both reasonable and reasonably explained." *Indiana Boxcar Corp. v. R.R. Retirement Bd.*, 712 F.3d 590, 591 (D.C. Cir. 2013). Agency action is arbitrary and capricious when the agency, *inter alia*, does not consider the relevant factors or entirely fails to consider an important part of the problem. *See Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43–44 (1983). In addition, "[r]easoned decision making … necessarily requires the agency to acknowledge and provide an adequate explanation for its departure from established precedent." *Dillmon v. NTSB*, 588 F.3d 1085, 1089–90 (D.C. Cir. 2009).

ARGUMENT

I. FDA's Refusal To Recognize 5-Year Exclusivity For Vascepa Is Contrary To Law.

By its terms, the Hatch-Waxman Act extends 5-year exclusivity to "a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under [Section 505(b)]." 21 U.S.C. §§ 355(c)(3)(E)(ii), 355(j)(5)(F)(ii). Vascepa is entitled to 5-year exclusivity under the express terms of the statute.

A. FDA's interpretation of "active ingredient" not to mean "active ingredient" fails at *Chevron* Step One.

FDA concedes that Vascepa and Lovaza do not have the same "active ingredient." The active ingredient in Vascepa is icosapent ethyl; the active ingredient in Lovaza is an undifferentiated, complex mixture. *Compare* AR000016 (describing Vascepa "[a]s a product that contains icosapent ethyl as its active ingredient") *with* AR000019 ("[T]he Agency agrees that the active ingredient of Lovaza is the Lovaza mixture as a whole … .").

Icosapent ethyl is not an ester or salt of the Lovaza mixture, and the Lovaza mixture is not an ester or salt of icosapent ethyl. This is undisputed. Thus, Vascepa is "a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under [Section 505(b)]," 21 U.S.C. §§ 355(c)(3)(E)(ii), 355(j)(5)(F)(ii), and has 5-year exclusivity under the plain terms of the statute. *See Abbott II*, 920 F.2d at 987–88 ("The parenthetical phrase ('including any ester or salt of the active ingredient') can refer to *either* the active ingredient of the original approved drug *or* to the active ingredient in the new drug … .").

FDA does not contest any of this science. Instead, FDA contends that when Congress said "active ingredient," Congress actually meant "active moiety." That position is contrary to the plain and unambiguous language of the Act, and therefore fails at *Chevron* Step One.

1. FDA cannot rewrite "active ingredient" to mean "active moiety."

Statutory interpretation "begins with the plain language of the statute." *United States v. Braxtonbrown-Smith*, 278 F.3d 1348, 1352 (D.C. Cir. 2002). The Supreme Court has "stated time and again that courts must presume that a legislature says in a statute what it means and means in a statute what it says there." *Conn. Nat'l Bank v. Germain*, 503 U.S. 249, 253–54 (1992). In this case, the language of the statute could hardly be plainer: "active ingredient" means "active ingredient."

As Judge Edwards correctly explained in *Abbott II*, FDA's "focus[] on 'active moiety' in place of 'active ingredient' … ignore[s] the literal terms of the statute." 920 F.2d at 991 (Edwards, J., dissenting). "'Active ingredient' is an unambiguous term of art and does not include 'active moiety.' The agency's suggestion to the contrary flies in the face of the clear terms of the [Hatch-Waxman] Act." *Id.* at 995; *see also id.* at 991 ("The agency concedes that 'active ingredient' and 'active moiety' are not the same; and the agency can point to no statutory provision supporting the gloss that it has placed on [the statute].").

Judge Edwards concluded that "active ingredient" does not mean "active moiety" because the term "active ingredient" already had a "plain and established meaning[] in scientific and regulatory parlance" when Congress passed the Hatch-Waxman Act. *Id.* at 992. Had Congress meant "active moiety" instead of "active ingredient," it would have said so. *See also* page 20 *infra* (explaining that other provisions of the Hatch-Waxman Act use the term "therapeutic ingredient" to refer to "active moiety").

Rather than faithfully apply the statute as written, FDA persists in seeking to rewrite it. FDA first attempted to interpret the phrase "active ingredient (including any salt or ester of the active ingredient)" to mean "active moiety." After the D.C. Circuit "reject[ed] the government's interpretation as *linguistically* infeasible," *Abbott II*, 920 F.2d at 988 (majority op.), FDA

switched gears and concluded that the bare term "active ingredient" itself means "active moiety," 59 Fed. Reg. at 50,358.[5] But this construction, too, contradicts the plain language of the statute.

2. FDA's position violates established principles of statutory construction.

"[T]o defeat application of a statute's plain meaning, [an agency] must 'show either that, as a matter of historical fact, Congress did not mean what it appears to have said, or that, as a matter of logic and statutory structure, it almost surely could not have meant it.'" *Performance Coal Co. v. Fed. Mine Safety & Health Review Comm'n*, 642 F.3d 234, 238 (D.C. Cir. 2011) (quoting *Engine Mfrs. Ass'n v. EPA*, 88 F.3d 1075, 1089 (D.C. Cir. 1996)). FDA cannot make that showing here. The statutory context confirms in multiple respects that when Congress said "active ingredient," it meant "active ingredient," not "active moiety."

First, the 5-year exclusivity provisions refer to drugs "no active ingredient … of which has been approved" in a previous application. Congress knew that, when FDA evaluates a proposed new drug for safety and efficacy, the agency analyzes the drug's "active ingredient," not its "active moiety." In approving Lovaza, FDA identified the drug's active ingredient as the entire mixture at the time of approval, but did not purport to identify the drug's active moiety until ten years later in connection with its exclusivity determination for Vascepa. The term "active ingredient" in the 5-year exclusivity provisions cannot plausibly mean "active moiety" when FDA need not identify, let alone "approve," a drug's active moiety when it approves an NDA.

[5] In *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760 (D.C. Cir. 2010), the D.C. Circuit made reference to FDA's "active moiety" definition. But the "precise question" at issue in that case was whether the 5-year exclusivity statute "obligates the FDA to identify the particular drug molecule that reaches the 'site' of the drug's action … regardless of the form of the molecule before it enters the body," *id.* at 764, which is entirely different than the question presented here. Indeed, in *Actavis*, FDA defended, and the D.C. Circuit upheld, the structure-centric interpretation of the statute that FDA abandons here.

Second, the term "active ingredient" appears not only in the Hatch-Waxman Act's exclusivity provisions, 21 U.S.C. §§ 355(c)(3)(E), 355(j)(5)(F), but also throughout the provisions governing FDA review and approval of abbreviated new drug applications ("ANDAs"). *See, e.g.*, 21 U.S.C. § 355(j)(2)(A)(ii) (requiring an ANDA filer "to show that the active ingredient of the new drug is the same as that of the listed drug"); *id.* § 355(j)(2)(C) (providing that "[i]f a person wants to submit an abbreviated application for a new drug which has a different active ingredient or whose route of administration, dosage form, or strength differ from that of a listed drug, such person shall submit a petition to the Secretary seeking permission to file such an application"); *id.* §§ 355(j)(4)(C), (E), (F) (requiring denial of an ANDA if, *inter alia*, "information submitted with the application is insufficient to show that the active ingredient is the same as that of the listed drug"). In applying those provisions, FDA has interpreted the term "active ingredient" to mean "active ingredient," not "active moiety." Thus, for example, in determining whether the drug proposed in an ANDA contains the same "active ingredient" as the prior-approved drug, FDA does not first isolate the "active moiety" by "excluding those appended portions of the molecule that cause the drug to be an ester, salt …, or other noncovalent derivative … of the molecule," 21 C.F.R. § 314.108(a). *See, e.g.*, 54 Fed. Reg. at 28,881 ("The agency interprets the requirement that the active ingredients in the proposed drug product be the same as those of the listed drug to mean that the active ingredients must be identical. For example, if the proposed drug product contained a different salt or ester of the active ingredient in the listed drug, the active ingredient in the proposed drug product would not be identical to the active ingredient in the listed drug, and could not, therefore, be approved in an ANDA. Active ingredient in this context means the active ingredient in the finished drug product prior to its administration.").

Third, the text of the act confirms that Congress knew the distinction between "active ingredient" and "active moiety." Section 505(j)(8) defines "bioavailability" and "bioequivalent," and, in doing so, refers to "active ingredient *or* therapeutic ingredient." 21 U.S.C. §§ 355(j)(8)(A)(i), 355(j)(8)(B) (emphasis added).[6] Notably, FDA considers "therapeutic ingredient" to be synonymous with "active moiety." 54 Fed. Reg. at 28,882. But Congress used two *different* terms, and reading them both to mean the same thing would render one superfluous. *See, e.g.*, *Indep. Ins. Agents of Am., Inc. v. Hawke*, 211 F.3d 638, 644–45 (D.C. Cir. 2000) (refusing to give *Chevron* deference to an agency interpretation that violated the surplusage canon); *Qi-Zhuo v. Meissner*, 70 F.3d 136, 139 (D.C. Cir. 1995) ("[A]ll words in a statute are to be assigned meaning, and that nothing therein is to be construed as surplusage.").

Hence, under well-established principles of construction, if Congress had meant 5-year exclusivity to turn on a drug's "active moiety" instead of on its "active ingredient," Congress would have used the term "therapeutic ingredient" just as it did in Section 505(j). *See Bates v. United States*, 522 U.S. 23, 29–30 (1997) ("'[W]here Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion.'" (quoting *Russello v. United States*, 464 U.S. 16, 23 (1983)).

Put differently, FDA's interpretation is contrary to the statute because the agency seeks to interpret the same term—"active ingredient"—to mean different things in different paragraphs of the *same subsection* of the Act. That interpretation conflicts with "[t]he normal rule of statutory construction … that 'identical words used in different parts of the same act are intended to have

[6] *See* 21 U.S.C. § 355(j)(8)(A)(i) ("The term 'bioavailability' means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.").

the same meaning,'" *Sorenson v. Sec'y of Treasury*, 475 U.S. 851, 860 (1986), a presumption that is only enhanced when those words appear in the same subsection of the statute, *see, e.g.*, *Japan Whaling Ass'n v. Am. Cetacean Soc'y*, 478 U.S. 221, 238–39 (1986) ("Without strong evidence to the contrary, we doubt that Congress intended the same phrase to have significantly different meanings in two adjoining paragraphs of the same subsection.").

The clash between FDA's interpretation of "active ingredient" in the 5-year exclusivity provisions and its interpretation of the same words in Section 505(j)(2) was the main reason why the District Court in *Abbott* rejected FDA's position that "active ingredient" means "active moiety." *See Abbott I*, 691 F. Supp. at 469–71; *id.* at 470 ("In the absence of an express congressional statement or other evidence of congressional purpose, the Agency's diametrically conflicting interpretations of 'active ingredient' cannot be accepted.").

Moreover, as the *Abbott II* majority explained, the purposes of the relevant provisions are not different. In both the provisions of Section 505(j) governing review and approval of ANDAs and the provisions of Section 505(j) governing 5-year exclusivity, "Congress was concerned with defining the chemical entity on which a [Section 505(j)] (generic drug) application is based." *Abbott II*, 920 F.2d at 988; *see also Abbott I*, 691 F. Supp. at 470 ("Rather than being different, their purposes are complimentary."). There is thus no "strong evidence" in the statute, *Japan Whaling*, 478 U.S. at 238–39, to support FDA's different treatment of the same term of art when it appears multiple times in the same subsection. *Abbott II*, 920 F.2d at 991 (Edwards, J., dissenting) ("The agency concedes that 'active ingredient' and 'active moiety' are not the same; and the agency can point to no statutory provision supporting the gloss that it has [applied].").

In sum, FDA's position violates the plain language of the statute and cardinal rules of statutory construction and should be set aside under *Chevron* Step One as "contrary to law."

B. FDA's interpretation also fails at *Chevron* Step Two.

Even if "active ingredient" somehow did not unambiguously mean "active ingredient," FDA's application of an "active ingredient"/"active moiety" distinction to naturally derived mixtures stretches beyond the bounds of reasonableness.

FDA consistently has viewed the 5-year exclusivity statute and regulations as adopting a "structure-based" or "structure-centric" approach to exclusivity. *See* AR000696 ("FDA's interpretation of the NCE exclusivity provisions has consistently focused on the specific chemical structure of the drug under consideration."); AR000698 ("The regulation promulgated by FDA relies on a relatively straightforward analysis of the chemical structure of the drug when analyzing eligibility for exclusivity."); AR000083.

Under that interpretive approach to 5-year exclusivity, FDA first identifies the "drug substance," 21 C.F.R. § 314.108(a)—a term synonymous with "active ingredient," *id.* § 314.3(b). Then, to identify the "active moiety," FDA "exclude[s]" from the drug substance or active ingredient "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)." *Id.* § 314.108(a).

FDA's 5-year exclusivity determination for Vyvanse, which the D.C. Circuit upheld in *Actavis*, 625 F.3d at 766, illustrates this structure-centric approach. To identify the drug's "active moiety," FDA began by identifying its "active ingredient" as lisdexamfetamine dimesylate. AR000698. Next, "because lisdexamfetamine dimesylate is a salt," FDA excluded the appended portions of the molecule that caused the active ingredient to be a salt. AR000698. FDA then considered whether the resulting molecule, lisdexamfetamine, was an ester or other non-covalent derivative of another molecule. AR000698. Answering that question in the negative, FDA determined that "lisdexamfetamine is the active moiety in Vyvanse." AR000698.

Amarin demonstrated to FDA that applying the agency's structure-centric approach to naturally derived mixtures would lead to the conclusion that the active ingredient of any naturally derived mixture is also its active moiety. *See* AR000083–86; AR000091–92; AR000095–96. Unlike a molecule, a mixture is not a substance of fixed structure. A mixture cannot be described as a salt, ester, or other non-covalent derivative of another molecule, and there are no "appended portions of the molecule" to "exclud[e]" when identifying the "active moiety" of an active ingredient that is a mixture. *See* AR000084.

FDA did not dispute that its structure-centric interpretation of the statute's 5-year exclusivity provisions would compel the conclusion that a drug whose active ingredient is a naturally derived mixture must also have that mixture as its active moiety. *See* AR000021–22. Rather, it announced a new position—that "the structure-centric approach is not applicable when determining which components of a naturally derived mixture potentially are its active moiety or moieties," AR000022, and that FDA would instead attempt to identify which "molecule or molecules … 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." AR000008. This is not a reasonable construction of the Act for several reasons.

First, unlike FDA's structure-centric approach to drugs whose active ingredient is a single molecule, FDA's new policy for naturally derived mixtures is completely untethered to the statute's text. The structure-centric approach produces results largely consistent with the statutory language, which instructs FDA to identify the "active ingredient" and then exclude "ester[s] or salt[s]." *See Abbott II*, 920 F.2d at 988 (noting that Congress seems to have concluded "that an active ingredient was to be regarded for purpose of this portion of the statute as equivalent to an ester or salt of itself"). FDA has now added a step with no foundation in the statute: After identi-

fying the "active ingredient," but before excluding "ester[s] or salt[s]," FDA considers which constituent(s) of the active ingredient "meaningful[ly] contribut[e]" to the physiological or pharmacological action. The statutory text cannot reasonably bear that interpretation.

Second, FDA's new approach to identifying the active moieties of naturally derived mixtures undermines the very policies that FDA has previously invoked. In defending the structure-centric approach, FDA argued to this Court that the 5-year exclusivity statute does not "require the agency to engage in difficult and sometimes even impossible decisionmaking … about which molecule provides the therapeutic effect of a given drug." Fed.l Defs.' Mem. in Supp. of Mot. to Dismiss or for SJ, *Actavis Elizabeth LLC v. Sebelius*, No. 109CV00362 (D.D.C.), 2009 WL 5899656 (Dec. 18, 2009). Such an interpretation, FDA contended, would "result[] in inconsistency and uncertainty for the regulated industry." *Id.*; *see* AR000706 ("Post approval research resulting in new understanding of the activity of the drug could give rise to requests to change the type of exclusivity granted to a given drug, with resulting uncertainty in the industry.").

Despite having prevailed upon that justification in a prior case, FDA would now adopt a new policy in which sometimes a prior-approved undifferentiated mixture will prohibit 5-year exclusivity and sometimes it will not. AR000008. Notably, FDA does not explain the details of the methodology proposed to apply going forward, other than to say that it will include a retrospective review by the agency of literature from both before and, remarkably, after FDA approved the original drug. *See* AR000002–3, 8; AR000757–768. This is a recipe for "difficult and sometimes even impossible decisionmaking," and "inconsistency and uncertainty for regulated industry," that would "give rise to requests to change the type of exclusivity granted" as understanding of a drug's activity evolves over time, each contrary to the incentive and certainty that Congress intended 5-year exclusivity to provide.

Third, FDA concedes that it now 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. *See* AR000021–22 ("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 presented here, and therefore, the structure-centric approach is not applicable … ."). But neither the Act nor the regulations contain any distinction to support this fluctuating interpretation. Even if FDA could permissibly interpret the words "active ingredient" to mean different things in *different* statutory provisions, "that is worlds apart from giving the same word[s], *in the same statutory provision*, different meanings *in different factual contexts*," an approach the Supreme Court has "forcefully rejected" because it "'would render every statute a chameleon.'" *United States v. Santos*, 553 U.S. 507, 522 (2008) (Scalia, Souter, and Ginsberg, JJ.) (quoting *Clark v. Martinez*, 543 U.S. 371, 382, 386 (2005)).

II. FDA's Retroactive Application To Amarin Was Arbitrary And Capricious.

Alternatively, this Court should set aside the agency's retroactive application of its new policy to Vascepa as arbitrary and capricious.

FDA's letter refusing to acknowledge 5-year exclusivity for Vascepa:

- acknowledges that FDA's action is inconsistent with its prior decisions involving Survanta, Infasurf, and Curosurf (AR000020);
- demonstrates FDA's inability to refute that its 5-year exclusivity decision for Qutenza also supports 5-year exclusivity for Vascepa (AR000021);
- concedes that FDA's regulation does not address directly how to apply 5-year exclusivity in the context of a previously approved undifferentiated mixture (AR000006); and
- admits that FDA is adopting and announcing a new framework to determine the "active moieties" of an undifferentiated mixture (AR000006–8).

At the same time, FDA's letter did *not* acknowledge the Agency's prior representation that Vascepa would be eligible for 5-year exclusivity; nor did it consider, evaluate or discuss whether it would be appropriate to apply its newly announced policy retroactively to Vascepa.

To determine whether a new policy adopted in an adjudication should be given retroactive effect, "the ill effect of the retroactive application" "must be balanced against the mischief of producing a result which is contrary to a statutory design or to legal and equitable principles.'" *SEC v. Chenery Corp.*, 332 U.S. 194, 203 (1947). "In this circuit, *Retail, Wholesale & Dep' t Store Union v. NLRB*, 466 F.2d 380 (D.C. Cir. 1972), provides the framework for evaluating retroactive application of rules announced in agency adjudications." *Clark-Cowlitz Joint Operating Agency v. FERC*, 826 F.2d 1074, 1081 (D.C. Cir. 1987) (en banc).

> Among the considerations that enter into a resolution of the problem are (1) whether the particular case is one of first impression, (2) whether the new rule represents an abrupt departure from well-established practice or merely attempts to fill a void in an unsettled area of law, (3) the extent to which the party against whom the new rule is applied relied on the former rule, (4) the degree of the burden which a retroactive order imposes on a party, and (5) the statutory interest in applying a new rule despite the reliance of a party on the old standard.

Retail, 466 F.2d at 390; *see Clark-Cowlitz*, 826 F.2d at 1081 (factors are "non-exhaustive").

As shown below, all five *Retail* factors weigh against retroactive application of FDA's new policy to Vascepa. Indeed, FDA's failure to acknowledge the *Retail* framework or to provide an explanation why retroactive application of its new policy is appropriate is *alone* sufficient ground for setting its aside its decision. *See Gilbert v. Fed. Mine Safety & Health Review Comm'n*, 866 F.2d 1433, 1441–43 (D.C. Cir. 1989) (agency's application of a new policy retroactively was arbitrary and capricious; agency "failed to offer any legitimate justification for the retroactive application" and did not "even recognize[] that such a justification is legally required"); *Yakima Valley Cablevision, Inc. v. FCC*, 794 F.2d 737, 745–48 (D.C. Cir. 1986) (agency was arbitrary and capricious in applying new rules retroactively without explanation).

FDA's failure to address the retroactivity question is all the more capricious because *on the very same day* that FDA retroactively applied a new policy to deny 5-year exclusivity to Vascepa, FDA announced that the agency intended to reconsider its approach to 5-year exclusivity for fixed-combination drugs but, citing the *Retail* factors, that it would apply that new policy only prospectively. *See* Fixed-Combination Drug Citizen Petition Response at 17; *Draft Guidance for Industry on New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products; Availability*, 79 Fed. Reg. 10,167 (Feb. 24, 2014).

A. FDA's identification of EPA as an "active moiety" in Lovaza breaks from agency precedent on naturally derived mixtures.

Retail factors (1) and (2) point against retroactive application, because FDA's decision that Vascepa is not entitled to 5-year exclusivity marks a clear break from agency precedent.

FDA acknowledges that three of its past decisions would be "incorrect" under the new policy articulated in FDA's Vascepa decision. AR000020. In each—Survanta, Infasurf, and Curosurf—FDA concluded that the new drug was entitled to 5-year exclusivity despite the fact that the active ingredient contained constituents also found in at least one previously approved drug. Citing a "sparse" record, AR000015, FDA now professes uncertainty about how the agency reached these prior conclusions. *See* AR000015, 19–20. But the answer is clear. As the longtime Director of FDA's Office of New Drugs, Dr. John Jenkins, explained: "Due to the complex nature of the physical interaction of the components that results in the pharmacological activity of naturally derived surfactants, the Division considers the entire mixture to be the active moiety." AR000071. Hence, FDA's prior position was that a drug whose active ingredient is a naturally derived mixture also has the mixture itself as its active moiety—a position consistent with FDA's approval of Lovaza as a single active ingredient product and the representation that Vascepa would be a "new chemical entity" for which Amarin would need to conduct additional studies.

FDA's determination that Qutenza was entitled to 5-year exclusivity despite the prior approval of Relevo demonstrates that the agency continued to apply the rule articulated by Dr. Jenkins until Vascepa. *See* pages 13–14 *supra*. FDA does not deny that it treated the whole Relevo mixture as the drug's active moiety. Unable to explain away the Qutenza precedent, FDA instead tried to avoid its import by declining to address it "in detail." AR000021; *see also* AR000047 n.102 ("[W]e are still reviewing the issue … .").

The Survanta line of decisions provides the agency's clearest articulation of its approach to identifying active moieties of naturally derived mixtures until its decision in this case. The fact that FDA found it necessary to overrule those decisions to deny 5-year exclusivity to Vascepa confirms that FDA's new policy marks an abrupt and retrospective break from agency precedent. In light of Dr. Jenkins' clear statement of policy, FDA suggestion that the agency is somehow excused from "follow[ing] a particular past decision," AR000022, because agency practice was not, as the record reflects, consistent, lacks support. In addition, FDA is not specific about which of the precedents give rise to the purported inconsistency. *See* AR000008.[7]

[7] The "analysis" section of FDA's decision addresses only one precedent (involving Premarin and Cenestin) that FDA argues is inconsistent with Amarin's request for 5-year exclusivity. *See* AR000019–22. But the Premarin decision is subject to multiple reasonable interpretations, because the agency did not explain at the time how it reached the conclusion that it did. *See* AR000074–78 (explaining that, unlike Lovaza and Vascepa, Premarin and Cenestin were both mixtures, and that the denial of 5-year exclusivity to Cenestin could be consistent with a determination that the Premarin and Cenestin mixtures were the drugs' active moieties). Other prior actions that FDA identified as "relevant" are clearly not. FDA's past treatment of drugs that contain naturally derived menotropin mixtures is irrelevant because, unlike Vascepa, none of the menotropin products had as its active ingredient the mixture as a whole. *See* AR00015–16. FDA's discussion of racemic mixtures is inapposite because a racemic mixture "is usually a synthetic product," AR000009, and because all of the molecules in the mixture have "the same molecular formula and chemical connectivity," AR000008; thus, racemic mixtures do not present the same issues as naturally derived mixtures and their constituents.

B. Amarin's reliance on FDA's prior precedent weighs strongly against retroactive application of FDA's new policy to Vascepa.

The third and fourth *Retail* factors also weigh strongly in favor of applying FDA's new policy only prospectively. Amarin clearly "relied on the former rule" to its detriment. *Retail*, 466 F.2d at 390. FDA initially represented to Amarin that Vascepa would qualify for 5-year exclusivity, then told Amarin that FDA would not make a final exclusivity determination until it approved Amarin's new drug application. In the meantime, Amarin invested time and money in conducting the carcinogenicity study that FDA "required" and "generally expected … to support the marketing approval of a new chemical entity for a chronic use indication." AR001041, AR001042.

The "burden which a retroactive order imposes" on Amarin is also significant. *Retail*, 466 F.2d at 390. Under FDA's new rule, Amarin loses from one year to four-and-a-half years of marketing exclusivity that it would have received under the old rule, and Amarin's potential competitors acquire the immediate opportunity to litigate the validity and infringement of the Amarin patents that claim Vascepa or uses of Vascepa. *See* AR000065.

C. The statutory interest weighs against retroactive application.

Finally, FDA cannot claim that retroactivity is justified by "the statutory interest in applying [the agency's] new rule." *Retail*, 466 F.2d at 390. FDA maintains that the statute does not "expressly address 5-year NCE exclusivity in the context of naturally derived mixtures" because the "relevant statutory … authorities on 5-year NCE exclusivity appear to focus principally on single component active ingredients." AR000006. Assuming *arguendo* that FDA is correct that Congress did not intend to address 5-year exclusivity "in the context of naturally derived mixtures," FDA can hardly appeal to congressional intent to justify retroactive application.

Ignoring the indisputable truth that Congress intended to encourage and incentivize pioneer research through the exclusivity provisions of the Hatch-Waxman Act, FDA avers that

"[t]he amount of research that a sponsor invests in a drug is not determinative of that drug's eligibility for NCE exclusivity." AR000023. This *ipse dixit* hardly demonstrates reasoned decisionmaking. In fact, obtaining FDA approval for a new drug that will be eligible for 5-year exclusivity often requires the applicant to conduct or sponsor more studies than would be necessary for a new drug not eligible for such exclusivity. *See*, *e.g.*, AR000703 (stating that covalent derivatives of previously approved drugs are treated as different active moieties in part because "[s]uch a change requires submission of an amount of data comparable to that required for an entirely new molecule"). Amarin's experience confirms this: FDA requested and Amarin performed additional studies that the agency said were necessary for approval of a new chemical entity. *See* AR001041–42; FDA *Actavis* Br. at 32–33 ("FDA approves a relatively modest number of new chemical entities each year. The NDA sponsors … must make significant investments in research and development and conduct expensive and time-consuming clinical trials.").

More generally, there are good reasons to incentivize the development of new drugs that have as their active ingredient a constituent of a prior-approved mixture. As explained in an internal FDA memorandum regarding the Vascepa NDA, "knowledge of the specific effects of EPA and DHA can lead to targeted drug therapy." AR000757; *see also* AR000764 ("[E]vidence shows differential effects of EPA and DHA on other lipid parameters [i.e., other than serum triglyceride levels]. These findings may lead to targeted drug therapy with major individual omega-3 fatty acids."). Thus, a new drug whose active ingredient is a constituent of a previously approved mixture may represent a significant innovation that expands patients' treatment options and improves health outcomes. Yet, FDA's decision fails to address how the policy that the agency adopted would affect the manufacturers' incentives to develop such products, or why that policy would strike the best balance between the policies underlying the Hatch-Waxman Act.

CONCLUSION

For the foregoing reasons, the Court should enter an order awarding summary judgment to Amarin and granting Amarin the relief sought in its Complaint.

Respectfully submitted,

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