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 ORAL ARGUMENT REQUESTED

PLAINTIFF'S MEMORANDUM OF POINTS AND AUTHORITIES IN OPPOSITION TO DEFENDANTS' SUMMARY JUDGMENT MOTION AND REPLY IN SUPPORT OF PLAINTIFF'S SUMMARY JUDGMENT MOTION

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INTRODUCTION

FDA's refusal to recognize Vascepa's 5-year exclusivity is inconsistent with the plain language and clear meaning of the controlling statute. In addition, FDA's retroactive application to Vascepa of a new policy for naturally derived mixtures is arbitrary and capricious. The Court should set aside the agency's decision and award Amarin full relief.

Congress granted 5-year exclusivity to any drug "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). Vascepa's "active ingredient" is icosapent ethyl. FDA refused to recognize Vascepa's 5-year exclusivity based on its prior approval of Lovaza. But Vascepa's "active ingredient" is different from Lovaza's. FDA and Amarin agree that Lovaza's "active ingredient" is the Lovaza mixture itself, as a whole. Mixtures necessarily do not have ester or salt derivatives. Therefore, based on FDA's own scientific determination, FDA acted contrary to the plain language of the statute in refusing to recognize Vascepa's 5-year exclusivity.

FDA did not apply the statute as written. Years after identifying Lovaza's undifferentiated mixture as the single "active ingredient" intended to furnish the drug's pharmacological activity, FDA disregarded that determination and identified as an "active moiety" any constituent that FDA found "responsible at least in part for the physiological or pharmacological action of the mixture" (AR000007–8). Thus, FDA contends the statute allows the agency, for exclusivity determination purposes, to later treat a drug whose active ingredient is a naturally derived mixture as a whole as if it contains multiple "active moieties" (thereby denying 5-year exclusivity to a wider variety of later-approved drugs). FDA contends that this new after-the-fact, "activity"-based analysis is permitted by the statute. But this framework is completely untethered from the statute's text, and FDA previously maintained that such an activity-based approach is bad policy.

FDA begins its Opposition with misdirection. FDA complains that Amarin challenges a "long-standing framework" FDA adopted in "regulations … promulgated nearly 20 years ago." (Opp. 1.) The problem is not the regulations. FDA concedes that they do not "expressly address 5-year NCE exclusivity in the context of naturally derived mixtures." (AR000006.) The problem is FDA disregarding the statute's plain meaning and structure-centric approach. Nor will a ruling for Amarin upend "hundreds of NCE exclusivity determinations." (Opp. 1.) Only a small fraction of FDA's past 5-year exclusivity decisions involved naturally derived mixtures, most such exclusivity terms have long expired, and FDA acknowledges that many if not all of them are consistent with recognizing 5-year exclusivity for Vascepa. (AR000006.)

FDA's discussion of deference to the agency's "scientific determinations" is another distraction. Amarin agrees with FDA's *scientific* determination that Lovaza's "active ingredient" is the mixture as a whole. Amarin disagrees with FDA's *legal* determination that a mixture's "active ingredient" is irrelevant to the 5-year exclusivity analysis.

Amarin also disagrees with FDA's *legal* determination that it could apply its new activity-based approach retroactively to Vascepa. FDA concedes that its decision on Vascepa is inconsistent with at least three prior agency precedents, Survanta, Infasurf, and Curosurf; FDA fails to address why its decision is not inconsistent with a fourth, Qutenza. FDA cannot excuse its failure to consider retroactivity with the counterfactual contention that it has simply "clarified" an approach that it never before announced. FDA has therefore acted arbitrarily and capriciously in retroactively applying its new activity-based framework to Vascepa.

For any and all of these reasons, this Court should grant summary judgment to Amarin.

ARGUMENT

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

As demonstrated in Amarin's Memorandum, FDA's refusal to recognize 5-year exclusivity for Vascepa is contrary to the statute. To reach its decision here, FDA has interpreted "active ingredient" to mean something other than "active ingredient." (Mem. 16–21.) Invoking the concept of "active moiety" does not solve the problem, because the statute is clear and does not permit FDA to take single "active ingredient" and convert it into multiple "active moieties" for the purpose of making an exclusivity decision or otherwise. (Mem. 22–25.)

A. The Court should enforce the plain language of the statute.

The statutory analysis is straightforward. The FDCA expressly provides 5-year exclusivity for any new 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). FDA refused to recognize 5-year exclusivity for Vascepa because of its prior approval of Lovaza. Under the plain language of the statute, however, Vascepa should have 5-year exclusivity:

1. The "active ingredient" of Lovaza is an undifferentiated, complex mixture. (AR000019 ("[T]he Agency agrees that the active ingredient of Lovaza is the Lovaza mixture as a whole … .").)

2. The "active ingredient" of Vascepa, a new drug, is icosapent ethyl. (AR000016.)

3. Icosapent ethyl is not an "ester or salt" of the undifferentiated Lovaza mixture, and that mixture is not an "ester or salt" of icosapent ethyl.

∴ Vascepa is entitled to 5-year exclusivity.

In rejecting this logic, FDA's decision renders a drug's "active ingredient" irrelevant to the exclusivity analysis. That approach cannot be squared with the plain text of the statute. FDA

nevertheless argues that "active ingredient" has no plain meaning, that the statute is therefore ambiguous, and that the Court must defer to FDA. FDA is wrong.

At *Chevron* Step One, "'the issue is not so much whether the [statutory language] … is, in some abstract sense, ambiguous, but rather whether, read in context and using the traditional tools of statutory construction, the term … encompasses [the government's interpretation].'" *Bennett v. Donovan*, No. 11-cv-0498, 2013 WL 5424708, at *3 (D.D.C. Sept. 30, 2013) (alterations in original) (quoting *Cal. Indep. Sys. Operator Corp. v. FERC*, 372 F.3d 395, 400 (D.C. Cir. 2004)); *accord HolRail, LLC v. STB*, 515 F.3d 1313, 1317 (D.C. Cir. 2008) (same). Courts therefore often resolve cases at *Chevron* Step One while recognizing that the statutory language at issue is ambiguous in some sense that does not control "the precise question at issue," *Chevron U.S.A. Inc. v. NRDC*, 467 U.S. 837, 842 (1984).[1]

Put differently, "[i]t does not matter whether the word 'yellow' is ambiguous when the agency has interpreted it to mean 'purple.'" *United States v. Home Concrete & Supply, LLC*, 132 S. Ct. 1836, 1847 n.1 (2012) (Scalia, J., concurring).

FDA's decision here is the equivalent of reading yellow to mean purple. FDA determined that the "active ingredient" of Lovaza is the Lovaza mixture as a whole and that the "active in-

[1] *See, e.g.*, *Sw. Airlines Co. v. Transp. Security Admin.*, 554 F.3d 1065, 1069–70 (D.C. Cir. 2009) (rejecting agency's interpretation of "screening passengers" even though "to screen" may have multiple meanings because the term is clear in context); *HolRail*, 515 F.3d at 1317 (holding that "the term 'cross' may have multiple meanings in some circumstances" but that "the statute, read in context, clearly resolves the case" and that there is therefore "no need to proceed to *Chevron* step two"); *New York v. EPA*, 443 F.3d 880, 884–90 (D.C. Cir. 2006) (rejecting agency's interpretation of "any physical change" even though "the phrase 'physical change' is susceptible to multiple meanings" and "the meaning of 'any' can differ depending on the statutory setting"); *Loving v. IRS*, 917 F. Supp. 2d 67, 74 (D.D.C. 2013) ("The [agency] hurries through *Chevron* step one, arguing that the statute is ambiguous because it defines neither 'representative' nor 'practice,' and both terms can have broad meanings. That simplistic approach will not fly, however." (internal citation omitted)).

gredient" of Vascepa is icosapent ethyl. Because neither drug's "active ingredient" is an "ester or salt" of the other drug's "active ingredient," 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," 21 U.S.C. §§ 355(c)(3)(E)(ii), 355(j)(5)(F)(ii) (emphases added), and is eligible for 5-year exclusivity. Whatever ambiguity the term "active ingredient" might have *in the abstract* is irrelevant because FDA and Amarin *agree* on the "active ingredient" of each drug—an undifferentiated complex mixture (Lovaza) and the discrete molecule icosapent ethyl (Vascepa). The statute is not ambiguous with respect to "the precise question at issue," *Chevron*, 467 U.S. at 842: whether, given these "active ingredients," Vascepa is entitled to 5-year exclusivity.

FDA nevertheless contends that the D.C. Circuit has already held that the term "active ingredient" is ambiguous, arguing that the Court has granted FDA license to decide that it means whatever FDA wants it to mean, and to change that meaning from application to application. (*See* Opp. 2, 12–15 (citing *Abbott Laboratories v. Young*, 920 F.2d 984 (D.C. Cir. 1990) ("*Abbott II*"); *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760 (D.C. Cir. 2010)). But neither *Abbott II* nor *Actavis* holds that the statute is ambiguous on "the precise question at issue" here, and neither suggests that "active ingredient" can mean something other than "active ingredient."

As FDA acknowledges (Opp. 13–14), the question in *Abbott II* was different. The D.C. Circuit concluded only that "[t]he 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 … ." *Abbott II*, 920 F.2d at 987 (majority opinion); *see also id.* at 988 ("[T]he ambiguity of reference in the phrase reflects the possibility that it can refer to the latest subsection (b) application as well as all prior subsection (b) applications."); *id.* at 987 ("the language is ambiguous *as it relates to the issue before us*" (emphasis added)). The majority declined

to decide whether FDA could interpret "active ingredient" to mean "active moiety," and Judge Edwards concluded that it could not. *See id.* at 987 (concluding that "we cannot consider" whether "active ingredient" may be read as "active moiety"); *id.* 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].").[2]

The question in *Actavis* was also different. There the Court considered whether "active ingredient" could mean either "the particular drug molecule that reaches the 'site' of the drug's action" or "the form of the molecule before it enters the body." *Actavis*, 625 F.3d at 764. As FDA concedes (Opp. 15), "[t]he specific issue in *Actavis* … is not relevant here."[3] The issue here is fundamentally different and much simpler: Given that Lovaza's "active ingredient" is an undifferentiated mixture, does the statute deny 5-year exclusivity to Vascepa, which has a different active ingredient, one that is not an ester or salt of the mixture? The answer is no.

Because FDA's decision rests on the premise that FDA has license under the statute to find that an "active ingredient" in an approved drug is something different than the "active ingre-

[2] FDA mischaracterizes the record when it denies (Opp. at 14) that its decision leading to *Abbott* "attempted to interpret the phrase 'active ingredient (including any salt or ester of the active ingredient)' to mean 'active moiety.'" *See* Brief for Respondent in Opposition at 5, *Abbott Labs. v. Kessler*, 502 U.S. 819 (1991) (No. 90-1898), 1991 WL 11178351, at *5 ("The agency explained that it interpreted the entire phrase 'active ingredient (including any ester or salt of the active ingredient)' in the exclusivity provisions of the Hatch-Waxman Amendments to refer to the 'active moiety' of the drug."). Although *Abbott II* rejected that interpretation, 920 F.2d at 988 (majority opinion), FDA has continued to invoke it in some decisions. (AR000268 (hyaluronidase exclusivity decision).)

[3] FDA suggests that *Actavis* "appears to have accepted without discussion" that only drugs that contain no previously approved "active moiety" are entitled to 5-year exclusivity. (Opp. 15.) But the parties and the court in *Actavis* could *assume* that "active ingredient" means "active moiety" because the product at issue was a single molecule drug and not a naturally derived mixture. The distinction made no difference in that case. This Court should not treat that assumption as a holding. *See Cent. Va. Community College v. Katz*, 546 U.S. 356, 363 (2006) (declining to treat as binding "dicta in a prior case in which the point now at issue was not fully debated").

dient" that FDA approved for that drug, FDA bears the burden of demonstrating that "Congress did not mean what it appears to have said." *Performance Coal Co. v. FMSHRC*, 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)). Amarin has shown through application of several canons of construction that there is no reason to doubt that Congress meant what it said. (*See* Mem. at 18–21.)

Seeking to avoid these arguments, FDA contends that the canons of statutory interpretation are relevant only to "the reasonableness of an agency interpretation" at *Chevron* Step Two. (Opp. 17.) This is wrong. *Chevron* Step One requires courts to apply all of the "traditional tools of statutory construction." *Chevron*, 467 U.S. at 843 n.9; *see Halverson v. Slater*, 129 F.3d 180, 184 (D.C. Cir. 1997) (holding that "the lower court erred by failing to 'exhaust the traditional tools of statutory construction'" (quoting *NRDC v. Browner*, 57 F.3d 1122, 1125 (D.C. Cir. 1995))); *Teva Pharms. USA, Inc. v. Sebelius*, 595 F.3d 1303, 1315–18 (D.C. Cir. 2010) (rejecting FDA's interpretation of an FDCA exclusivity provision at *Chevron* Step One based on the statutory structure even though the plaintiff's "linguistic argument … hardly rules out alternative readings that, absent consideration of statutory structure, also appear plausible"). These tools confirm that "active ingredient" means "active ingredient."[4]

[4] FDA also cites (Opp. 16) *Abbott II*'s dictum that "it is 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*." *Abbott II*, 920 F.2d at 987 (emphasis added). As Amarin explained, however, the "purposes" of the various subsections containing the term "active ingredient" are *not* "different." (Mem. at 21.); *see also Abbott Labs. v. Young*, 691 F. Supp. 462, 470 (D.D.C. 1988) ("*Abbott I*") ("Rather than being different, their purposes are complementary."). FDA fails to respond on this point. In addition, *Abbott II* does not say that the canon is irrelevant at *Chevron* Step One; it suggests at most that the canon, standing alone, may be insufficient to eliminate ambiguity. Here, however, the statute's plain meaning and multiple canons of construction all point in Amarin's favor.

B. The statute does not support FDA's new "activity"-based interpretation.

As Amarin explained in its opening brief (Mem. 22), and Defendants agree (Opp. 18–19), prior to its Vascepa decision, FDA consistently applied a strictly "structure-based" or "structure-centric" approach to identifying a drug's "active moiety." Under that approach, FDA first identifies the "active ingredient" and then identifies the "active moiety" by "excluding" from the 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)." 21 C.F.R. § 314.108(a). The regulation thus describes a very specific relationship between the concepts of "active ingredient" and "active moiety," based on the *structure* of the "active ingredient," not the *activity* of its constituents.

FDA admits that it did not adhere to this strictly structure-centric approach in identifying the active moiety of the Lovaza mixture. Rather, FDA announced that its "structure-centric approach is not applicable when determining which components of a naturally derived mixture potentially are its active moiety or moieties." (AR000022.) FDA then announced for the first time in its Vascepa decision that it would apply an "activity"-based approach to identifying the active moieties of naturally derived mixtures. (AR000008.) FDA's new, activity-based approach is contrary to the statute and unreasonable for at least three reasons.

First, no language in the statute can be interpreted to mean that after identifying a drug's "active ingredient," FDA should proceed to (1) identify the molecules in the active ingredient, (2) determine whether those molecules are "consistently present" in the active ingredient, and (3) evaluate whether the molecules identified are "responsible at least in part" for the activity of the active ingredient, and *then* (4) evaluate the structure of the molecule(s) identified to determine the active moiety. (*See* Mem. 23–24.) FDA does not even attempt to explain the statutory basis underlying the three newly-announced criteria for identifying the active moiety of a naturally

derived mixture ("characterization," "consistent presence," and "activity"). FDA cannot; the agency spun these criteria out of whole cloth.

Second, FDA's approach here is an approach that the agency previously rejected. FDA told the D.C. Circuit in *Actavis* that "an 'activity' based approach … would result in … much *greater uncertainty* for the regulated industry." Brief for Federal Appellees at 2, 15, *Actavis Elizabeth LLC v. FDA*, 625 F. 3d 760 (D.C. Cir. 2010) (No. 10-5066), 2010 WL 3207405, at *2, *15 (emphasis added). Having taken and prevailed on that position, FDA should not be heard to tell this Court that FDA's "clarification of FDA's interpretation provides more certainty to the regulated industry." (Opp. 20.) FDA's attempt to have it both ways, and its failure to acknowledge or explain the agency's shift in thinking is the hallmark of arbitrary and capricious agency action.[5]

Third, FDA's different approaches to single-molecule drugs and naturally derived mixtures gives the same statute different meanings in different factual contexts. (*See* Mem. 25.) FDA says that "[t]he 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." (Opp. 19 n.9.) This is either a concession or a non-response. Doing an analysis in a different order is not doing the same analysis. Under the approach to naturally derived mixtures that FDA articulated in its

[5] FDA quotes from the preamble to the proposed rule in which FDA "introduc[ed] the terms 'new chemical entity' and 'active moiety'" (Opp. 17–18), and argues that the regulation's focus on "active moiety" advances the purpose of the statute (Opp. 18). But FDA cannot justify its approach to identifying the active moiety of naturally derived mixtures by reference to the regulations, because (according to FDA) the regulations do not "expressly address 5-year NCE exclusivity in the context of naturally derived mixtures" (AR000006), and (according to FDA) the regulation's structure-centric approach to identifying a drug's active moiety "is not applicable when determining which components of a naturally derived mixture potentially are its active moiety or moieties." (AR000022.) If the question is whether the purposes of the statute are best advanced in the context of naturally derived mixtures: (1) by applying the three criteria announced by FDA in its letter to Amarin; or (2) by treating the active ingredient as the active moiety, the references to the preamble and congressional intent are question-begging.

letter to Amarin, FDA *adds* a step (or steps) to the process that it uses to identify the active moiety of a single-molecule drug based on its active ingredient—and the step that it adds is the same activity-based analysis that FDA previously rejected.

Thus, for single-molecule drugs, FDA: (1) identifies the active ingredient; and (2) then excludes any appended portions that cause the active ingredient to be an ester, salt, or other noncovalent derivative. *See* 21 C.F.R. § 314.108. For naturally derived mixtures, however, FDA now (1) identifies the active ingredient; (2) then identifies one or more molecules that are "consistently present" in the active ingredient, (3) then evaluates which of those molecule(s) meaningfully contribute to the physiological or pharmacological action of the active ingredient; and (4) then excludes from that subset any appended portions that cause the active ingredient to be an ester, salt, or other noncovalent derivative. (*See* AR000007–8 & n.34.) These new steps have no basis in the statute or in FDA's own regulation.[6]

* * *

Finally, and contrary to FDA's argument, enforcing the statute as written would not mean striking down any regulation or even a long-standing FDA policy. FDA concedes that reading "active ingredient" to mean "active ingredient" would have "negligible" results in the context of single-molecule drugs. (AR000006.) FDA further concedes that its regulations do not expressly address naturally derived mixtures. (*Id.*) FDA's refusal to recognize 5-year exclusivity for Vascepa rests on FDA's decision *not to apply* the statue and the regulation's structure-based

[6] FDA's brief includes a lengthy string citation about the deference afforded to the agency on questions of science. (*See* Opp. 11–12.) But Amarin agrees with FDA's scientific conclusion that the "active ingredient" of Lovaza is the undifferentiated mixture, and Amarin is not asking the Court to review FDA's evaluation of the "activity" of Lovaza's constituents. The challenge is to FDA's refusal to recognize the exclusivity that Vascepa receives under the statute, because Vascepa's active ingredient is not the Lovaza mixture or a salt or ester thereof.

interpretation of active moiety but to apply instead an activity-based analysis that has no basis in the statute or regulation, or, as discussed further below, in prior agency practice.[7]

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

FDA also acted arbitrarily and capriciously by applying to Vascepa a previously unannounced policy for identifying the active moieties of naturally derived mixtures without considering whether doing so is consistent with retroactivity principles. (*See* Mem. at 25–30.) Indeed, FDA does not dispute that if the policy it applied here is "new," the *Retail* factors—*Retail, Wholesale & Dep't Store Union v. NLRB*, 466 F.2d 380 (D.C. Cir. 1972)—would preclude FDA from applying that policy retroactively to Vascepa. (Opp. 19 n.10.)

A. FDA has applied a new policy, not "clarified" an old one.

Hoping to excuse its failure, FDA contends that the "framework" applied here is not "new" at all. As explained below, this Court should not condone FDA's *ipse dixit* attempt to label its action as "clarifying" agency policy when FDA has never before explained a 5-year exclusivity decision by referencing the new activity-based framework. Moreover, even if FDA's characterization of its decision could be squared with the record, that still would not excuse FDA from engaging in the retroactivity analysis required by *Retail*. There are many reasons why FDA's "clarification" argument cannot be credited.

[7] Of course, whether an agency policy is "long-standing" does not preclude courts from enforcing the statute that ultimately controls. *See, e.g.*, *Mayo Found. for Medical Educ. & Research v. United States*, 131 S. Ct. 704, 712 (2011) (*Chevron* deference does not turn on a policy's "antiquity"); *Int'l Union of Operating Eng'rs v. NLRB*, 635 F.3d 1233, 1233 (D.C. Cir. 2011) (holding that "a National Labor Relations Board policy that has been followed for over thirty years [since 1977], and which the Ninth Circuit has endorsed," "does not accord with the National Labor Relations Act"). And an agency regulation cannot rewrite the text that Congress enacted. *See, e.g.*, *Ind. Mich. Power Co. v. Dep't of Energy*, 88 F.3d 1272, 1276 (D.C. Cir. 1996) (rejecting agency decision where its "treatment of this statute is not an interpretation but a rewrite" that "blue-pencils out the phrase 'not later than January 31, 1998'").

First, FDA acknowledges that the framework described in its Vascepa decision is inconsistent with at least three of its prior 5-year exclusivity determinations involving mixtures, including one determination that predates any precedent on which FDA relies—Survanta (1991), Infasurf (1998), and Curosurf (1999). FDA recognized that each of these lung surfactant mixtures was eligible for 5-year exclusivity, even though each mixture contained at least one constituent of a previously-approved product.[8] FDA recognized Survanta's 5-year exclusivity even though the Survanta mixture contained colfosceril palmitate, which was also in the previously approved Exosurf. It later recognized Infasurf's 5-year exclusivity even though the Infasurf mixture contained the SP-B protein, which was also in the Survanta mixture. And it later recognized Curosurf's 5-year exclusivity even though the Curosurf mixture contained both colfosceril palmitate and SP-B. This consistent line of precedent squarely contradicts FDA's newly announced policy of deeming a single complex mixture to be multiple individual active moieties defined as each individual active (and consistently present) constituent, and instead reflects FDA's pre-existing structure-centric approach, under which a single active ingredient has a single active moiety.

Second, FDA does not dispute that the agency's clearest articulation of its approach to identifying the active moieties of naturally derived mixtures was Dr. John Jenkins' explanation in connection with Survanta and Infasurf that FDA treats the entire mixture as the active moiety. (*See* Mem. 13, 28; AR000071.)[9] Instead, FDA fails to acknowledge Dr. Jenkins' decision at all.

[8] FDA's brief mistakenly refers to "two erroneous decisions" (Opp. 21), overlooking FDA's conclusion that it erred in granting 5-year exclusivity to Survanta in light of its prior approval of Exosurf (AR000015, 19–20).

[9] Dr. Jenkins was then Director of FDA's Division of Pulmonary Drug Products. He has since served as Director of FDA's Office of New Drugs for more than a decade.

But, clearly, FDA's new "activity"-based approach announced to deprive Vascepa of exclusivity goes beyond treating the mixture as a whole as the active moiety.[10]

Third, FDA fails to address the fact that the framework articulated in the Vascepa decision is inconsistent with FDA's 5-year exclusivity determination for Qutenza—the most recent precedent identified in FDA's letter to Amarin. (*See* Mem. 13–14, 28.) FDA says (AR000021 and Opp. 21 n.11) that FDA's *patent term extension* decision for Qutenza is not relevant because that decision did not require FDA to identify the active moiety of Qutenza. This is a non-sequitur. FDA also determined that Qutenza was a new active moiety eligible for 5-year exclusivity. To do so, FDA must have identified the active moieties of both Qutenza and the prior-approved Relevo Liniment. Yet, FDA refuses to offer any explanation of how the agency could have reached its decision that Qutenza is eligible for 5-year exclusivity if it had applied the framework articulated in the Vascepa decision. The agency's refusal to offer a rational explanation for how to reconcile its 5-year exclusivity decisions for Qutenza and Vascepa is itself arbitrary and capricious. *See, e.g., Jicarilla Apache Nation v. U.S. Dep't of Interior*, 613 F.3d 1112, 1120 (D.C. Cir. 2010)

[10] FDA is also incorrect that Amarin "relies solely on the lung surfactant decisions that FDA now acknowledges were incorrect and fails to discuss the other agency decision mentioned in FDA's letter." (Opp. 21.) Amarin's brief did explain why all of the decisions that FDA claims support its new position are really inapposite (Mem. at 28 n.7), and as just discussed, it is FDA's brief that fails to respond to Amarin's points. The only precedents cited in FDA's letter but not Amarin's brief are those involving pancrelipase, hyaluronidase, and Condylox (AR000009–11)—decisions that support Amarin's position but that Amarin does not need to establish that FDA has never before articulated the policy it applied to Vascepa. For products containing pancrelipase or hyaluronidase, FDA has treated the mixture as a whole as both the active ingredient and the active moiety—the very approach that Amarin asked FDA to apply to Vascepa. (*See* AR000009–10, 253–67, 268–80.) And FDA recognized that Condylox (podofilox) was eligible for 5-year exclusivity because the "previously approved NDA's [for certain naturally derived mixtures] did not characterize podofilox as an active ingredient" (AR000294), a principle that would likewise require FDA to recognize 5-year exclusivity for Vascepa. Seeking to avoid this conclusion, FDA's letter to Amarin describes the Condylox decision as "based, at least in part," on arguments that FDA's Condylox decision expressly declined to address. (*Compare* AR000011 *with* AR000281–93 *and* AR000295 n.2.)

(agency decision is arbitrary and capricious when it "should have confronted … conflicting precedent" but did not); *LeMoyne-Owen College v. NLRB*, 357 F.3d 55, 61 (D.C. Cir. 2004) ("[W]here, as here, a party makes a significant showing that analogous cases have been decided differently, the agency must do more than simply ignore that argument."); *Speedtrack Prods. Group, Ltd. v. NLRB*, 114 F.3d 1276, 1279 (D.C. Cir. 1997) (agency impermissibly "ignored its own precedent without offering any explanation as to why this precedent was inapplicable.").

Fourth, Amarin reasonably relied not only on these precedents but also on explicit representations from FDA officials that Vascepa would be eligible for 5-year exclusivity. (*See* Mem. 10.) Those representations led Amarin to invest in studies that would not have been required for a drug that was not eligible for 5-year exclusivity. (*See id.*) Unable to explain why it required Amarin to do these studies, FDA simply declines to discuss its initial representations to Amarin.

Fifth, in none of the prior agency actions that FDA cites in an effort to justify its Vascepa decision did FDA publicly explain that the agency would apply an activity-based approach to naturally derived mixtures so that a drug whose active ingredient is a mixture as a whole might have multiple active moieties.

While FDA argues that "FDA's decision on Vascepa is largely consistent with *the outcomes of, and/or bases for*, relevant prior agency decisions on well-characterized mixtures" (Opp. 20 (emphasis added)), its characterization of the *results* of prior agency decisions just soft-pedals the facts that FDA has never before come close to publicly articulating the framework that it applied to Amarin's application or even to recognize any inconsistency in FDA's prior decisions. Similarly, FDA's efforts to identify a few precedents for its newly announced policy are exercises in historical revisionism. FDA suggests that "the Agency *appears* to have considered and rejected a 'one-to-one' approach" for menotropins. (AR000015 (emphasis added).) But FDA

has no answer (Opp. 20) to the point that FDA's treatment of menotropins does not provide precedent for its decision here because none of the menotropin products had as its active ingredient the mixture as a whole. (Mem. 28 n.7; *see also* AR000015–16.)

Similarly, FDA did not publicly articulate in connection with its Cenestin exclusivity determination the justification that FDA reconstructs in its letter to Amarin. FDA cites in support of its new activity-based interpretation of "active moiety" the Federal Register notice in which FDA proposed to refuse ANDAs referencing Premarin. (AR000008 (citing AR000222–47).) But this notice cannot support an activity-based interpretation of "active moiety" because ANDA approval turns on drugs' "active ingredients," not their active moieties. (Mem. 19-20.) FDA's brief fails to respond to Amarin's explanation that granting 5-year exclusivity to Vascepa would be consistent with the Cenestin decision. (*Compare* Mem. 28 n.7 *with* Opp. 20.)

The fact that FDA has attempted to reconstruct in hindsight the reasoning of past decisions to try to make them appear consistent with its Vascepa decision further demonstrates that FDA is creating new policy, not clarifying any prior precedent. Indeed, FDA concedes (by not addressing) that the only clearly articulated statement concerning the active moiety of a complex mixture was Dr. Jenkins' express statement in connection with the Survanta and Infasurf decisions and similarly concedes that the Agency initially treated Vascepa as a new active moiety as well, requiring Amarin to conduct additional studies. In announcing its new policy, FDA has had to disavow those prior precedents and to reverse its initial position on Vascepa's eligibility for 5-year exclusivity. This disavowal and reversal make clear beyond dispute that the policy announced in connection with denying 5-year exclusivity to Vascepa constitutes a new policy, and not a clarification of past practice.

B. FDA's failure to consider the retroactivity factors requires that its action be set aside.

Finally, even if one were to accept that FDA has "clarified" (Opp. 19) an approach that previously failed to "result[] in consistent outcomes" (AR000006), that would not excuse FDA's failure to consider the retroactivity issue. Even in the case of a "clarification" as opposed to a new policy, "retroactivity will be denied 'when to apply the new rule to past conduct or to prior events would work a manifest injustice.'" *Verizon Tel. Cos. v. FCC*, 269 F.3d 1098, 1109 (D.C. Cir. 2001) (quoting *Clark-Cowlitz Joint Operating Agency v. FERC*, 826 F.2d 1074, 1081 (D.C. Cir. 1987) (en banc)). Given (1) that there was ample agency precedent indicating that Vascepa *should* have 5-year exclusivity; (2) that FDA told Amarin that it *would* be eligible for that exclusivity; and (3) that Amarin did additional studies that FDA required for applications eligible for 5-year exclusivity, Amarin has a claim of "manifest injustice." (*See* Mem. 10–11); *see Gilbert v. FMSHRC*, 866 F.2d 1433 (D.C. Cir. 1989) (rejecting as "grossly unfair" an agency's retroactive application of its decision limiting the role of individual complaints when petitioner had been "explicitly instructed by the Secretary that he had a right to pursue a complaint in his own behalf" and petitioner acted "in reasonable reliance on the Commission's old Rule").

Hence, FDA acted arbitrarily and capriciously in failing to address the retroactivity issue. (*See* Mem. 26 (citing *Gilbert*, 866 F.2d at 1441–43).) And because FDA does not even argue that it could permissibly apply a "new" policy retroactively to Vascepa under *Retail*, (Opp. 19 n.10.) the Court can set FDA's denial of 5-year exclusivity aside and grant the requested relief without remanding for further proceedings on that issue.

CONCLUSION

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

Respectfully submitted,

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