UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

AMARIN PHARMACEUTICALS IRELAND LIMITED,	)	
Plaintiff,	)	
v.	)	**Civil Action No. 14-cv-00324 (RDM)**
FOOD AND DRUG ADMINISTRATION, MARGARET A. HAMBURG, M.D., Commissioner of Food and Drugs, and KATHLEEN SEBELIUS, Secretary of Health and Human Services,	)	
Defendants.	)	

MEMORANDUM OPINION

Amarin Pharmaceuticals Ireland Limited ("Amarin") challenges the Food and Drug Administration's determination that Amarin's new drug, Vascepa (icosapent ethyl) Capsules ("Vascepa"), is not entitled to a five-year period of market exclusivity under the Federal Food, Drug, and Cosmetic Act ("FDCA"). That period of exclusivity is available for a new drug, if "no active ingredient (including any ester or salt of the active ingredient)" of the drug "has been approved in any other application" for new drug approval. Here, the Food and Drug Administration ("FDA" or "Agency") denied five-year market exclusivity for Vascepa because Vascepa's active ingredient—a single molecule—is one component of a mixture that makes up the "active ingredient" of a previously approved drug. For the reasons set forth below, the Court concludes that the FDA's decision must be set aside, and the matter is remanded to the Agency for further proceedings consistent with this decision.

I. BACKGROUND

A. Statutory and Regulatory Background

1. *The Hatch-Waxman Amendments*

In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984). Popularly known as the "Hatch-Waxman Amendments," the Act sought to balance two competing policy goals: (1) encouraging the development of generic drugs to increase competition and lower prices in the pharmaceutical industry, while (2) maintaining incentives for pharmaceutical companies to invest in innovation and the creation of new drugs. Facing this "classic question of the appropriate trade-off between greater incentives for the invention of new products and greater affordability of those products," *Abbott Labs. v. Young*, 920 F.2d 984, 985 (D.C. Cir. 1990), Congress struck a compromise. It established an expedited process for obtaining approval for generic drugs, but, at the same time, it provided increased intellectual property rights and periods of market exclusivity for those pioneer manufacturers that invent new drugs.

The two sides of the compromise are codified in separate aspects of the Hatch-Waxman Amendments. On the one hand, to streamline the process for bringing new generic drugs to market, Congress created the "abbreviated new drug application" ("ANDA") process, under which a manufacturer can obtain FDA approval for a generic drug by demonstrating that it has the same "active ingredient" or "active ingredients" as a drug previously approved as safe and effective and that the generic drug is otherwise equivalent to that drug. *See* 21 U.S.C. § 355(j)(2)(A). This significantly reduces the time and expense required to obtain approval for generic drugs; previously, in order to obtain approval in most cases, manufacturers were required to submit a full "new drug application" ("NDA") with clinical data sufficient to demonstrate the

drug's safety and effectiveness, even where the drug was merely a generic version of a previously approved drug.

On the other hand, in order to maintain incentives for pioneer drug manufacturers to research and invest in new drugs, Congress provided that most drugs with new "active ingredients" would be entitled to a five-year period of marketing exclusivity. Specifically, Congress provided a five-year period of 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). Esters and salts are molecules that form in chemical reactions when the hydrogen atom of an acid molecule is replaced by another substance.[1] Esters and salts are typically closely related to their parent acid molecules.

Congress also provided a more limited three-year period of exclusivity for new drugs that contain "an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application" in certain circumstances where the drug's sponsor was required to conduct new research to gain approval. *See* 21 U.S.C. §§ 355(c)(3)(E)(iii), 355(j)(5)(F)(iii). This three-year exclusivity period applies where, for instance, a previously approved drug is approved to treat a new condition, or where approval is sought for a new salt or ester form of the active ingredient in a previously approved drug. In practice, however, more than two years separates the five- and three-year exclusivity periods, since the five-year exclusivity provision bars the FDA from *accepting* an application for approval of a competing drug, *see* 21 U.S.C. §§ 355(c)(3)(E)(ii), 355(j)(5)(F)(ii), while the three-year exclusivity provision merely precludes

[1] A salt is formed when the hydrogen in an acid is replaced by a metal or its equivalent, *Hawley's Condensed Chemical Dictionary* 1105 (Richard J. Lewis, Sr., rev., 15th ed. 2007), while an ester is formed when the hydrogen of an acid is replaced by an organic radical, *see id.* at 512.

FDA from *approving* such an application, 21 U.S.C. §§ 355(c)(3)(E)(iii), 355(j)(5)(F)(iii). Because it often takes considerable time for the FDA to approve an application once it is accepted, the difference in the length of the actual periods of exclusivity under the two provisions can be significantly greater than two years.

2. *FDA Regulations And* Abbott Labs

Section 314.108 of the FDA's regulations implements the five-year exclusivity provision. *See* 21 C.F.R. § 314.108. Although the statute refers to a new drug's "active ingredient," the regulations do not directly define that term. Instead, they grant five-year exclusivity to "new chemical entit[ies]." 21 C.F.R. § 314.108(b)(2).[2] The regulations define a "new chemical entity" (or "NCE") as any "drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b)." 21 C.F.R. § 314.108(a). "Active moiety," in turn, is defined as "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."[3]

---

[2] As a result, five-year exclusivity is often called "new chemical entity" or "NCE" exclusivity.

[3] Several separate provisions of the FDA regulations define the term "active ingredient" as: "[A]ny component 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 body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." *See* 21 C.F.R. § 210.3(b)(7) (defining "active ingredient" for purposes of Good Manufacturing Practice provisions); 21 C.F.R. § 60.3(b)(2) (supplying the same definition of "active ingredient" for Patent Term Restoration provisions); *see also* 21 C.F.R. § 201.66(b)(2) (supplying same definition for over-the-counter drug labelling provisions, except that definition applies only to components intended to affect the body of "humans," rather than "man or other animals"). An "inactive ingredient" means any component of a drug other than an active ingredient. 21 C.F.R.

Id. For salts, esters, and noncovalent derivatives, a molecule's "active moiety" can be thought of as its core; salt, ester and noncovalent derivative versions of the same basic molecule have different appendages, but they share the same active moiety. In other words, the FDA interpreted the statutory requirement that five-year exclusivity be granted to drugs no "active *ingredient* (including any ester or salt of the active ingredient) of which has been approved" to provide five-year exclusivity only to drugs that contain no active *moiety* that has been approved in a prior application.

The regulatory history makes clear that the Agency adopted the "active moiety" approach to address an issue that is not implicated in this case: the availability of exclusivity for multiple closely related forms of the same basic molecule. By defining "active moiety" to mean "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt, *. . . or other noncovalent derivative (such as a complex, chelate, or clathrate)* of the molecule," 21 C.F.R. § 314.108(a) (emphasis added), the FDA was able to withhold exclusivity not only from esters or salts of a previously approved molecule, but also from other derivative molecules that it concludes are insufficiently innovative to merit five-year exclusivity.

When the FDA first proposed regulations implementing this "active moiety" approach in 1989, it explained that the approach was justified because, in its view, Congress "did not intend to confer significant periods of exclusivity on minor variations of previously approved chemical compounds." *See Abbreviated New Drug Application Regulations*, 54 Fed. Reg. 28,872, 28,898 (proposed July 10, 1989). Almost a year and a half after the FDA issued those proposed regulations, the Court of Appeals addressed the FDA's interpretation of the statutory exclusivity

§§ 210.3(b)(8), 201.66(b)(8). Neither party, however, suggests that these definitions of "active ingredient" apply to the statutory provisions at issue in this case.

provision in *Abbott Laboratories v. Young*, 920 F.2d 984 (D.C. Cir. 1990) ("*Abbott Labs*"). In that case, the FDA argued that it could treat all forms of a molecule that eventually produce the same "active moiety" alike for purposes of exclusivity.[4] *See id.* at 988. The Agency sought to tether this authority to the statutory text by construing the term "including" broadly, and arguing that the parenthetical phrase "(*including* any ester or salt of the active ingredient)" was "merely illustrative." *Id.* With the statute so construed, the FDA argued that it was permitted to treat other forms of an active ingredient in the same manner as "esters" and "salts." *See id.*; *Abbreviated New Drug Application Regulations; Patent And Exclusivity Provisions*, 59 Fed. Reg. 50,338, 50,358 (final rule) (explaining that in *Abbott Labs*, the FDA interpreted the term "active ingredient" "narrowly to refer to the form of the moiety in the product, but interpreted the parenthetical phrase '(including any salt or ester of the active ingredient)' broadly to include all active ingredients that are different but contain the same active moiety."). The Court of Appeals rejected that interpretation of the exclusivity provision as "linguistically infeasible." *Abbott Labs*, 920 F.2d at 988.

The FDA did not retreat from its "active moiety" approach. Instead, in 1994 it promulgated the final regulations discussed above, under which five-year exclusivity is available only for "new chemical entities"—that is, drugs that do not contain any previously approved "active moiety."[5] But rather than justifying the regulations on an expansive reading of the word

---

[4] The *Abbott Labs* case involved 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. Other than substituting 10-year for 5-year exclusivity, the relevant language of that provision is identical to that in the five-year exclusivity provisions relevant here, 21 U.S.C. §§ 355(c)(3)(E)(ii) and 355(j)(5)(F)(ii).

[5] In all respects relevant here, those regulations are identical to the proposed regulations that the FDA issued before the *Abbott Labs* decision. *Compare* 54 Fed. Reg. at 28,897 (defining "new chemical entity" as "a drug that contains no active moiety that has been approved . . ." and

"including," as it had proposed in *Abbott Labs*, the FDA explained in the preamble to the Final Rule that its construction of the statute now turned on the meaning of the phrase "active ingredient." *See* 59 Fed. Reg. at 50,358. In particular, the Agency construed "active ingredient" to mean "active moiety," *see id.*, and then defined "active moiety" to mean "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt, . . . or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule." 21 C.F.R. § 314.108(a). Although taking a different route, the FDA ultimately reached the same conclusion that it did before *Abbott Labs*: The five-year exclusivity provision, in FDA's view, applies only to drugs that do not contain a previously approved "active moiety."

B. Factual And Procedural Background

1. *Lovaza*

In 2004, the FDA approved a new drug application for Lovaza (omega-3-acid ethyl esters) Capsules ("Lovaza"), an adjunct to diet intended to reduce triglyceride levels in adults with severe hypertriglyceridemia. AR 2-3, AR 144. The sole "active ingredient" of Lovaza is a mixture that is primarily composed of seven kinds of omega-3 fatty acid ethyl esters. Two of the seven esters—the esters of eicosapentaenoic acid ("EPA") and docosahexaenoic acid ("DHA")—make up approximately 85% of the mixture.[6] The rest of the mixture consists of the other five ethyl esters and other uncharacterized components.

"active moiety" as excluding "those appended portions of the molecule that cause the drug to be an . . . other noncovalent derivative"), *with* 59 Fed. Reg. at 50,358 (same).

[6] Specifically, each one-gram capsule of Lovaza contains at least 900 mg of omega-3 fatty acids, including approximately 465 mg of EPAee and 375 mg of DHAee.

Although portions of Lovaza's label refer to specific components of the mixture, there is no dispute that its sole "active ingredient" is the mixture as a whole.[7] Indeed, as recently as 2014, the FDA rejected a request by Lovaza's sponsor to re-characterize Lovaza's "active ingredients" as the separate components of the mixture. In denying that request, the FDA explained that because the Lovaza mixture has not been "fully characterized," the FDA has identified the "entire fish oil mixture as the active ingredient of Lovaza." FDA, Citizen Petition Response, Docket No. FDA-2013-P-0148 (Feb. 21, 2014) ("Lovaza Citizen Petition Response").[8] As the Agency explained, "when naturally derived mixtures are not sufficiently characterized to precisely identify every molecule that meaningfully contributes to the activity of the mixture, it is difficult to define the active ingredient in terms of the specific components of [the] mixture." *Id.* at 6. Accordingly, "[i]n such cases, the Agency may identify the entire mixture as the active ingredient of the product." *Id.* Consistent with this approach, the FDA's directory of *Approved Drug Products with Therapeutic Equivalence Evaluations* (known as the "Orange Book"), which lists each drug that the FDA has approved "for safety and effectiveness" as required by 21 U.S.C. § 355(c)(7)(A), identifies the entire Lovaza mixture—that is, "omega-3-acid ethyl esters"—as Lovaza's "active ingredient." *See Electronic Orange Book Query*, *available at* http://www.accessdata.fda.gov/scripts/cder/ob/docs/temptn.cfm (last visited on May 27, 2015).

[7] The "patient information" insert describes the "active ingredient" as "omega-3-acid ethyl esters, mostly EPA and DHA," AR 153, and the label discusses the uptake of EPA and DGA, AR 148. More generally, the label describes Lovaza as "the ethyl esters of omega-3 fatty acids sourced from fish oils," and notes that "[t]hese are predominantly a combination of [EPA] and [DHA]." AR 147-48.

[8] *Available at* http://www.regulations.gov/#!documentDetail;D=FDA-2013-P-0148-0006 (last visited May 27, 2015).

This case deals with a collateral consequence of the FDA's "active moiety" approach that arises when a drug's "active ingredient" is made up of multiple molecules and thus potentially multiple "active moieties." As explained above, when the FDA determines whether a new drug is eligible for five-year exclusivity, it focuses on the "active moiety" of the new drug. When comparing single-molecule drugs, the inquiry is straightforward: The FDA takes a new drug's single-molecule active ingredient, removes certain appendages (those that make it a salt, ester, or other noncovalent derivative) to identify its "active moiety," and then evaluates whether any previously approved single-molecule drug shares that same "active moiety." As discussed below, this analysis becomes more complicated when the FDA applies its "active moiety" approach to mixtures that contain a single "active ingredient" but multiple "active moieties."

2. *Vascepa*

Amarin is a biopharmaceutical company that focuses on products to improve cardiovascular health. On July 26, 2012, the FDA approved Amarin's new drug application for Vascepa. Like Lovaza, Vascepa was approved as an adjunct to diet to reduce triglyceride levels in adults with severe hypertriglyceridemia. The sole active ingredient of Vascepa is a single molecule: icosapent ethyl, the ethyl ester of EPA. EPA, as noted above, is a significant component of the previously approved Lovaza mixture.

When Amarin applied for approval of Vascepa, it had already been in discussions with the FDA regarding both the approval process and the level of exclusivity to which Vascepa would be entitled. On June 14, 2008, representatives from Amarin attended a pre-investigational new drug ("Pre-IND") meeting with the FDA to discuss what studies the FDA would require to approve Vascepa. The FDA's minutes from that meeting indicate that the parties discussed the FDA's preliminary answers to a list of Amarin's questions. AR 1044. Two of those questions

were whether Vascepa, if approved, would qualify as a "new chemical entity" based on the fact that it was a "single-entity active product that is molecularly distinct from any other approved product," and whether it would accordingly be entitled to five years of exclusivity. AR 1044. The FDA's preliminary answer to both questions was "Yes." AR 1044. The Agency's guidance regarding Vascepa's proposed clinical research protocol, moreover, was expressly predicated on the assumption that Vascepa was a "new chemical entity." The FDA required Amarin, for instance, to perform extra carcinogenicity studies 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." AR 1042 (emphasis added).

Based on the FDA's guidance at the pre-IND meeting, Amarin developed a research protocol and began conducting research in accordance with that guidance. *See* Dkt. 28 at 4. Ten months later, however, on May 20, 2009, an FDA representative informed Amarin that the Agency's previous indication that Vascepa would be entitled to five years of exclusivity was "not correct" because ethyl EPA is "a component of an approved product." AR 1039. Amarin asked for an opportunity to dispute that conclusion, AR 1038, and, the next day, the company sent the FDA a letter explaining the basis for its understanding that its "EPA drug product" should be entitled to five-year exclusivity, AR 1046. Among other things, Amarin argued that "Lovaza is a single active ingredient product containing" multiple "omega-3-acid ethyl esters." AR 1047. In an effort to satisfy the FDA's "active moieties" approach, Amarin then argued that the ester of EPA is just one of the multiple esters that combine to form a "single active moiety" in Lovaza. AR 1047. Following this logic, Amarin maintained that "[b]ecause the single active moiety in Lovaza encompasses more than EPA, it must be distinct from EPA alone," and thus Vascepa does not contain a previously approved active ingredient or active moiety. AR 1047.

Four months later, on September 21, 2009, the FDA responded that it would not consider whether Vascepa was entitled to five-year exclusivity until it reviewed the final new drug application for Vascepa. AR 1047.

Amarin submitted its new drug application, along with a request for five-year exclusivity, in September 2011. AR 1032-37. In its request for exclusivity, Amarin emphasized that EPA was not an "active ingredient" that was "approved in the NDA covering Lovaza," because Lovaza was approved as a single active ingredient product and there was "no evidence" demonstrating whether specific components of the Lovaza mixture were active ingredients. AR 1033. In subsequent filings, Amarin explained that in its view, the "key legal issue" was "whether the prior approval of a drug product, the active ingredient of which is a complex mixture of constituents, constitutes approval of each constituent as an active ingredient so as to preclude NCE exclusivity for a new drug product in which one of those constituents alone is the active ingredient." AR 51.

Amarin's new drug application for Vascepa was approved on July 26, 2012, but the FDA did not make a decision regarding five-year exclusivity at that time. *See* AR 73. Instead, the FDA issued a "General Advice" letter asking for Amarin's response to several precedents that the Agency viewed as consistent with the denial of exclusivity for Vascepa, and Amarin responded to that inquiry. AR 1050. The FDA reached a decision on February 21, 2014, eighteen months after Vascepa was approved. It concluded that Vascepa is not entitled to five-year exclusivity because "EPA, the single active moiety in Vascepa, was also an active moiety contained in" Lovaza. AR 1.

3. *The FDA's Decision Denying Exclusivity*

In its decision, the FDA explained that the statutory and regulatory authorities "focus principally on single component active ingredients," rather than naturally derived mixtures, and "that neither the statute nor the regulations expressly address 5-year NCE [new chemical entity] exclusivity in the context of naturally derived mixtures." AR 6. The Agency further noted that its prior decisions and statements "have not necessarily resulted in consistent outcomes" or "used precise terminology in addressing exclusivity" in the context of naturally derived mixtures. *Id.*

The FDA then explained that, although they are "often conflated," it is important to distinguish between "the meaning of the terms 'active ingredient' and 'active moiety.'" *Id.* Where a request for exclusivity involves "drugs that are composed of a single, well-characterized molecule, the distinction between 'active moiety' and 'active ingredient[ ]' generally is negligible." *Id.* That is because the "active ingredient typically contains the only active moiety in the drug product, and the two regulatory concepts refer to the same molecule for the purposes of the exclusivity analysis." *Id.* Thus, to take an easy case, if drug A contains a salt of molecule X, and drug B contains an ester of molecule X, the drugs would contain the same active moiety (molecule X) and would also—to use the key statutory phrase—contain the same "active ingredient (including any ester or salt of the active ingredient)" (molecule X).

For naturally derived mixtures comprising multiple molecules, on the other hand, the FDA explained that "the distinction between 'active ingredient' and 'active moiety' . . . becomes crucial." *Id.* If more than one of the molecules contained in a naturally derived mixture "could be responsible for the physiological or pharmacological action of the drug substance," the FDA must decide what constitutes the "active ingredient" and what constitutes the "active moiety" or "active moieties." AR 6-7. To do so, the Agency decided to treat "poorly characterized" and

"well-characterized" mixtures differently. For "poorly characterized mixtures," where "it is difficult to determine with any certainty . . . which molecules in the mixture are consistently present or potentially are responsible for the physiological or pharmacological activity of the drug," the Agency treats "the entire mixture as the active moiety." AR 7. This result is "born of necessity," and "each new version of such a naturally derived mixture would be eligible for 5-year NCE exclusivity." *Id.* In contrast, for "well characterized" mixtures, where at least "some components of the mixture . . . are consistently present and active," the FDA decided to treat "the entire mixture [as a] single active ingredient," while recognizing that the "active ingredient" contains "more than one component active moiety." *Id.*

The FDA then proceeded to lay out, for the first time, a three-part "framework" "for identifying the active moiety or moieties of such mixtures." AR 6. Under that framework, the FDA "generally" considers component molecules of a mixture to be previously approved "active moieties" for purposes of determining a subsequent drug's eligibility for five-year exclusivity where (1) specific molecules in the mixture have been identified; (2) those specific molecules are "consistently present in the mixture"; and (3) those 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." AR 7-8. The determination of whether a particular molecular component of a previously approved mixture meets these criteria is based on "technological tools and scientific concepts available" at the time the FDA evaluates the exclusivity of a new drug—not the understanding that the FDA had when it approved the mixture in the first place. AR 8, n. 36.

The FDA thus identified two different approaches to the five-year exclusivity analysis. When dealing with single molecule drugs, the FDA applies a "one-to-one" approach. That is, the

drug product contains a "single active ingredient" and a "single active moiety," so there is a simple, "one-to-one" relationship between the active ingredient and the active moiety. AR 6. "[O]f necessity," the FDA applies this same approach to poorly characterized mixtures. AR 7. But, "where at least part of the mixture is well characterized," the FDA applies a different approach. It identifies the entire mixture as the single "active ingredient" of the drug, yet treats each component molecule that is consistently present and that contributes, at least in part, to the physiological or pharmacological activity of the mixture as containing a distinct "active moiety." In the FDA's words, "[t]his approach recognizes that there can be a 'one-to-many' relationship between the [single] active ingredient and its [many] component active moieties." *Id.*

Applying this framework, the FDA concluded that "Lovaza is a well-characterized mixture with respect to its omega-3 acid components," and it thus applied its "one-to-many" approach. AR 16. The FDA further concluded that (1) "the EPA in the Lovaza mixture" "has been identified as a specific molecule present in the mixture," (2) it "is consistently present in the . . . mixture," and (3) "the available evidence establishes that EPA has meaningful pharmacological activity in lowering serum triglyceride levels, the approved indication for both Lovaza and Vascepa." *Id.* Because EPA is the "active moiety" in Vascepa, the FDA concluded that both drugs contain the same "active moiety" and that Vascepa, accordingly, does not qualify for five-year exclusivity.

The FDA acknowledged that it "has not always clearly set out its rationale for its determinations in the past"; that "neither the Agency nor regulated industry has used consistent terminology in this context"; and that "past [FDA] exclusivity determinations have not always been consistent." AR 22. Nonetheless, it concluded that "in light of the relevant authorities, applicable scientific principles and past Agency action," its newly announced three-part test

"best harmonizes the relevant authorities and the outcomes of relevant prior Agency actions." *Id.* Although Amarin invested in the studies necessary to obtain market approval for Vascepa, in the FDA's view, "[t]he amount of research that a sponsor invests in a drug is not determinative of that drug's eligibility for 5-year NCE exclusivity." AR 23. Investment of that type, instead, is "a central factor in whether a drug is eligible for 3-year exclusivity." *Id.* Here, because Vascepa and Lovaza contain the same active moiety (EPA), the FDA concluded that Vascepa is entitled only to 3-year exclusivity.

II. STANDARD OF REVIEW

Amarin's challenge to the FDA's decision denying five-year exclusivity to Vascepa implicates the Agency's interpretation of the Hatch-Waxman Amendments and its reasoning in its administrative decision denying Amarin's request for exclusivity, AR 1-24. The case thus involves at least "two distinct but potentially overlapping standards of APA review." *Fox v. Clinton*, 684 F.3d 67, 74 (D.C. Cir. 2012).

First, to the extent the FDA's denial of five-year exclusivity for Vascepa was governed by its interpretation of the Hatch-Waxman Amendments, its decision is subject to review under the two-step framework established in *Chevron U.S.A. v. Natural Resources Defense Council*, 467 U.S. 837 (1984). Under the first step of *Chevron*, the Court must consider "whether Congress has directly spoken to the precise question at issue." *Id.* at 842. If so, the Court must "give effect to the unambiguously expressed intent of Congress." *Id.* at 843. In making this determination, the Court applies the "traditional tools of statutory construction," *id.* at 843 n.9, including looking to "the text, structure, and the overall statutory scheme, as well as the problem Congress sought to solve," *Financial Planning Assoc. v. SEC*, 482 F.3d 481, 487 (D.C. Cir. 2007); *see also Cal. Indep. Sys. Operator Corp. v. FERC*, 372 F.3d 395, 399 (D.C. Cir. 2004);

Indep. Ins. Agents of Am., Inc. v. Hawke, 211 F.3d 638, 643-44 (D.C. Cir. 2000). If the Court concludes that Congress has left an ambiguity or "gap" to fill on the "precise question at issue," the Court proceeds to the second step of *Chevron*. *Chevron*, 467 U.S. at 843. Under the second step, the Court asks whether the agency's construction of the statute is a "permissible" one. If it is, the Court must defer to that construction.

Second, more generally, the APA precludes agency action that is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). An agency's decision, accordingly, must be the product of "reasoned decisionmaking." *Motor Vehicle Mfrs. Ass'n of U.S. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 52 (1983). An agency action will normally be set aside as "arbitrary and capricious" if the agency "has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise." *Id.* at 43.

These standards overlap and are, at times, intertwined. Most significantly, because *Chevron*'s second step asks whether an agency's interpretation is "arbitrary or capricious in substance," *Judulang v. Holder*, 132 S.Ct. 476, 483 n. 7 (2011) (citing *Mayo Found. for Med. Educ. & Research v. United States*, 131 S.Ct. 704, 711 (2011)), "the analysis required pursuant to *Chevron* [s]tep [t]wo, and that required under the arbitrary and capricious standard enunciated in *State Farm*" overlap, *EchoStar Satellite L.L.C. v. FCC*, 704 F.3d 992, 1001-02 (D.C. Cir. 2013). Similarly, mirroring the arbitrary and capricious standard, a court will affirm an agency's interpretation at *Chevron* step two only if the agency has "offered a reasoned explanation for why it chose that explanation." *Vill. of Barrington, Ill. v. Surface Transp. Bd.*, 636 F.3d 650, 660

(D.C. Cir. 2011). Ultimately, under either standard of review, the relevant question is whether the FDA's decision represents the result of a reasonable exercise of its authority.

III. DISCUSSION

Under the text of the Hatch-Waxman Amendments, a drug manufacturer is entitled to five-year exclusivity if its newly-approved drug does not contain an "active ingredient" that was previously approved in another drug application. 21 U.S.C. §§ 355(c)(3)(E)(ii), 355(j)(5)(F)(ii). Under the FDA's implementing regulations, in contrast, the drug manufacturer is entitled to exclusivity only if its drug does not contain an "active moiety" that was previously approved in another drug application. 21 C.F.R. § 314.108(a). In most cases, this distinction is inconsequential. When dealing with single molecule drugs, the "active ingredient" and the "active moiety" refer to the same molecule and thus the distinction typically makes no difference to the Agency's exclusivity analyses. The same is true when the FDA addresses poorly characterized mixtures, where it treats the entire mixture as both a single "active moiety" and a single "active ingredient," again maintaining the symmetry with the statutory text. In both cases, the exclusivity analysis will rarely turn on any minor distinctions between an "active ingredient" and an "active moiety."

This is not so, however, where the exclusivity regulations are applied under the FDA's new "framework" to fully or partially characterized mixtures, like Lovaza. In that context, the symmetry between the regulatory and statutory language breaks down, because the FDA maintains that the drug may have a single "active ingredient"—the entire mixture—but multiple "active moieties." *See* AR 6-7. The challenge the FDA faces here, and that it faced in the administrative proceeding, is how, if at all, it can justify this departure from the statutory text, which premises exclusivity on a comparison between "active ingredients."

In its administrative decision, the FDA espouses two conflicting definitions of "active ingredient." At times, the Agency asserts that "active ingredient" and "active moiety" mean different things, and, indeed, the FDA criticizes Amarin for "conflat[ing]" the two concepts. AR 6. In a footnote, however, the FDA quotes from the Final Rule adopting the five-year exclusivity regulations, which asserts that, for relevant purposes, "active ingredient" means "active moiety." *Id*. Unsurprisingly, the FDA does not now rely on the first of these interpretations in its effort to reconcile the statutory reference to a drug's "active ingredient" with the regulatory reliance on the drug's "active moiety." If these concepts are distinct, as the administrative decision suggests, the statutory language must control, and the decision must be set aside. As Amarin correctly observes, the one thing that can be said with certainty about the meaning of the statute is that "active ingredient" cannot logically mean "not active ingredient."

Thus, for purposes of this action, the FDA focuses its argument on the interpretation it offered in the footnote, under which "active ingredient" and "active moiety" mean the same thing, and it argues that this definition survives scrutiny under the two-step framework in *Chevron*. Following this framework, the FDA first argues that the statutory phrase "active ingredient" is ambiguous, and that Congress, accordingly, left a gap for the FDA to fill. It then maintains that its decision to adopt the "active moiety" approach in the face of this ambiguity was reasonable and that it is entitled to the Court's deference.

A. *Chevron* Step One

Under *Chevron* step one, the Court must consider "whether Congress has directly spoken to the precise question at issue." 467 U.S. at 842. If so, the Court must "give effect to the unambiguously expressed intent of Congress." *Id.* at 843. In making this determination, the Court applies the "traditional tools of statutory construction," *id.* at 843 n.9, including looking to

"the text, structure, and the overall statutory scheme, as well as the problem Congress sought to solve," *Fin. Planning Ass'n*, 482 F.3d at 487; *see also Cal. Indep. Sys. Operator Corp.*, 372 F.3d at 400. Here, the "precise question at issue" is whether, for purposes of exclusivity, the Hatch-Waxman Amendments permit the FDA to interpret "active ingredient" that "has been approved" to mean any "active moiety" in a previously approved drug.

1. Abbott Labs *and* Actavis Elizabeth

The FDA starts by arguing that the phrase "active ingredient" is ambiguous, leaving room for the Agency to read it to mean "active moiety" for purposes of the five-year exclusivity provision. According to the FDA, the Court of Appeals has twice held that the phrase "active ingredient," as used in the exclusivity provision, is ambiguous—first in *Abbott Labs*, 920 F.2d at 987-88, and again in *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 764 (D.C. Cir. 2010). With respect to *Abbott Labs*, the Agency misreads the decision. There, the appellant argued that the phrase "active ingredient" has a "well understood meaning," while the FDA argued that, even though it has construed the phrase "narrowly" in another passage of the Act, "active ingredient" could reasonably be read in the exclusivity provision "as a virtual synonym for active moiety." *Abbott Labs*, 920 F.2d at 997. In response, the Court of Appeals agreed that "it is not impermissible under *Chevron* for an agency to interpret an imprecise term differently in two separate sections of a statute which have different purposes." *Id*. But the court went on to hold that it could not "consider whether active ingredient is such a term because the agency did not in its decision . . . employ this theory." *Id*. The Court of Appeals, in short, simply did not decide the issue.

The FDA's reliance on *Actavis* is better placed but also fails to advance the Agency's position. In *Actavis*, the plaintiff argued that the phrase "active ingredient" unambiguously

refers to the post-ingestion form of a single-molecule active ingredient, rather than to the ingredient's form before it is ingested. The Court of Appeals rejected that argument and concluded that the phrase "active ingredient" was in relevant respects ambiguous, and that the FDA had acted within the scope of its delegated authority when it interpreted "active ingredient" to refer to the "prodrug[]" form of a molecule.[9] 625 F.3d at 764-65. But even though *Actavis* makes clear that the term "active ingredient" is ambiguous at least to the extent that it may refer to either a pre- or post-ingestion form of a drug, that conclusion does not resolve whether "Congress has directly spoken to the precise question at issue" here, *Chevron*, 467 U.S. at 842. A judicial decision concluding that a statutory term admits of *some* ambiguity does not open the door at *Chevron* step one for purposes of *all* interpretations.

2. *The FDA's Interpretation Of "Active Ingredient"*

Because the Court of Appeals has not previously addressed whether the Hatch-Waxman Amendments "encompass" the "active moiety" interpretation at issue here, the Court must consider whether the statute "unambiguously forbids the Agency's interpretation." *Barnhart v. Walton*, 535 U.S. 212, 218 (2002). The question is not whether the phrase is, "in some abstract sense, ambiguous," or whether it may be susceptible to various interpretations in another context, but "whether, read in context and using the traditional tools of statutory construction, [it] encompasses" the agency's construction. *Cal. Indep. Sys. Operator Corp.*, 372 F.3d at 400; *see also Indep. Ins. Agents*, 211 F.3d at 644-45. This analysis may "sound like *Chevron* step two" because the term "active ingredient" is ambiguous in *some* applications, but, under *Chevron* step

[9] As the Court of Appeals noted in *Actavis Elizabeth*, the Federal Circuit has held that the term "active ingredient" "has a plain meaning that, if adopted, would allow more prodrugs to attain five year exclusivity than the FDA's current interpretation." 625 F.3d at 764, n. 6. *See also PhotoCure ASA v. Kappos*, 603 F.3d 1372, 1376 (Fed. Cir. 2010); *Glaxo Operations UK Ltd. v. Quigg*, 894 F.2d 392, 395 (Fed. Cir. 1990).

one, "where the text and reasonable inferences from it give a clear answer against the government . . . that . . . is the end of the matter." *Cal. Indep. Sys. Operator Corp.*, 372 F.3d at 401 (quotation marks omitted). In any event, whether analyzed under *Chevron* step one or two, the answer is the same; the statute's text, structure, and purpose do not "encompass" or "permi[t]" the construction the Agency has given it. *Barnhart*, 535 U.S. at 218; *Chevron*, 467 U.S. at 843. As explained below, the FDA's interpretation of the statute suffers from at least three difficulties.

a. The Canon Against Surplusage

First, the contention that "active ingredient" means "active moiety" is at odds with the canon against surplusage. *See Indep. Ins. Agents*, 211 F.3d at 644-45 (rejecting agency's interpretation at *Chevron* step one based on the tandem canons "of avoiding surplusage and *expressio unius*"). "It is 'a cardinal principle of statutory construction' that 'a statute ought, upon the whole, to be construed'" in manner that ensures that "'no clause, sentence, or word shall be superfluous, void, or insignificant.'" *TWR Inc. v. Andrews*, 534 U.S. 19, 31 (2001) (citation omitted). The FDA's contention that "active ingredient" means "active moiety," however, would render the parenthetical clause in the exclusivity provisions either redundant or incomprehensible.

If "active ingredient" means "active moiety," and "active moiety" is defined as a molecule excluding (among other things) those portions that render the molecule a salt or an ester, 21 C.F.R. § 314.108(a), there are no circumstances in which the parenthetical clause would have any coherent meaning. As defined by the FDA, the relevant statutory text would read as follows: A new drug is entitled to five-year exclusivity as long as "no molecule, excluding those appended portions that cause it to be an ester, salt or other noncovalent derivative (including any

ester or salt of the molecule, excluding those appended portions that cause it be an ester, salt or other noncovalent derivative)" has been approved in any previous new drug application. Indeed, under this construction, the parenthetical is not merely surplusage; the exclusivity provision makes sense only if the parenthetical is omitted. The statutory provision includes two references to the term "active ingredient." Defining either to mean "active moiety" would render the statute incoherent; reading both to mean "active moiety"—as required to maintain any semblance of consistency in statutory interpretation—results in a mind-numbing muddle.[10]

The regulatory history highlights why the FDA's "active moiety" approach cannot be reconciled with the statutory text. Although the parenthetical clause expressly refers only to "any ester or salt of the active ingredient," 21 U.S.C. §§ 355(c)(3)(E)(ii), 355(j)(5)(F)(ii), the FDA has long sought to include "other noncovalent derivatives," in addition to "esters" and "salts," in order to ensure that "significant periods of exclusivity" are not conferred "on minor variations of previously approved chemical compounds." 54 Fed. Reg. at 28,898. Originally, the Agency sought to achieve this goal by construing the statutory parenthetical to provide a non-exhaustive list of molecules that are closely related to a drug's "active ingredient"—that is, it construed the *parenthetical* to mean including "esters," "salts," and "other noncovalent derivatives." *See* 59 Fed. Reg. at 50,358. The Court of Appeals, however, rejected that

[10] In *Abbott Labs*, the Court of Appeals held that the Agency could interpret the "active ingredient" in the parenthetical clause to refer to the "active ingredient" of the drug for which exclusivity is sought, the older drug against which the new drug is being compared, or both. *See* 920 F.2d at 988-89. Thus, the FDA may withhold exclusivity for drugs that are different derivative forms of previously approved drugs regardless of which form of the drug is first approved. The FDA does not dispute that the statute, as interpreted, requires it to compare the same components of old and new drugs to determine exclusivity; it simply argues that this analysis can be based on a comparison between "active moieties" rather than "active ingredients."

approach in *Abbott Labs*, 920 F.2d at 988. It was only at this point that the FDA shifted its focus, and asserted that the term "active ingredient" itself means "active moiety," such that all closely-related forms of a molecule—including esters, salts, and other noncovalent derivatives—would have the same "active ingredient" for exclusivity purposes. *Id.*; 59 Fed. Reg. at 50,358 (explaining that in light of *Abbott Labs*, "[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") (emphasis added). But, because the parenthetical already expressly addresses "esters" and "salts," this led to an inescapable redundancy in the statute. By defining "active ingredient" such that "esters" and "salts" (along with "other noncovalent derivatives") share the same "active ingredient," the FDA has deprived the parenthetical of any coherent meaning.

b. The Presumption Of Consistent Usage

The second problem with the Agency's interpretation is that it requires the Agency to interpret the phrase "active ingredient" differently for purposes of the ANDA and exclusivity provisions of the Act. In the ordinary course, however, "identical words used in different parts of the same Act are intended to have the same meaning." *Sorenson v. Sec'y of Treasury*, 475 U.S. 851, 860 (1986) (quotation marks omitted); *see also, e.g.*, *Powerex Corp. v. Reliant Energy Servs., Inc.*, 551 U.S. 224, 232 (2007) ("A standard principle of statutory construction provides that identical words and phrases within the same statute should normally be given the same meaning."); *IBP, Inc. v. Alvarez*, 546 U.S. 21, 34 (2005) (noting that "identical words used in different parts of the same statute are generally presumed to have the same meaning"). Absent good reason, it is safe to assume that Congress intended "active ingredient" to have the same meaning when it used that term in different, but closely related, places in the same statute.

In the present context, there are strong reasons to conclude that the presumption of consistent usage applies. First, the Hatch-Waxman Amendments were designed to strike a compromise between the interests in bringing generic drugs to market quickly and inexpensively and providing a period of market exclusivity to innovators. *See Abbott Labs*, 920 F.2d at 985; *see also, e.g.*, 130 Cong. Rec. 23058-59 (1994) (statement of Rep. Synar) ("This bill is an important compromise that improves research and development and increases price competition in the drug marketplace."). Although not conclusive, this suggests that Congress intended, at least at a general level, to treat the pro-generic and pro-branded provisions of the law as flip-sides of the same coin, a coherent set of incentives for stakeholders with competing interests. *Cf. Teva Pharm. Indus. Ltd. v. Crawford*, 410 F.3d 51, 54 (D.C. Cir. 2005) ("Because the balance struck" in the Hatch Waxman Act is "quintessentially a matter for legislative judgment, the court must attend closely to the terms in which the Congress expressed that judgment."); *Ranbaxy Labs. Ltd. v. Leavitt*, 469 F.3d 120, 126 (D.C. Cir. 2006) ("The FDA may not . . . change the incentive structure adopted by the Congress.").

Congress, moreover, enacted the relevant references to "active ingredients" at the same time, in the same amendments, and inserted the language into the same subsection of the FDCA. *See* 21 U.S.C. §§ 355(j)(2)(A)(ii)(I)-(III), 355(j)(4)(C)(i)-(iii), 355(j)(5)(F)(ii). It used the phrase precisely, and, significantly, it understood how to instruct the FDA to focus its analysis on different components of a drug. Thus, unlike in the provisions permitting the filing of ANDAs, 21 U.S.C. §§ 355(j)(2)(A)(ii)(I)-(III), 355(j)(4)(C)(i)-(iii), the five-year exclusivity provisions add the parenthetical "(including any ester or salt of the active ingredient)," 21 U.S.C. §§ 355(c)(3)(E)(ii), 355(j)(5)(F)(ii). Where Congress intended to modify the term, it did so expressly and specifically. Its decision explicitly to treat certain forms of "active ingredients"

(that is, salts and esters) alike for purposes of exclusivity, but not for ANDA purposes, reinforces the conclusion that it did not intend to delegate to the FDA the authority *otherwise* to give the phrase "active ingredient" different meanings for exclusivity and ANDA purposes.

As the FDA correctly observes, the presumption of consistent usage is not unrebuttable. It will give way, for example, where application of the presumption creates a genuine conflict with the purpose or text of the statute or where Congress uses a term "profligate[ly]" in an Act, including in contexts where a consistent definition is "incompatible" with the overall statutory structure. *See Util. Air Regulatory Grp. v. EPA*, 134 S. Ct. 2427, 2441-42 (2014). At oral argument, the FDA further argued that the meaning of the phrase "active ingredient" turns on context. Tr. Oral Arg. 68. When Congress provided that a generic drug may take advantage of the ANDA process if its "active ingredient(s)" are "the same as" the "active ingredient(s)" contained in a previously approved and "listed" drug, Congress intended to refer to entire molecules or mixtures, and not simply the "active moiety." *See* 21 U.S.C. §§ 355(j)(4)(C)(i)-(iii). But, when Congress provided five-year exclusivity for a new drug "no active ingredient (including any ester or salt of the active ingredient) of which has been approved in" a prior new drug application, the FDA contends that Congress permitted, and the Agency's regulations adopted, a different construction of the phrase. In that context, the FDA maintains, "active ingredient" means "active moiety." *See* 59 Fed. Reg. at 50,358.

In *Abbott Labs*, the Court of Appeals confirmed that Congress may, in some circumstances, use the same word to mean different things within the same statute. There, as here, the FDA argued that "Congress was using the term active ingredient loosely" in the five-year exclusivity provision, "possibly as a virtual synonym for active moiety." *Abbott Labs*, 920

F.3d at 987. But in *Abbott Labs*, the Court declined to consider that theory because the agency had not "employ[ed]" it in its administrative decision. *Id.*

As in *Abbott Labs*, 920 F.2d at 987, the Court does not foreclose the possibility that the Agency might reasonably construe and apply the phrase "active ingredient" to have a different meaning in different contexts or when dealing with different "kind[s] of drugs," *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1319 (D.C. Cir. 1998) (upholding FDA's interpretation of statutory requirement that active ingredient in ANDA be the "same as" previously approved active ingredient to require "clinical identity," rather than "chemical identity," in context of category of drugs for which "slight natural variations" in molecular structure were expected). But, as discussed above, this not a circumstance where Congress has used the phrase loosely or where a consistent definition is "incompatible" with the statutory structure or purpose, *see Util. Air Regulatory Grp.*, 134 S. Ct. at 2441-42. The ANDA and exclusivity provisions may serve different functions, but they are part of a single statutory structure, and Congress added a modifying parenthetical evincing its attention to how, if at all, the references might apply differently in the different contexts.

The FDA's own practices, moreover, demonstrate that adopting a consistent interpretation of "active ingredient" would not result in any "incompatibility" with the statutory structure or purpose. To the contrary, in other contexts, the FDA has made its exclusivity determination based on an entire mixture, rather than the mixture's "active moieties." *See, e.g.*, AR 413 (noting that the same "'active' components" were present in different quantities in InfaSurf and Survanta, but explaining that the agency would treat the "entire mixture" as the active moiety); AR 71 (noting that the FDA considered "the entire mixture to be the active moiety" for Orphan Drug exclusivity purposes). Indeed, the FDA concedes that its approach in

some prior cases is irreconcilable with its new framework. *See* Dkt. 13-1 at 21; AR 20. And even under the framework the FDA announced in this case, for poorly characterized mixtures, the FDA's exclusivity analyses will continue to focus on mixtures as a whole.

Notably, the statute contemplates that the FDA will approve drugs containing multiple "active ingredients," and, with respect to at least one naturally derived mixture, the FDA has taken precisely this approach. *See* AR 15-16; Tr. Oral Arg. 77-78 (discussing the FDA's characterization of Menotropins as mixtures composed of multiple active ingredients). The FDA's approach with respect to Lovaza stands in contrast: Not only did the FDA treat the Lovaza mixture as a single "active ingredient" for purposes of approval, it also denied a Citizens' Petition requesting that the mixture be re-characterized as containing multiple "active ingredients" on the same day that it issued its decision in the instant dispute. *See* Lovaza Citizen Petition Response. Ultimately, the FDA is free to determine whether any particular naturally derived mixture is better understood as containing one or multiple active ingredients. To the extent that the FDA is concerned that granting five-year exclusivity for different mixtures will unduly allow pharmaceutical companies to obtain exclusivity for components of mixtures that were already well-understood, it can take precisely that approach.

Although the FDA did not discuss the issue in its administrative process, it argues before this Court that the exclusivity and ANDA provisions serve different purposes, because the exclusivity provision is designed to promote novelty while the ANDA provisions require the FDA to ascertain whether generic drugs are safe and effective. Tr. Oral Arg. 55; *id.* at 7. But, as explained above, while the two provisions do, of course, play different roles, they are part of a unified statutory scheme intended to strike a balance between fostering innovation and

promoting access to affordable medications. When the phrase is interpreted to mean the same thing, each provision still performs its function within the statute.

In any event, the Agency's interpretation cannot be squared with what the Agency actually said in its decision. Rather than positing that, when it asserted that Lovaza's "active ingredient" was the entire mixture, it was using the term "active ingredient" in a different manner than it is used in the exclusivity provision, the FDA said just the opposite. Throughout the decision, it is clear that the FDA is using the phrase as it is used in the exclusivity provision. The decision says "*under FDA's regulations*, a drug's active ingredient is distinct from its active moiety, and, at least in the case of a naturally derived mixture, a single active ingredient can have multiple active moieties." AR 23 (emphasis added). The Agency's use of the phrase "active ingredient" in its administrative decision, accordingly, cannot be reconciled with the statutory text, and any post-hoc re-characterization of the decision is insufficient, *see Williams Gas Processing v. FERC*, 475 F.3d 319, 326 (D.C. Cir. 2006) ("'agency rationales developed for the first time during litigation do not serve as adequate substitute'" for "'reasoned decisionmaking *at the agency level*'") (quoting *Kansas City v. HUD*, 923 F.2d 188, 192 (D.C. Cir. 1991)).

To be sure, an agency need not set forth its reasoning in each individual adjudication, where it has done so in prior adjudication or in a rulemaking that supplies a generally applicable rationale or explanation that is then simply applied in the adjudication. *See WLOS TV, Inc. v. FCC*, 932 F.2d 993, 995 (D.C. Cir. 1991) (Where "an agency merely implements prior policy, an explanation that allows this court to discern 'the agency's path' will suffice.") (quoting *Hall v. McLaughlin*, 864 F.2d 868, 972-73 (D.C. Cir. 1989)). But the Agency still must demonstrate that it has "given reasoned consideration to all the material facts and issues." *See Ventura Broad. Co v. FCC*, 765 F.2d 184, 189 (D.C. Cir. 1985) (quotation marks omitted). Yet, at no

point does the FDA appear to have considered how its new application of the "active moiety" approach to naturally derived mixtures can be reconciled with the text, structure, or purposes of the Hatch-Waxman Amendments. Although the Agency's Final Rule does state that the phrase "active ingredient" should be construed to mean "active moiety," 59 Fed. Reg. at 50,358, there is no evidence that the Agency ever considered, much less explained, how this approach might sensibly apply in the context of naturally derived mixtures or other drugs where the Agency has construed "active ingredient" and "active moiety" to refer to significantly different substances. To the contrary, the administrative decision candidly observes that the regulations do not "address 5-year NCE exclusivity in the context of naturally derived mixtures" but rather "focus principally on single component ingredients." AR 6.

c. *The Statutory Focus On An Active Ingredient That "Has Been Approved"*

The third (and related) difficulty with the Agency's approach is that its focus on a drug component that was never the subject of the FDA's approval is also inconsistent with the statutory text, which considers whether the new drug contains an "active ingredient" "which *has been* approved in [a prior] application." 21 U.S.C. §§ 355(c)(3)(E)(ii), 355(j)(5)(F)(ii) (emphasis added). Under the FDA's approach, the relevant "active moieties" are not even identified until the Agency acts on an application for exclusivity. The determination is not made based on information that was actually before the FDA at the time it decided to approve the first drug. Rather, the FDA explained in its administrative decision that "the Agency [should] make this determination at the time it determines whether a particular molecule is an active moiety of a previously approved mixture, *using the technological tools and scientific concepts available at that time*." AR 8, n.36 (emphasis added).

Thus, although there is no dispute that at the time the NDA for Lovaza was approved, the entire mixture of "omega-3 acid ethyl esters" was "list[ed]" as the drug's "active ingredient," AR 2, the FDA applied its three-step test to determine the "active moieties" in Lovaza more than seven years later, at the time Vascepa was approved. *See* AR 7-8. In 2014, the Agency assessed (1) whether the mixture is well-characterized, (2) whether "one or more specific molecules . . . are consistently present," and (3) whether those molecules "are responsible at least in part for the physiological or pharmacological action of the mixture." AR 7-8. The FDA denied Vascepa exclusivity based on studies that it found showed that EPA independently lowers triglyceride levels. But the Agency concedes that these studies were not relied upon by Lovaza's sponsor in the NDA for the mixture, or, presumably, by the FDA in approving Lovaza's NDA. Dkt. 29 at 1-2 ("Because approval of Lovaza was sought based on the entire mixture, the supporting studies tested the entire mixture rather than individual components."). Although the FDA contends that it is "likely" that Lovaza's sponsor "was aware" of studies regarding EPA's pharmacological effect, *id.*, even if that were the case, the sponsor's awareness of the studies does not support the conclusion that EPA was previously "approved." The FDA's approach fails to make temporal or substantive sense of the statutory reference to an "active ingredient" "which *has been approved*," and thus, once again, is at odds with the statute.

The FDA does not argue that an "active moiety" contained in a naturally derived mixture is ever "approved" in any sense of the word. At oral argument, the FDA explained that it approves "drugs" and not "active ingredients." Tr. Oral Arg. 62-63. It thus argues that the statutory reference to an "ingredient" that "has been approved" cannot carry significant weight. Put differently, the FDA argues that Congress made a mistake when it referred to the FDA's approval of an "active ingredient," and that, as a result, it is reasonable for the Agency to

consider any "component of a drug which [the Agency] has approved," Tr. Oral Arg. 63, when it later identifies the constituent moieties of the approved drug. According to the FDA, this reasoning applies even where the moiety is a molecule that was not independently evaluated by the FDA.

It is not correct, however, to say that the FDA does not approve "active ingredients" when it approves drugs or drug products. In at least one other case, the FDA has affirmatively argued—and the Court agreed—that the FDA approves "active ingredients as well as finished drug products." *Pharmanex v. Shalala*, 221 F.3d 1151, 1154-56 (10th Cir. 2000) (accepting FDA's argument that the phrase "an article that is approved as a new drug" includes active ingredients, and explaining that "[i]t is evident from § 355 that approval of active ingredients is integral to the overall new drug approval process"). At times, the FDCA refers to the approval of "drugs," *see, e.g.*, 21 U.S.C. § 355(j)(6); at times, it refers to the approval of "active ingredients," *see, e.g.*, *id.* at § 355(j)(3)(E)(v) (referring to drugs which "include an active ingredient . . . that has been approved"). Most frequently, including in the provisions at issue in this case, the statute suggests that it is the new drug application, or NDA, that is subject to "approval." *See* 21 U.S.C. §§ 355(c)(3)(E)(ii), 355(j)(5)(F)(ii). And, here, in the FDA's own words, the "FDA approved [the] NDA . . . for Lovaza," and that NDA "lists 'Omega-3 acid ethyl esters' as [Lovaza's] active ingredient." AR 2. It does not require a substantial leap to conclude that the approval of an NDA that lists the entire mixture as the drug's "active ingredient" means that the mixture "has been approved in [a prior] application" or NDA, especially given that the FDCA contemplates that "active ingredients," as well as drugs, may be the subject of the FDA's approval. *See Pharmanex*, 221 F.3d at 1156.

Moreover, even if Congress could have been more precise, its intent is evident. It makes no material difference whether it is the "active ingredient" that is approved in an NDA—as Congress wrote—or whether, slightly more literally, it is the NDA that lists the "active ingredient" that is approved. What is apparent is that Congress intended for exclusivity determinations to hinge on a component of the drug that the FDA actually reviewed in its approval process. Although the Lovaza mixture, as the drug's "active ingredient," can fairly be said to have "been approved," the same is not true for EPA, standing alone. As the FDA concedes, the studies submitted in support of Lovaza's NDA "tested the entire mixture rather than individual components." Dkt. 29 at 1.

Determining which molecules of previously approved drugs are relevant for exclusivity determinations based on information that was not before the FDA when it approved those drugs is also inconsistent with the statutory purpose of the exclusivity provision, which was intended to provide incentives for drug manufacturers to invest in innovation. *See Actavis Elizabeth*, 625 F.3d at 764. Under the FDA's approach, a would-be innovator would not know whether its new drug would qualify for market exclusivity until after the drug was fully developed and approved by the FDA. At that point in time, the FDA would then consider whether a component of a previously approved drug was consistently present in that drug and whether it was "responsible at least in part for the physiological or pharmacological action of the mixture." AR 7-8. As this case illustrates, that approach would inject substantial uncertainty into the process and would detract from the incentives for innovation that Congress intended to provide. The Agency has not even hinted at a statutory purpose or policy rationale that would render that approach a reasonable interpretation of the statute.

Of course, as the FDA points out, there is inherent uncertainty as to whether a particular drug will be entitled to five-year exclusivity because there is always a risk that a would-be innovator will be beaten to the punch by another manufacturer of a drug with the same "active ingredient." But the FDA's approach multiplies this uncertainty. Innovators would not only be required to race against each other, they would not know whether they were destined to lose even before beginning the race because the FDA might conclude that a long-ago-approved mixture contained a disqualifying "active moiety." The FDA has offered no basis to justify its decision to construe the statute's reference to an "active ingredient" that "has been approved" as referring to any "active moiety" that the FDA might someday find is consistently present and responsible at least in part for the mixture's pharmacological action.

3. *The FDA's Alternative Arguments*

In an effort to avoid at least some of these difficulties, the FDA intermittently argues that it interprets the entire clause "active ingredient (including any ester or salt of the active ingredient)"—rather than just the phrase "active ingredient"—to mean "active moiety." *See, e.g.*, Dkt. 29 at 2-3; Tr. at 88 (explaining that the surplusage problem is "what FDA was getting at when they said in the regs that this was interpreting the entire phrase with the parenthetical"). But that interpretation is not the one stated in the administrative decision or the Final Rule. The FDA was clear: "The agency has concluded that the term '*active ingredient*,' as used in the phrase 'active ingredient (including any ester or salt of the active ingredient),' means active moiety." AR 6, n.31 (quoting 59 Fed. Reg. at 50,358) (emphasis added). Although the FDA was defining "active ingredient" as used in the context of the broader clause, the term that the Agency was defining was "active ingredient." It is on this basis that the Agency must defend its decision. *See Williams Gas Processing*, 475 F.3d at 329 ("We do not ordinarily consider agency

reasoning that appears nowhere in the agency's order.") (quoting *Vill. of Bensenville v. FAA*, 376 F.3d 1114, 1121 (D.C. Cir. 2004) (internal quotation marks and brackets admitted)).

Moreover, even if the Agency had attempted to define the entire clause to mean "active moiety," that approach would run into problems of its own, stemming from the Court of Appeals' holding in *Abbott Labs*. In *Abbott Labs*, the FDA argued that the parenthetical clause expressed Congress's intention to treat all forms of a molecule that reduce to the same moiety—not just salts and esters—alike for purposes of exclusivity. 920 F.2d at 988. The Court of Appeals rejected "the government's unconvincing attempts to employ the 'including' clause to cover all possible permutations of active ingredient." *Id.* To the extent that the FDA now relies on the entire clause, including the parenthetical, rather than just the term "active ingredient," it encounters the same difficulty that the Court of Appeals identified in *Abbott Labs*. If "[i]t 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.*, it seems equally implausible to read the entire phrase "active ingredient (including any ester or salt of the active ingredient)" to have that meaning. It is difficult to discern what this variation adds to the argument rejected in *Abbott Labs*.

More narrowly, the FDA suggests that, even in the absence of a relevant textual ambiguity in the statute, Congress may, at a minimum, have left a "gap" for the Agency to fill when dealing with naturally derived mixtures. *Chevron*, 467 U.S. at 843. The Agency notes that the statute does not "expressly address 5-year NCE exclusivity in the context of naturally derived mixtures" and that the "relevant statutory and regulatory authorities on 5-year NCE exclusivity appear to focus principally on single component active ingredients." AR 6; *see also* Dkt. 13-1 at 16 ("[T]he fact that Lovaza and Vascepa are made of a naturally derived mixture offers another

reason to reject Amarin's suggested interpretation of 'active ingredient' here."); Oral Arg. Tr. 56, 72-73. Because there is no evidence that Congress considered this unique context, the FDA submits that it is left with discretion to fashion a reasonable solution for the problem.

This argument misunderstands both *Chevron* and the problem with the Agency's interpretation of the exclusivity provisions. *Chevron* does not ask whether Congress affirmatively considered each context in which the statute might be applied. Rather, it requires that courts apply the "traditional tools of statutory construction" and, only after doing so, ask whether the statute is in relevant respects plain. Here, even if Congress did not consider how the law might apply to mixtures, it did not leave a relevant statutory gap for the FDA to fill.

The problem with the FDA's interpretation, moreover, is not that Congress failed to delegate to the FDA some discretion to address how to identify the "active ingredient(s)" of a naturally derived mixture; there may well be circumstances, for example, where the Agency must exercise its discretion, and expertise, to determine whether a particular mixture contains one active ingredient or several. Instead, the problem is that the statutory text and structure foreclose the exclusivity inquiry that the Agency undertook in these circumstances. Even assuming that Congress lacked a particular intent with respect to how the Agency should identify a mixture's "active ingredient(s)," the FDA's authority stemming from that "gap" extends only to answering that question—it does not confer an authority on the Agency to make exclusivity determinations based on something other than the mixture's "active ingredient(s)." The fact that the exclusivity provision's plain text applies to "situations not expressly anticipated by Congress does not demonstrate ambiguity. It demonstrates breadth." *PGA Tour, Inc. v. Martin*, 532 U.S. 661, 689 (2001) (internal quotation marks omitted).

The Court does not doubt that there are other contexts in which the FDA is entitled to deference in its interpretation of the Hatch-Waxman Amendments, particularly where that interpretation turns on scientific or medical expertise. *See, e.g.*, *A.L. Pharma., Inc. v. Shalala*, 62 F.3d 1484, 1490 (D.C. Cir. 1995) ("[C]ourts give a high level of deference to an agency's evaluations of scientific data within its area of expertise."). There may be times, moreover, where the meaning of the statutory phrase may vary based on "the context of the kind of drug at issue." *Cf. Serono*, 158 F.3d at 1320-21 (interpreting "same as" in context of menotropins, which naturally vary such that an overly restrictive definition of "variability" would make it impossible to demonstrate "sameness" for ANDA purposes). But even "where Congress has established an ambiguous line, the agency can go no further than the ambiguity will fairly allow." *City of Arlington, Tex. v. FCC*, 133 S.Ct. 1863, 1874 (2013). In this case, the Court concludes that Congress has exceeded the bounds of its statutory authority to interpret the exclusivity provision, and that its interpretation, accordingly, fails at *Chevron*'s first step.

B. *Chevron* Step Two and Arbitrary and Capricious Review

Even if the statute were in relevant respects ambiguous, the FDA's interpretation would still fail at *Chevron*'s second step, which requires the Court to determine whether the FDA has permissibly exercised its delegated authority. "At *Chevron* step two," the Court "defer[s] to the agency's permissible interpretation, but only if the agency has offered a reasoned explanation for why it chose that interpretation." *Vill. of Barrington*, 636 F.3d at 660. This analysis overlaps substantially with the APA's "arbitrary and capricious" inquiry, because "[w]hether a statute is unreasonably interpreted is close analytically to the issue whether an agency's actions under a statute are unreasonable." *Am. Fed'n of Gov't Employees, AFL-CIO, Local 46 v. Nicholson*, 475 F.3d 341, 355 (D.C. Cir. 2007) (quotation marks omitted); *see also, e.g.*, *Agape Church, Inc. v.*

FCC, 738 F.3d 397, 410 (D.C. Cir. 2013) ("The analysis . . . under *Chevron* Step Two and arbitrary and capricious review is often the same, because under *Chevron* step two, the court asks whether an agency interpretation is arbitrary or capricious in substance.") (quotation marks and brackets omitted).

"An agency's action," moreover, "must be upheld, if at all, on the basis articulated by the agency itself." *State Farm*, 463 U.S. at 50. Although lack of "clarity" alone is not a sufficient basis to strike down an agency decision, *Bowman Transp., Inc. v. Arkansas-Best Freight Systems, Inc.*, 419 U.S. 281, 285-86 (1974), neither counsel nor the Court may amend or supply the agency's rationale, *see Riffin v. Surface Transp. Bd.*, 592 F.3d 195, 198 (D.C. Cir. 2010). "In order to survive judicial review . . . , an agency action must be supported by 'reasoned decisionmaking.'" *Tripoli Rocketry Ass'n v. Bureau of Alcohol, Tobacco, Firearms and Explosives*, 437 F.3d 75, 77 (D.C. Cir. 2006) (citations omitted). The "result must be logical and rational," *id*., as well as "adequately explained" and "coheren[t]," *Fox*, 684 F.3d at 75 (citations and internal quotation marks omitted).

Focusing on the analysis actually contained in the FDA's administrative decision, as opposed to the arguments made by counsel, it is apparent that the decision is both procedurally and substantively flawed. Most notably, the administrative decision does not offer—or even attempt—any reasoned explanation for how its application of the regulatory focus on "active moiety" can be reconciled with the statutory focus on "active ingredient." To the contrary, the decision affirmatively embraces the notion that "active ingredient" and "active moiety" have *different* meanings. *See* AR 6 (explaining that although the terms are "often conflated," in the context of mixtures, "the distinction between active ingredient and active moiety . . . become[s] crucial"). The decision thus concedes that Vascepa's "active ingredient"—EPA—is not an

"active ingredient" in Lovaza, *see* AR 7, AR 18-19; but because it concluded that EPA is an "active *moiety*" in both Vascepa and in Lovaza's single-active-ingredient mixture, it denies exclusivity.

The decision's sole acknowledgment of the apparent divergence between the statutory and regulatory inquiries is both minimal and confounding. In the course of its 24-page, single spaced administrative decision, the FDA refers to the statutory text only twice—in a background recitation of the governing legal framework, and in a parenthetical in a footnote. Quoting from the Final Rule adopting the five-year exclusivity regulations, that parenthetical states: "The agency has concluded that the term 'active ingredient,' as used in the phrase 'active ingredient (including any salt or ester of an active ingredient),' means active moiety." AR 6, n.31. The footnote, however, raises more questions than it answers.

Most importantly, the footnote conflicts with other portions of the Agency's decision. The decision, for example, criticizes Amarin for "conflat[ing]" the terms "active ingredient" and "active moiety." AR 6; *id.* at n.29. It stresses that "the distinction between active ingredient and active moiety" is "crucial" in the context of "naturally derived mixtures," AR 6, and emphasizes more generally that "a drug's active ingredient is distinct from its active moiety," AR 23. The decision's entire "one-to-many" analysis turns on the premise that some drugs may have "one" "active ingredient," but "many" "active moieties." AR 5, AR 19; AR 23. And, it repeatedly concludes that "the active ingredient of Lovaza is the Lovaza mixture as a whole," and not EPA or any other "active moiety." *E.g.* AR 19 ("the Agency agrees that the active ingredient of Lovaza is the Lovaza mixture as a whole"). Thus, although the footnote appears to treat the phrases "active ingredient" and "active moiety" as synonymous for purposes of the five-year

exclusivity determination, the remainder of the decision is emphatic in concluding that the terms have distinct meanings, at least in the context of naturally derived mixtures.

Moreover, although an administrative decision can rely on an agency's prior consideration of an issue, the FDA has never addressed why the phrase "active ingredient" should be given different meanings in different provisions of the Act, let alone explained how the regulatory focus on "active moiety" can apply where the "active ingredient" and "active moiety" refer to different substances. The Agency makes no attempt to explain how its approach furthers Congress's purposes or is otherwise a reasonable policy choice, especially in light of the clear interest in providing notice to potential innovators of the exclusivity to which they might eventually be entitled. And the FDA's regulations do not provide any further gloss on this point. The decision to identify a mixture's "active moiety" based on information available at the time the FDA evaluates a subsequent drug's request for exclusivity, rather than at the time drug was "approved," is similarly unexplained, and, as discussed above, runs counter to the exclusivity provision's purpose of incentivizing innovation.

The Agency's ultimate conclusion that Vascepa, a drug "no active ingredient of which . . . has been approved" in a previous NDA, was not entitled to exclusivity, is contrary to the statute's plain meaning. Rather than explaining this discrepancy, the administrative decision only adds to the problem by emphasizing the divergence between the Agency's regulatory inquiry and the statutory requirement. Whether the problems with the FDA's decision are characterized as failures under *Chevron* step one, step two, or the APA's requirement of reasoned decision-making, the Agency's decision must be set aside.[11]

[11] Amarin also argues that the FDA acted arbitrarily and capriciously by applying its new framework retroactively to Vascepa. The FDA declined to address this argument directly,

IV. CONCLUSION

For the reasons set forth above, Plaintiff's Motion for Summary Judgment is **GRANTED** and Defendants' Cross-Motion for Summary Judgment is **DENIED**. The decision denying Amarin's claim for exclusivity vacated and the matter is remanded to the FDA for proceedings consistent with this Opinion.

/s/ Randolph D. Moss
RANDOLPH D. MOSS
United States District Judge

Date: May 28, 2015

instead asserting that its framework did not constitute a new policy, but merely clarified the application of its regulations for mixtures. Because the Court concludes that the FDA's application of its framework must be set aside under *Chevron*, the Court need not address this issue.