UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

OTSUKA PHARMACEUTICAL CO., LTD., *et al.*, Plaintiffs, v. SYLVIA MATHEWS BURWELL, *in her official capacity as* Secretary of the United States Department of Health and Human Services, *et al.*, Defendants, and ALKERMES, INC., *et al.*, Intervenor-Defendants.	Civil Action No. 15-cv-1688 (KBJ)

MEMORANDUM OPINION

To incentivize the development and marketing of safe, effective, and affordable drug products, the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 321 *et seq.*, provides a variety of benefits for drug manufacturers, including prescribed periods of "exclusivity" in the marketplace. Drug manufacturers that develop and get approval for drug products containing entirely new chemical entities—i.e., drugs in which "no active ingredient" has ever before been approved for marketing—receive a five-year period of exclusivity for marketing that drug product, during which time the Food and Drug Administration ("the FDA") is prohibited from approving applications for the marketing of certain other drugs. 21 U.S.C. § 355(c)(3)(E)(ii); *see also* 21 C.F.R.

§ 314.108(b)(2). Similarly, if a manufacturer submits an application for a drug product that contains a previously approved active ingredient, and if certain "new clinical investigations" are included in that application, that manufacturer can claim a three-year period of marketing exclusivity for the drug in that application. *See* 21 U.S.C. § 355(c)(3)(E)(iii); *see also* 21 C.F.R. § 314.108(a), (b)(4). These provisions and others demonstrate Congress's clear intent to establish a statutory and regulatory scheme that provides a substantial reward (marketing exclusivity) for those pharmaceutical companies that either invest in the development of entirely new drug substances or that study existing chemical compounds to demonstrate that they can be safe and effective when prescribed for use in a new way.

In the instant case, Plaintiff Otsuka Pharmaceuticals Company Limited (along with related entities, collectively referred to herein as "Otsuka") asserts that the FDA has improperly truncated its right to marketing exclusivity for its drug Abilify Maintena, which the FDA approved in 2013 for the treatment of schizophrenia in acutely relapsed patients. It is undisputed that Abilify Maintena and a related supplement received three-year periods of exclusivity under the FDCA; in the instant lawsuit, Otsuka maintains that the FDA ran afoul of the FDCA and its own regulations in October of 2015, when it approved Intervenor Alkermes's application for Aristada—a drug product that also treats schizophrenia and is administered in the same way as Abilify Maintena but that contains a different "active moiety" than Otsuka's drug. (*See* Compl., ECF No. 1, ¶ 52 ("FDA denied Otsuka's citizen petition and approved the Alkermes [new drug application] in derogation of Otsuka['s] exclusivity rights.").) Otsuka's three-count complaint, which it filed against the FDA and other associated

official-capacity defendants (referred to herein, collectively, as the "FDA"), specifically asserts that the FDA's approval of Aristada within the three-year windows of exclusivity that were afforded to Abilify Maintena and its supplement violated the Administrative Procedure Act ("APA"), 5 U.S.C. §§ 701–06, because that approval contravened the FDCA (Count One) and the agency's own regulations (Count Two), and because, without implementing the APA's notice-and-comment procedures, the agency essentially promulgated a new rule regarding the circumstances under which the FDA will consider a subsequent drug application to be barred (Count Three). (*See* Compl. ¶¶ 51–74.)

Before this Court at present are three cross-motions for summary judgment that the parties in this matter have filed. (*See* Pls.' Mot. for Summ. J. ("Pls.' Mot."), ECF No. 24; Defs.' Cross Mot. for Summ. J. ("Defs.' Mot."), ECF No. 26; Intervenor-Defs.' Mot. for Summ. J. ("Alkermes's Mot."), ECF No. 27.) Each motion first addresses a question of statutory interpretation regarding the meaning of the applicable exclusivity provisions of the FDCA, and in particular, the issue of whether or not the FDA may read that statute and its own regulations to establish an exclusivity bar that extends only to second-in-time applications for a drug with the same "active moiety" as the drug with exclusivity. This Court has applied the legal analysis established in *Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984), and as explained fully below, it concludes that the FDCA does not unambiguously prevent the FDA from determining that the FDCA's three-year exclusivity bar blocks only subsequent applications for drugs with the same active moiety, and that it was not unreasonable for the FDA to have employed that interpretation when it considered the applications at

issue here. Similar reasoning compels the Court to reject Otsuka's contention that the FDA violated its own regulations, and Otsuka's notice-and-comment claim also necessarily fails because it is premised on the faulty contention that, when the FDA decided to approve Aristada despite Abilify Maintena's exclusivity, the agency thereby amended a regulation that unambiguously required the opposite result. Consequently, the summary judgment motions that the FDA and Alkermes have filed will be **GRANTED** and Otsuka's motion for summary judgment will be **DENIED**. A separate order consistent with this Memorandum Opinion will follow.

I. BACKGROUND

A. Marketing Approval And Exclusivity Under The FDCA

Originally enacted in 1938, the FDCA "governs the pharmaceutical drug approval process for both new and generic drugs." *Veloxis Pharm., Inc. v. FDA*, 109 F. Supp. 3d 104, 107 (D.D.C. 2015) (citation omitted); *see also Christopher v. SmithKline Beecham Corp.*, 132 S. Ct. 2156, 2163 n.4 (2012). In 1984, Congress amended the statute via the Drug Price Competition and Patent Term Restoration Act ("Hatch-Waxman Amendments"), Pub. L. No. 98–417, 98 Stat. 1585, in a manner that strikes a balance between "'two competing interests in the pharmaceutical industry: (1) inducing pioneering research and development of new drugs[,] and (2) enabling competitors to bring low-cost, generic copies of those drugs to market[,]'" *Takeda Pharm., U.S.A., Inc. v. Burwell*, 78 F. Supp. 3d 65, 68 (D.D.C. 2015) (quoting *Janssen Pharmaceutica, N.V. v. Apotex, Inc.*, 540 F.3d 1353, 1355 (Fed. Cir. 2008)). As mentioned, one critical aspect of this Hatch-Waxman balance is the period of marketing exclusivity that is afforded to pharmaceutical companies under certain circumstances, the primary purpose

of which is to incentivize companies to invest substantial time and money into developing useful drug products. *See, e.g.*, *Abbott Labs. v. Young*, 920 F.2d 984, 985 (D.C. Cir. 1990) (noting that the exclusivity provisions aim, in part, to protect "the interests of drug manufacturers who produce new drugs" by providing "greater incentives for the invention of new products"); *see also* Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions ("1994 Rule"), 59 Fed. Reg. 50,338, 50,358 (Oct. 3, 1994) ("1994 Rule") (observing that the three-year-exclusivity provision was "created . . . to protect products whose development required a significant time commitment and 'an investment of some magnitude'" (citing legislative history)).

The first step on the road to receiving marketing exclusivity is to seek and obtain FDA approval for the marketing of a "new" drug pursuant to a process that is set forth in the U.S. Code and that has been fully explained in several published opinions in this district. *See, e.g.*, *Takeda Pharm.*, 78 F. Supp. 3d at 71–72 (discussing 21 U.S.C. § 355); *see also Ferring Pharm., Inc. v. Burwell*, No. 15-0802, 2016 WL 1060199, at *2 (D.D.C. March 15, 2016) (same).[1] Specifically, as amended, the FDCA "requires drug manufacturers seeking to market a new drug to first obtain FDA approval via one of three different application pathways: (1) a full New Drug Application ('NDA'); (2) an Abbreviated New Drug Application ('ANDA'); or (3) an intermediate process known as a Section 505(b)(2) NDA." *Takeda Pharm.*, 78 F. Supp. 3d at 71 (citing 21 U.S.C.

[1] As relevant here, a drug is "new" when its "composition . . . is such that such drug is not generally recognized, among experts . . . as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof," or if its "composition . . . is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions." 21 U.S.C. § 321(p)(1)–(2).

§ 355). The requirements for the full NDA and Section 505(b)(2) pathways, which are the only methods implicated in the instant case, are set forth in section 505(b) of Hatch-Waxman, which has been codified at 21 U.S.C. § 355(b).[2]

Hatch-Waxman's subsection 505(b)(1) provides a detailed list of what a full NDA must include. *See* 21 U.S.C. § 355(b)(1). The only NDA requirement that is relevant to the instant case is located in subdivision (A): the application must include "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use[.]" 21 U.S.C. § 355(b)(1)(A); *see also Warner-Lambert Co. v. Shalala*, 202 F.3d 326, 327 (D.C. Cir. 2000).

The Section 505(b)(2) NDA pathway relates to a subset of new drug applications: those that are submitted "for a drug for which the investigations described in [subsection 505(b)(1)(A)] and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use[.]" 21 U.S.C. § 355(b)(2); *see also Ferring Pharm.*, 2016 WL 1060199, at *2. A Section 505(b)(2) NDA applicant must include certain patent-related certifications "with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval[.]" 21 U.S.C. § 355(b)(2)(A). Thus, so long as the requisite patent certifications are provided, Section 505(b)(2) NDA applicants may discharge their duty to demonstrate the safety and efficacy of the drug for which they seek approval by relying upon investigations they did not conduct or have not licensed

[2] The approval pathway for ANDAs is described in 21 U.S.C. § 355(j); it "provides a framework for the introduction of generic versions of previously approved branded drugs." *Ethypharm S.A. France v. Abbott Labs.*, 707 F.3d 223, 227 (3d Cir. 2013). As the parties all agree, the ANDA pathway is not pertinent here.

(hereinafter "unoriginal" investigations), which can include "clinical studies that were previously submitted to [the] FDA in support of another drug[,]" *Takeda Pharm.*, 78 F. Supp. 3d at 72, or "published literature" that may not have any association with a specific, previously approved drug application (*see* Draft Guidance for Industry: Applications Covered by Section 505(b)(2), Admin. R. App. ("AR"), ECF Nos. 35-1–35-6, 001328–29). *See also Ferring Pharm.*, 2016 WL 1060199, at *2; Erika Lietzan, *The Myths of Data Exclusivity*, 20 Lewis & Clark L. Rev. 91, 97 (2016).

Once a drug application is submitted to the FDA pursuant to the full NDA or Section 505(b)(2) NDA pathways and the agency approves it, the FDCA's separate exclusivity provisions—which are set forth and discussed at length *infra* Part III.A—can apply automatically to prevent the FDA from approving subsequent drug products for a specified number of years. *See, e.g.*, 21 U.S.C. § 355(c)(3)(E)(ii)–(iv) (creating and demarcating five-year and three-year exclusivities). Notably, as explained below, the statutory exclusivity provisions specifically address the circumstances under which an approved new drug is entitled to exclusivity, as well as the circumstances under which subsequent products are to be deemed barred by that exclusivity. Thus, the FDCA itself delineates the scope of an approved drug product's exclusivity benefit.

B. The FDA's Approval Of Otsuka's Abilify Drug Products

In 2002, Otsuka submitted, and the FDA approved, a drug application for Abilify Tablets, an orally administered drug for the treatment of several mental disorders, most notably schizophrenia. (FDA Decision Rejecting Otsuka's Exclusivity Petition ("FDA Decision"), Ex. A to Compl., ECF No. 1-2, at 14–15; Abilify Tablet Original Approval

Letter, AR 000373.)[3] The active moiety of Abilify Tablets is the molecule aripiprazole, which is also the drug's active ingredient. (*See* FDA Decision at 14–15.)[4] Otsuka supported the drug application for Abilify Tablets with multiple original studies (*see, e.g.*, Abilify Tablet Original Approval Letter, AR 000374–75; Abilify Tablet Original Labeling, *id.* 000383). Furthermore, because the FDA had never before approved a drug with aripiprazole as its active moiety or ingredient, Abilify Tablets received a five-year period of marketing exclusivity (*see* FDA Decision at 14). *See also* 21 U.S.C. § 355(c)(3)(E)(ii) (directing that, once the FDA approves a new drug application for a drug with a never-before-approved active ingredient, no subsequent application that "refers to [that] drug" and that relies on unoriginal investigations under section 505(b)(2) may be submitted (or approved) for five years).

Otsuka's five-year exclusivity period for Abilify Tablets has long since come and gone. The events giving rise to the exclusivities in question here took place in February of 2013, when the FDA approved an application for another Otsuka drug—Abilify Maintena—which has aripiprazole as its active moiety and active ingredient, just like Abilify Tablets. (*See* FDA Decision at 16; Abilify Maintena Approval Letter,

[3] Page-number citations to the documents the parties have filed (other than the administrative record) refer to the page numbers that the Court's electronic filing system automatically assigns.

[4] FDA regulations define active moiety 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." 21 C.F.R. § 314.108(a). Although no regulation directly defines the term "active ingredient," *Amarin Pharm. Ir. Ltd. v. FDA*, 106 F. Supp. 3d 196, 199 (D.D.C. 2015), the FDA has long asserted that "active ingredient"—as used in the exclusivity provisions at issue here—"means active moiety[,]" 1994 Rule, 59 Fed. Reg. at 50,358. A recent opinion from this district has questioned the propriety of that equivalency in at least some contexts, *see Amarin Pharm.*, 106 F. Supp. 3d at 207–10, 216–17; however, in the instant case, no one disputes that the active moiety and active ingredient of the relevant Abilify drugs are one and the same (aripiprazole). Furthermore, no one argues that the issue to be decided here—i.e., the scope of Abilify Maintena's exclusivities—turns on the proper definition of active ingredient.

AR 000487; Abilify Maintena Exclusivity Summary, *id.* 000600–01.) Abilify Maintena's novelty was that it is administered through extended-release injectable suspension rather than orally. (FDA Decision at 16; Abilify Maintena Approval Letter, AR 000487.) Otsuka established the efficacy of Abilify Maintena partly "on the basis of efficacy data from trials with the oral formulation of aripiprazole" (Abilify Maintena Original Labeling, AR 000530), and it also sponsored "new clinical investigations[,]" 21 U.S.C. § 355(c)(3)(E)(iii), without which the FDA would not have approved the drug for marketing (*see* Abilify Maintena Exclusivity Summary, AR 000602–05).[5] Significantly for present purposes, the fact that Otsuka relied on new, essential studies when it sought approval for Abilify Maintena (a drug that contained a previously approved active ingredient) meant that Abilify Maintena was indisputably entitled to a three-year period of exclusivity under 21 U.S.C. § 355(c)(3)(E)(iii), which is referred to herein as "romanette iii."[6] There is no dispute that Abilify Maintena deserved this period of marketing exclusivity. (*See* Pls.' Mem. in Supp. of Pls.' Mot. ("Pls.' Mem."), ECF No. 24-1, at 9–10; Defs.' Mem. in Supp. of Defs.' Mot. ("Defs.' Mem."), ECF No. 26-1, at 16–17; Intervenor-Defs.' Mem. in Supp. of Alkermes's Mot. ("Alkermes's Mem."), ECF No. 27-1, at 20–21; FDA Decision at 16, 21.)

[5] A "new clinical investigation" is "an investigation in humans" that produced results that "have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population" and "do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product." 21 C.F.R. § 314.108(a). An investigation is essential to approval if "there are no other data available that could support approval of the application." *Id.*

[6] A "romanette" is a "lower case version of a Roman numeral[.]" *Karmely v. Wertheimer*, 737 F.3d 197, 198 & n.1 (2d Cir. 2013).

Thereafter, on December 5, 2014, the FDA approved an application supplement, which is also known as a "supplemental new drug application," for Abilify Maintena. (*See* Abilify Maintena Supplement Approval Letter, AR 000607–611; FDA Decision at 16 & n.55.) An application supplement is a filing that updates an already approved application in a new way, *see* 21 C.F.R. § 314.70—e.g., with a different indication for the drug. *See AstraZeneca Pharm. LP v. FDA*, 713 F.3d 1134, 1136 (D.C. Cir. 2013); *ViroPharma, Inc. v. Hamburg*, 898 F. Supp. 2d 1, 7 (D.D.C. 2012); Lietzan, *supra*, at 141–42. Pursuant to such a supplement, Otsuka updated its application for Abilify Maintena with "the results of a controlled clinical study treating adult patients with schizophrenia experiencing an acute relapse" (FDA Decision at 16 n.55 (internal quotation marks omitted)). And per what this Memorandum Opinion calls "romanette iv," Otsuka's application supplement received a separate three-year exclusivity period analogous to the one romanette iii provides, *see* 21 U.S.C. § 355(c)(3)(E)(iv); it is also undisputed that Otsuka's supplement was entitled to that exclusivity. (*See* Pls.' Mem. at 9–10; Defs.' Mem. at 16–17; Alkermes's Mem. at 20–21; FDA Decision at 16, 21.)

C. The FDA's Approval Of Alkermes's Aristada (Over Otsuka's Objection)

What is at issue in the instant case is the *scope* of the exclusivities that were conferred to Abilify Maintena and its supplement by statute; the reach of the exclusivity benefit became a point of contention when, late in 2014, Alkermes submitted to the FDA a Section 505(b)(2) NDA for its drug Aristada. Aristada treats schizophrenia, and it is administered through an extended-release injectable suspension formula, like Abilify Maintena. (*See* Aristada Approval Letter, AR 001217; FDA Decision at 16.) However, Aristada's chemical structure differs from the Abilify line of drugs.

Aristada's active ingredient is aripiprazole lauroxil—a substance that metabolizes in the body into N-hydroxymethyl aripiprazole, which is Aristada's active moiety. (*See* Active Moiety Determination For Aripiprazole Lauroxil, AR 000665–67, 000670; Pls.' Mem. at 16 n.7 (disclaiming any challenge to the FDA's determination on these points).) Furthermore, although some of the unoriginal investigations that Alkermes provided to establish the safety and effectiveness of Aristada were studies that Otsuka had sponsored with respect to Abilify Tablets (*see* FDA Decision at 17 ("The 505(b)(2) NDA for Aristada relied for approval, in part, on the [FDA's] finding of safety and effectiveness for the listed drug, Abilify (aripiprazole) Tablets[.]"); Memorandum: Division Director Summary Review of Aristada ("Division Director Review"), AR 001177 (same)), Alkermes did not rely on the new clinical investigations that Otsuka had undertaken with respect to Abilify Maintena. Instead, Alkermes conducted and submitted its own original studies to support the Section 505(b)(2) NDA for Aristada. (*See* FDA Decision at 17; Division Director Review, AR 001177 (observing that the FDA's "previous finding of safety and efficacy from oral aripiprazole tablets was considered as evidence," as well as "pharmacokinetic evidence from [Alkermes's] studies that demonstrate[d] similar serum concentrations for oral aripiprazole given daily at approved doses and aripiprazole lauroxil given monthly at the studied doses").)

1. Otsuka's Citizen Petition Urging Rejection Of The Aristada Application

Otsuka objected to Alkermes's Section 505(b)(2) drug application for Aristada in a citizen petition that it filed with the FDA on July 13, 2015. (*See generally* Otsuka's Citizen Petition, AR 000025–44.)[7] Otsuka's objection related specifically to the FDA's

[7] Federal regulations permit any "interested person" to petition the FDA "to issue, amend, or revoke a

failure to apply the statutory provisions that confer exclusivity, which are discussed briefly here and at length below. As already mentioned, both romanette iii and iv delineate and describe the new drug applications that are entitled to exclusivity (the industry refers to this language as the "eligibility clause"). (*See, e.g.*, FDA Decision at 11–12 (discussing 21 U.S.C. § 355(c)(3)(E)(iii), (iv)).) In addition, these statutory provisions also identify the particular subset of second-in-time applications that are barred by that exclusivity. (*See id.* at 12–13 (calling the language identifying that subset of applications the "bar clause").) The text and function of the bar clauses in romanettes iii and iv are crucial to the legal issue presented in this case (*see infra* Part III.A–B); for now, it suffices to note that romanette iii's bar clause limits the FDA for a period of three years, preventing it from approving a second-in-time Section 505(b)(2) NDA that is "for the conditions of approval of such drug in the approved subsection (b) application[.]" 21 U.S.C. § 355(c)(3)(E)(iii). The bar clause in romanette iv pertains to supplements that have received exclusivity; for a three-year period, the FDA is prohibited from approving a second-in-time Section 505(b)(2) application if that application is "for a change approved in the supplement[.]" 21 U.S.C. § 355(c)(3)(E)(iv). The implementing regulations (also discussed at length below) contain bar clauses that are structured similarly. *See* 21 C.F.R. § 314.108(b)(4)–(5).

Otsuka's citizen petition maintained that the Aristada application fell within the scope of the bar clauses that pertained to Abilify Maintena's exclusivity periods, and that, thus, Aristada should not be approved. In this regard, Otsuka specifically asserted that Abilify Maintena's "conditions of approval" were the "treatment of schizophrenia

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regulation or order, or to take or refrain from taking any other form of administrative action." 21 C.F.R. § 10.25(a).

using a once-monthly, long-acting injectable formulation of aripiprazole[,]" (Otsuka's Citizen Petition, AR 000033), and that the Aristada application was for Abilify Maintena's conditions of approval because it treated the same condition in a similar way and had relied on the same sort of clinical trials, despite the fact that Aristada and Abilify Maintena have different active ingredients and active moieties (*see id.* 000030, 000038–39.) Accordingly, and based solely on these allegedly overlapping "conditions of approval," Otsuka maintained that Abilify Maintena's romanette iii exclusivity should bar Aristada. (*Id.* 000039.) Similarly, Otsuka asserted that the "change" spoken of in romanette iv refers to changes in conditions of approval as addressed in a supplement, and thus, Otsuka argued, the exclusivity afforded to Abilify Maintena's supplement per romanette iv should have also precluded Aristada's approval because Aristada purports to treat schizophrenia in the way described in the supplement. (*Id.* 000034, 000036–37.)

2. The FDA's Response To Otsuka's Citizen Petition

The FDA disagreed that Aristada was barred. In a detailed letter decision issued on October 5, 2015, the FDA explained that, in its view, the FDCA's exclusivity provisions do not bar a second-in-time drug application if the drug with exclusivity and the drug for which approval is being sought have different active moieties. (*See* FDA Decision at 12 (explaining that the "FDA interprets [the statute] to mean that, for a single entity drug to be potentially barred by 3-year exclusivity for another single entity drug, the drug must contain the same active moiety as the drug with 3-year exclusivity").) The FDA explained that it interprets the phrase "for the conditions of approval *of such drug* in the approved subsection (b) application" in romanette iii, 21 U.S.C. § 355(c)(3)(E)(iii) (emphasis added), to mean that the FDA may not approve "a

505(b)(2) NDA for 'such drug' (i.e., a drug containing the active moiety [of the drug with exclusivity]) for those same conditions of approval for 3 years after the approval" of the drug with exclusivity. (FDA Decision at 21). Thus, as the FDA reads the statute, "such drug" directs the agency to consider certain defining characteristics of the drug with exclusivity as compared to the drug in the second-in-time application (including the relative active moieties of these drugs), and that only a second-in-time application that relates to a drug with *both* the same active moiety ("such drug") *and* the same conditions of approval as the drug with exclusivity will be blocked. (*See, e.g.*, *id.* at 21–22 (explaining that "any approval of Aristada will not be an approval of 'such drug' (a drug containing the active moiety aripiprazole) and therefore will not be for the 'conditions of approval of such drug'" in the Abilify Maintena application); *see also id.* at 21 ("[B]ecause the scope of the 3-year exclusivities for Abilify Maintena, like the scope of any 3-year exclusivity, is tied to the active moiety of Abilify Maintena and because Aristada contains a different active moiety than Abilify Maintena, FDA concludes that approval of the Aristada NDA is not blocked.").)

The FDA's response letter applied similar logic to the exclusivity that pertains to supplements under romanette iv. According to the letter, the FDA does not permit active-moiety changes through supplemental new drug applications; thus, "a change approved in a supplement must [necessarily] be a change in conditions of approval for the same drug (active moiety) approved in the original NDA." (*Id.* at 13; *see also* Letter from Janet Woodcock, M.D., Director, CDER, FDA to William H. Carson, Otsuka and Ralph S. Tyler, Venable LLP, AR 000353 & n.43; Guidance for Industry—Submitting Separate Marketing Applications and Clinical Data for Purposes of

Assessing User Fees, *id.* 001593; Otsuka's Citizen Petition, *id.* 000034 (agreeing that the "change referred to in [romanette iv] is simply a change in the conditions of approval" (internal quotation marks and footnote omitted).) As a result, the FDA concluded that a second-in-time application is only barred as being for "a change approved in [a] supplement" if the second-in-time application pertains to a drug that has the same active moiety as the drug that was the subject of the approved supplemental application. (FDA Decision at 13.) And based on the undisputed fact that Abilify Maintena and Aristada do not have the same active moiety, the FDA concluded that the Abilify Maintena supplement's exclusivity period did not bar the approval of a second-in-time application for Alkermes's Aristada. (*See id.* at 21.)

D. Procedural History

On October 15, 2015, Otsuka filed a complaint against the FDA in this Court, claiming that the agency's decision to approve Aristada violates the APA in three ways. First, Otsuka argues that the FDA "severely misconstrued the three-year exclusivity provisions" of the FDCA (Compl. ¶ 55), and thereby reached a conclusion with respect to the scope of Abilify Maintena's exclusivities that was arbitrary and capricious and "directly contrary to law" (*id.* ¶ 59). Second and similarly, Otsuka asserts that the FDA's decision arbitrarily and capriciously contradicted the agency's implementing regulations. (*See id.* ¶¶ 60–64.) Third and finally, Otsuka maintains that the FDA's decision to approve Aristada required notice and comment, because the agency effectively "amended" the terms of its exclusivity-related regulations by creating an inconsistent rule of future applicability. (*See id.* ¶¶ 65–74.)

This Court permitted Alkermes to intervene in the litigation on October 26, 2015 (*see* Order, ECF No. 11), after which Otsuka moved for summary judgment (*see* Pls.'

Mot.; Pls.' Mem.). The FDA filed a brief in opposition and simultaneously moved for summary judgment in its favor. (*See* Defs.' Mot.; Defs.' Mem.) And, thereafter, Alkermes filed its own motion for summary judgment, agreeing with the FDA's position. (*See* Alkermes's Mot.; Alkermes's Mem.) This Court held a hearing regarding these motions on January 7, 2016, and took each of the cross-motions for summary judgment under advisement.[8]

II. LEGAL STANDARDS

Although Federal Rule of Civil Procedure 56 provides the ordinary summary judgment standard, it is well established that, in cases "involving review of a final agency action[,] . . . the standard set forth in [Rule 56] does not apply because of the limited role of a court in reviewing the administrative record." *ViroPharma, Inc. v. Hamburg*, 916 F. Supp. 2d 76, 79 (D.D.C. 2013) (internal quotation marks omitted) (quoting *Sierra Club v. Mainella*, 459 F. Supp. 2d 76, 89 (D.D.C. 2006)). The Court's function in administrative-law cases is solely "to determine whether or not as a matter of law the evidence in the administrative record permitted the agency to make the decision it did." *Id.* (internal quotation marks and citation omitted). Moreover, as applicable here, the APA permits the Court to set aside agency action "only if it is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law."

[8] On February 29, 2016, Defendants filed a notice informing the Court that the three-year exclusivity period afforded to Abilify Maintena under romanette iii had expired the previous day (on February 28, 2016). (*See* Notice, ECF No. 36.) This meant that the scope and applicability of romanette iii (and its implementing regulation) was no longer a live issue; however, Otsuka maintained its claim that the FDA violated the APA when it failed to block Aristada based on the exclusivity that pertains to the Abilify Maintena supplement pursuant to romanette iv and its implementing regulation, and in this Court's view, it is not possible to analyze Otsuka's argument that the supplement's exclusivity bars Aristada separate and apart from Otsuka's arguments regarding the scope and applicability of the exclusivity conferred by romanette iii. Consequently, this Court has proceeded to analyze all of the issues in full in the context of this Memorandum Opinion.

Zevallos v. Obama, 793 F.3d 106, 112 (D.C. Cir. 2015) (internal quotation marks and citations omitted); *see also* 5 U.S.C. § 706(2)(A).

It is routine in this jurisdiction to analyze APA claims that arise out of the FDA's letter-decision interpretations of the FDCA under the familiar two-step framework of *Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984), which applies to "an agency's interpretation of a statute that it administers[,]" *W. Minn. Mun. Power Agency. v. FERC*, 806 F.3d 588, 591 (D.C. Cir. 2015). *See AstraZeneca Pharm.*, 713 F.3d at 1139 (applying *Chevron* to an FDA statutory interpretation contained in a letter decision); *Mylan Labs., Inc. v. Thompson*, 389 F.3d 1272, 1279–80 (D.C. Cir. 2004) (same, collecting cases). Step One directs that, if "Congress has directly spoken to the precise question at issue," the court must give effect to that "unambiguously expressed intent," *Nat'l Treasury Emps. Union v. Fed. Labor Relations Auth.*, 414 F.3d 50, 57 (D.C. Cir. 2005) (internal quotation marks omitted) (quoting *Chevron*, 467 U.S. at 842–43), and the question is not whether the pertinent statutory terms are "in some abstract sense, ambiguous, but rather whether, read in context and using the traditional tools of statutory construction," the terms unambiguously mean what the party claiming victory at Step One says they mean. *Cal. Indep. Sys. Operator Corp. v. FERC*, 372 F.3d 395, 400 (D.C. Cir. 2004) (citation omitted); *see also Sierra Club v. EPA*, 551 F.3d 1019, 1027 (D.C. Cir. 2008) (explaining that the tools used to evaluate statutory provisions include an examination of the provision in its full context and, as appropriate, references to legislative history).

If the statute at issue "can be read more than one way" and thus is ambiguous, *AFL-CIO v. FEC*, 333 F.3d 168, 173 (D.C. Cir. 2003) (citation omitted), or if the statute

is "silent" regarding the relevant question, *see Van Hollen, Jr. v. FEC*, 811 F.3d 486, 495 (D.C. Cir. 2016), then the Court proceeds to Step Two. At Step Two, the statutory ambiguity or silence is effectively deemed "'an implicit delegation from Congress to the agency to fill in the statutory gaps.'" *Id.* at 495 (quoting *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 159 (2000) (emphasis omitted)). Consequently, the court must "accept the agency's [reasonable] construction of the statute, even if the agency's reading differs from what the court believes is the best statutory interpretation[,]" *Nat'l Cable & Telecomm. Ass'n v. Brand X Internet Servs.*, 545 U.S. 967, 980 (2005) (citation omitted). This reflects the principle that the agency is "the authoritative interpreter (within the limits of reason)" of "an ambiguous statute [it] is charged with administering[.]" *Id.* at 983. Moreover, the nature of judicial review at Step Two is "highly deferential[,]" *Vill. of Barrington, Ill. v. Surface Transp. Bd.*, 636 F.3d 650, 667 (D.C. Cir. 2011) (internal quotation marks and citation omitted), which means that plaintiffs bear an "arduous[]" burden at this stage, *Am. Meat Inst. v. USDA*, 968 F. Supp. 2d 38, 59 (D.D.C. 2013), *aff'd*, 746 F.3d 1065 (D.C. Cir. 2014), *aff'd after reh'g en banc*, 760 F.3d 18 (D.C. Cir. 2014).

The deference framework that the Supreme Court recognized in *Auer v. Robbins*, 519 U.S. 452 (1997), is also potentially applicable in the instant case, because Otsuka contends that the FDA's approval of Aristada not only contradicts the mandates of the FDCA but also transgresses the boundaries of the agency's own regulations. Under *Auer*, when an agency interprets "its own ambiguous regulation[s]," courts will defer to that interpretation unless it is "plainly erroneous or inconsistent with the regulation[s][,]" or there "is reason to suspect that the agency's interpretation does not

reflect the agency's fair and considered judgment on the matter in question." *Christopher*, 132 S. Ct. at 2166 (internal quotation marks and citations omitted). Thus, "an agency's interpretation need not be the only possible reading of a regulation—or even the best one—to prevail." *Decker v. Nw. Environ. Def. Ctr.*, 133 S. Ct. 1326, 1337 (2013). And courts have generally concluded that the *Auer* standard provides for "an even greater degree of deference" to the agency than the standard that *Chevron* establishes. *Conservation Force v. Salazar*, 919 F. Supp. 2d 85, 91 (D.D.C. 2013) (internal quotation marks omitted) (quoting *Consarc Corp. v. U.S. Treasury Dep't, Office of Foreign Assets Control*, 71 F.3d 909, 915 (D.C. Cir. 1995)). Be that as it may, the clear corollary of the *Auer* rule is that deference to the agency's interpretation of its own regulations is not required if the meaning of the regulation is plain. *See, e.g.*, *Christensen v. Harris Cty.*, 529 U.S. 576, 588 (2000) (declining to apply *Auer* deference where the regulation was unambiguous).

Finally, with respect to Otsuka's claim that the FDA violated the APA when it failed to employ notice-and-comment procedures, no special deference standard applies. Instead, whether an agency action necessitates the notice-and-comment process is a legal question that is subject to *de novo* review. *See Mendoza v. Perez*, 754 F.3d 1002, 1020 (D.C. Cir. 2014); *Nat'l Min. Ass'n v. Jackson*, 768 F. Supp. 2d 34, 46 (D.D.C. 2011) (citing *Cement Kiln Recycling Coal. v. EPA*, 493 F.3d 207, 215 (D.C. Cir. 2007)). As a general matter, the agency is permitted to forgo notice-and-comment procedures if its act qualifies as an adjudication (formal or informal), *see Blanca Tel. Co. v. FCC*, 743 F.3d 860, 867 (D.C. Cir. 2014); *Int'l Internship Program v. Napolitano*, 718 F.3d 986, 988 (D.C. Cir. 2013)), or if it issues an "interpretative rule" under 5 U.S.C.

§ 553(b)(A), *see Perez v. Mortg. Bankers Ass'n*, 135 S. Ct. 1199, 1204 (2015). But other forms of rulemaking (e.g., legislative rulemaking) trigger the notice-and-comment requirements. *See, e.g.*, *Ass'n of Flight Attendants-CWA, AFL-CIO v. Huerta*, 785 F.3d 710, 716–17 (D.C. Cir. 2015).

III. ANALYSIS

Otsuka's APA claims require this Court to evaluate the FDA's analysis regarding the scope of the exclusivity balance that Congress has struck in romanettes iii and iv. *See* 21 U.S.C. § 355(c)(3)(E)(iii), (iv). In essence, Otsuka maintains that the FDA was plainly prohibited from approving Alkermes's drug Aristada during the relevant time period, and thus the agency's authorization of the marketing of Aristada was arbitrary, capricious, and in violation of the law, because the three-year periods of marketing exclusivity that Abilify Maintena and its supplement received under romanettes iii and iv (and their accompanying regulations) were broad enough to block the approval of subsequent drug applications that have the same "conditions of approval." But the FDA has taken the position that the exclusivity provisions in the FDCA and the agency's regulations only prohibit approval of a subsequent new drug application that pertains to a drug that has the same active moiety as the drug that received exclusivity, regardless of any overlap with respect to the conditions of approval, and so, the FDA argues, because Aristada and Abilify Maintena have different active moieties, the agency was permitted to approve the Aristada NDA within Abilify Maintena's exclusivity periods.

As explained below, this Court has employed the familiar deference principles of *Chevron* and *Auer* and has reached several conclusions. First, the Court concludes that the FDCA's terms do not unambiguously preclude the FDA from viewing the

exclusivity bar as pertaining only to drugs that contain the same active moiety as the drug with exclusivity, and, in fact, the Court finds that the FDA's interpretation of the FDCA's exclusivity provisions is entirely reasonable. Furthermore, to the extent that the FDA reads its own implementing regulations in the same way as it has interpreted the pertinent statutory provisions, this Court concludes that the agency's reading is not plainly erroneous and is entitled to deference. In this same vein, the Court also finds that the agency's resolution of the regulation's ambiguity through its active-moiety interpretation is not a "de facto" rulemaking, as Otsuka argues. Consequently, the summary judgment motions that the FDA and Alkermes have submitted must be granted; Otsuka's motion for summary judgment must be denied; and Otsuka's claims against the FDA will be dismissed.

A. The FDCA Did Not Unambiguously Preclude Aristada's Approval

As explained, per *Chevron*, this Court must begin by evaluating whether or not the bar clauses of romanettes iii and iv unambiguously required the FDA to reject the Aristada NDA as barred by Abilify Maintena's exclusivities, and if not, the Court must proceed to determine whether the FDA's interpretation of those statutory provisions as permitting approval of an application concerning a drug with a different active moiety than the drug with exclusivity is reasonable. *See Vill. of Barrington*, 636 F.3d at 659–60. Otsuka insists that romanettes iii and iv speak unambiguously to the matter of the scope of the exclusivities conferred upon Abilify Maintena, and that, when read along with other statutory provisions related to the submission of drug applications, the text makes crystal clear that the FDA could not approve Alkermes's drug Aristada within three years of the agency's approval of Abilify Maintena and its supplement (*see* Pls.' Mem. at 21–23). For the reasons that follow, this Court disagrees with Otsuka's

assessment.

1. The Bar Clauses Are Susceptible Of More Than One Interpretation

A careful parsing of the relevant statutory provisions is required in order to determine Congress's intent for the purpose of the *Chevron* Step One inquiry. *See Sierra Club*, 551 F.3d at 1027. The dense text of romanettes iii and iv is quoted below; the Court has used different font styles (italics and underlining) to assist in demonstrating that each of these provisions contains varying criteria that relate to different aspects of the exclusivity dynamic.

The first part of romanette iii—the previously mentioned "eligibility clause," which is italicized below—establishes which of the many new drug applications that the FDA receives is entitled to claim a three-year period of marketing exclusivity upon approval. The second portion of romanette iii is the previously mentioned "bar clause" (underlined below); this language defines those subsequent new drug applications that are barred or blocked during the exclusivity period and thereby establishes the scope of the exclusivity that the eligibility clause confers. The full text of romanette iii is as follows:

> *If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section, is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant*, the Secretary may not make the approval of an application submitted under subsection (b) of this section for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) of this section if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant

> has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

21 U.S.C. § 355(c)(3)(E)(iii) (italics and underlining added). Both clauses of romanette iii mention "an application submitted under subsection (b)," which refers to the full NDAs and Section 505(b)(2) NDAs described in section 505(b) of the Hatch-Waxman Amendments and set forth at 21 U.S.C. § 355(b), *see supra* Part I.A, and when one recognizes this, romannette iii's directives begin to come into focus. That is, per the text of romanette iii's eligibility clause, three years of marketing exclusivity must be granted if a new drug application submitted per section 505(b) is approved, when two criteria are met: (1) the drug product for which the application was submitted includes an active ingredient that has previously been approved, and (2) the application contains reports of new clinical investigations essential to approval that the applicant itself conducted or sponsored. *See* 130 Cong. Rec. 24,425 (1984) (statement of Rep. Waxman) ("[A] 3-year period of exclusive market life is afforded to nonnew chemical entities approved after enactment of the bill which have undergone new clinical studies essential to FDA approval."); *see also* 21 C.F.R. § 314.108(b)(4). If a drug application satisfies these two criteria and is approved, thereby receiving a three-year period of marketing exclusivity, then the statute's bar clause directs the FDA to refrain from approving subsequent (herein called "second-in-time") new drug applications based on two other statutory criteria: (1) the second-in-time drug application must be "for the conditions of approval of such drug," and (2) the second-in-time drug application must rely at least in part upon investigations to prove safety and efficacy that the applicant did not conduct/sponsor or license. Thus, per the plain text of the statute, subsequent drug applications that are for "the conditions of approval" of the drug with exclusivity

and that are of the Section 505(b)(2) NDA variety (insofar as they rely on unoriginal studies) are blocked during the three-year period.

Romanette iv, which confers exclusivity for supplemental new drug applications, reflects, and builds upon, this framework:

> *If a supplement to an application approved under subsection (b) of this section is approved after September 24, 1984, and the supplement contains reports of new clinical investigations (other than bioavailabil[i]ty studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement*, the Secretary may not make the approval of an application submitted under subsection (b) of this section for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) of this section if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

21 U.S.C. § 355(c)(3)(E)(iv) (footnote omitted) (italics and underlining added). The italicized portion—what this Court will call the "supplement eligibility clause"—plainly grants exclusivity to supplemental new drug applications that update existing drug applications on the basis of new investigations conducted by the applicant. The "supplement bar clause" explains that this exclusivity bars a second-in-time Section 505(b)(2) application if that application is "for a change approved in the supplement[.]" 21 U.S.C. § 355(c)(3)(E)(iv). That is, those later applications are barred if (1) they are for a change approved in the supplement, and (2) the applicant relies on clinical investigations that the applicant did not conduct/sponsor or license.

Significantly for present purposes, the term "active moiety" does not appear on the face of either exclusivity provision, and in this limited sense, Congress obviously has not spoken directly to "the precise question[,]" *Chevron*, 467 U.S. at 842, of

whether new drug applications for drugs that have a different active moiety than the drug with exclusivity are blocked by the exclusivity benefit that romanettes iii and iv confer. At a different level of abstraction, however, a more substantial question of congressional intent emerges: whether the bar-clause criteria in romanettes iii and iv so unambiguously apply to the Aristada NDA that the FDA had no choice but to deny Alkermes' new drug application on the basis of its prior approval of Abilify Maintena and its supplement. *See Vill. of Barrington*, 636 F.3d at 659 (observing that Congress may speak directly to the precise question at issue "either by prescribing a precise course of conduct" for the agency or by setting forth a clearly delineated "range of interpretive discretion"); *Depomed, Inc. v. U.S. Dep't of Health & Human Servs.*, 66 F. Supp. 3d 217, 228 (D.D.C. 2014) (explaining that the mandate at *Chevron* Step One is to "give effect to the unambiguously expressed intent of Congress" (internal quotation marks omitted) (quoting *Chevron*, 467 U.S. at 842–43)). Put another way, the relevant Step One question is whether the requirements that Congress has listed in the statutory bar clauses—that the blocked application be a Section 505(b)(2) NDA that is "for the conditions of approval of such drug in the approved subsection (b) application[,]" 21 U.S.C. § 355(c)(3)(E)(iii), or one that is "for a change approved in [a] supplement" that received exclusivity, *id.* § 355(c)(3)(E)(iv)—are susceptible of multiple plausible interpretations and are thus ambiguous, *see AFL-CIO v. FEC*, 333 F.3d at 174, or whether there is only *one* possible interpretation of this statutory language. *See Petit v. U.S. Dep't of Educ.*, 675 F.3d 769, 781 (D.C. Cir. 2012) (explaining that victory at Step One requires plaintiffs to show the pertinent language "is susceptible of only [one] possible interpretation" (alteration in original) (internal quotation marks and citation

omitted)). Upon examination of the text and structure of the exclusivity provisions, the legislative history of the FDCA, and the parties' arguments, this Court concludes that there are multiple plausible interpretations of the bar clauses of romanettes iii and iv, and thus, these provisions are ambiguous for Step One purposes, for several reasons.

The first clue to the ambiguous nature of the provisions in question is that neither the FDCA's overarching definition section nor the particular section at issue here specifically defines the phrases "conditions of approval of such drug" or "change approved in the supplement." *See generally* 21 U.S.C. § 321 (FDCA's definition section); *id.* § 355 (FDCA's section governing "new drugs"). True, standing alone, "the absence of a statutory definition does not render a word ambiguous[,]" *Petit*, 675 F.3d at 781 (internal quotation marks and citation omitted), but the operative words in these statutory provisions have multiple potential meanings. For example, a "condition" can be (among other things) a "future and uncertain event on which the existence or extent of an obligation or liability depends[,]" or alternatively, a "state of being; an essential quality or status." Black's Law Dictionary 354, 356 (10th ed. 2014). And contextualizing the term in the context of the phrase "conditions of approval" does not help, because that phrase could reasonably be interpreted to mean all sorts of things in the drug-approval context, including the tasks that the FDA tells an applicant must be completed before the application's approval, or the diseases (the "conditions") for which the drug is approved as a treatment, or the particular circumstances that the FDA finds relevant to its determination that a drug should be approved for marketing, such as its method of delivery, the class of patients to whom it is to be delivered, or the nature of the chemical substance involved. *Cf. Veloxis Pharm.*, 109 F. Supp. 3d at 120

(observing that the parties "essentially concede[d] that [conditions of approval] is ambiguous" and proceeding to *Chevron* Step Two).

The phrase "such drug"—as in the "conditions of approval of *such drug* in the approved subsection (b) application[,]" 21 U.S.C. § 355(c)(3)(E)(iii) (emphasis added)—also has different potential meanings. To be sure, "such, when used as an adjective, . . . nearly always operates as a reference back to something previously discussed[,]" *Takeda Pharm.*, 78 F. Supp. 3d at 99 (internal quotation marks omitted) (citing, *inter alia*, *United States v. Ashurov*, 726 F.3d 395, 398–99 (3d Cir. 2013)), but, here, more than one drug is being referenced in the previous part of romanette iii because the text specifically mentions more than one subsection (b) application: there is the application that is "submitted under subsection (b) for a drug" that is presently eligible for exclusivity per the eligibility clause, *and* there is the application that was previously "approved under subsection (b)" that contained an active ingredient shared by the drug that is eligible for exclusivity. This renders "such drug" ambiguous when one attempts to ascertain what Congress meant when it used the phrase "conditions of approval of such drug."

What is more, it is also unclear from the statutory text *what role* "such drug" plays in the phrase "conditions of approval of such drug"; and there are at least two possibilities. On the one hand, "such drug" might serve only to point the reader to the relevant cluster of conditions of approval—i.e., those attached to whichever drug Congress intended to reference with that phrase—regardless of any essential qualities of the drug not encompassed in its "conditions of approval." (Otsuka makes this type of argument when it asserts that Abilify Maintena was approved for the "treatment of

schizophrenia using a once-monthly, long-acting, injectable formulation of aripiprazole[,]" (Otsuka's Citizen Petition, AR 000033), and suggests that these "conditions of approval"—which Aristada shared—were, alone, sufficient to trigger the bar clause, irrespective of active moiety differences. (*See id.* 000033, 000039; Pls.' Mem. at 21; Pls.' Reply in Supp. of Pls.' Mot. ("Pls.' Reply"), ECF No. 30, at 12.)) Alternatively, "such drug" might have been intended not only to identify the relevant conditions of approval but also to establish that only subsequent applications for duplicative drugs—i.e., those with the same active moieties—are barred, and only if the second-in-time application for the marketing of that same drug has the same conditions of approval. (The FDA adopts this reading when it "focuses on the drug at issue" as the first step of its determination regarding whether the bar clause blocks a second-in-time application (FDA Decision at 12)). Nothing in the text of romanette iii clearly resolves this dispute or otherwise establishes Congress's intent with respect to the meaning of "such drug."

And romanette iv presents similar ambiguities. The bar clause of that statutory provision states that "the Secretary may not make the approval of an application submitted under subsection (b) of this section *for a change approved in the supplement*[,]" 21 U.S.C. § 355(c)(3)(E)(iv) (emphasis added), but nowhere is the phrase "change approved in the supplement" defined. By their nature, supplements are additive; therefore, "change" likely refers to some new knowledge or utility brought into being via the supplement that is entitled to eligibility. *See, e.g.*, *ViroPharma*, 898 F. Supp. 2d at 7; Merriam-Webster's Collegiate Dictionary 206 (11th ed. 2003) (defining the noun change, *inter alia*, as "alteration" or "transformation"). But the

nature and scope of the relevant change is not patently obvious, and one could imagine that Congress might intend for subsequent drug applications to be blocked under romanette iv only if the second-in-time application involves *both* the same chemical substance present in the drug product that was initially approved and then supplemented, *and also* the particular change that was approved in the supplement. Alternatively, the only concern of Congress might be whether the subsequent application involves the same change in circumstances that the approved supplement requested (e.g., where the supplement sought a change in the method of administration of a previously approved drug and the second-in-time application seeks approval for that same new method of administration), and thus, the active moiety or ingredients of the drug in the supplement versus that in the second-in-time application could be considered irrelevant to the application of the bar clause. Notably, the D.C. Circuit has already found analogous supplement-exclusivity language to be "permeated by ambiguities." *AstraZeneca Pharm.*, 713 F.3d at 1139 (considering 21 U.S.C. § 355(j)(5)(F)(iv) and finding ambiguity in the phrase "a change approved in the supplement"). This Court sees no reason to believe that the meaning of "change" in the context of NDA-supplement exclusivity is any clearer.

All this means that, in this Court's reading, the plain text of the bar clauses of romanettes iii and iv "can support [multiple] plausible interpretations[.]" *AFL-CIO v. FEC*, 333 F.3d at 174 (citation omitted). Moreover, this Court has found nothing in the legislative history of the FDCA that would resolve or remove the many ambiguities in the pertinent provisions. *See Sierra Club*, 551 F.3d at 1027 (explaining that legislative history may be consulted at *Chevron* Step One). Therefore, the conclusion that

romanettes iii and iv are "ambiguous for purposes of *Chevron* analysis[,]" *AFL-CIO*, 333 F.3d at 174 (citation omitted), appears inescapable.

2. Otsuka's Arguments Fail To Demonstrate That The Key Terms Have A Single Plain Meaning

Otsuka's arguments to the contrary are wholly unpersuasive. The first questionable aspect of Otsuka's reasoning is its insistence that this Court should not focus so intently on the plain text of the bar clauses themselves, because the clear and unambiguous intent of Congress to prohibit approval of Aristada can be gleaned from reading the bar-clause provisions in conjunction with an entirely different set of statutory criteria with a dissimilar role—i.e., the criteria for successful submission of a Section 505(b)(2) application. (*See* Pls.' Mem. at 23 (arguing that the exclusivity provisions of romanettes iii and iv "must be interpreted together" with the section of the FDCA that establishes the pathways for submission of a Section 505(b)(2) NDA).) Otsuka never adequately explains how operative phrases in the pertinent provisions that are themselves rife with ambiguity (*see supra* Part III.A.1) can be deemed unambiguous because of how Congress defined the class of applications that romanettes iii and iv block. Nevertheless, according to Otsuka, romanettes iii and iv "can *only* be read so that a 505(b)(2) application cannot be approved for the conditions of approval of *the drug it relies on* to meet the FDCA's drug approval requirements" (Pls.' Mem. at 25–26 (emphasis added)), which, Otsuka says, means that the Aristada application was unambiguously barred because that application (1) relies on aripiprazole-related research that Otsuka submitted to support Abilify Tablets, and (2) has the same conditions of approval as Abilify Maintena (*see id.* at 31; Pls.' Reply at 9, 16).

To say that Otsuka's reasoning is difficult to follow is an understatement. But as far as this Court can tell, Otsuka's point appears to be that the FDA contravened romanettes iii and iv when it approved Alkermes's Section 505(b)(2) application for Aristada because that application relied upon clinical investigations that had originally supported Abilify Tablets (a drug approved pursuant to section 505(b)(1) of the Hatch-Waxman Amendments), and even though the five-year exclusivity period for Abilify Tablets has long expired, the bar clause related to the three-year exclusivity period for Abilify Maintena was triggered due to the fact that Aristada and Abilify Maintena have the same "conditions of approval" (romanette iii) and same "change" (romanette iv). (*See* Pls.' Mem. at 21, 25–26; Otsuka's Citizen Petition, AR 000033–34, 000039); *see also Koretoff v. Vilsack*, 707 F.3d 394, 398 (D.C. Cir. 2013) (per curiam) (explaining that a plaintiff challenging agency action in federal court may only make the "specific argument[s]" it made to the agency below).

This Court fully appreciates the considerable amount of creativity and effort that it took for Otsuka to craft a textual argument that transcends the plain text of romanettes iii and iv in an attempt to deliver Otsuka's desired result. Indeed, it requires considerable planning and foresight to proceed down the tortuous path that Otsuka constructs: it appears that one must, first, notice that romanettes iii and iv establish that the barred applications are of the Section 505(b)(2) variety and accept Otsuka's bald contention that "Sections 505(b)(2) and [romanettes iii & iv] must be interpreted together[.]" (Pls.' Mem. at 23.) Then, one must discount entirely the common understanding of "such" as it relates to "such drug" in romanette iii, and instead of viewing that word as referencing a previously mentioned drug, *see Takeda Pharm.*, 78

F. Supp. 3d at 99, read "such drug" in romanette iii to refer *prospectively* to the portion of the bar clause that mentions "subsection (b)(1)[.]" (*See* Pls.' Mem. at 24 (arguing that "such drug" refers to "multiple drugs" including "the drug in the first-in-time 505(b)(1) application" because "such . . . refer[s]" to "something to come later in the sentence" (internal quotation marks and citations omitted))). Then, one must ignore the obvious possibility that the bar clause's reference to "subsection (b)(1)" serves not to enshrine reliance on a drug approved under that subsection as the key marketing-exclusivity consideration but simply to establish that the bar clause only reaches Section 505(b)(2) applications, i.e., applications that contain unoriginal "*investigations* . . . relied upon by the applicant for approval of the application[,]" 21 U.S.C. § 355(c)(3)(E)(iii) (emphasis added). (*See* Pls.' Mem. at 22 ("When the word 'drug' is appropriately considered in the statutory structure, it is clear that a 505(b)(2) NDA is blocked by exclusivity attaching to the 'conditions of approval' or 'change' *of the drug the 505(b)(2) relies on* to meet the drug approval requirements." (emphasis added)).) And, finally, after reading romanette iii to establish that Alkermes's reliance on Abilify Tablets somehow matters with respect to the determination of the scope of exclusivity, one must infer that the "conditions of approval" or "change" of Abilify Maintena or its supplement impermissibly overlap with the *same* "conditions of approval" and "change" that the Aristada application seeks, and reason that, for that reason alone, Abilify Maintena's exclusivity bar applies even though Aristada and Abilify Maintena have an admittedly distinct active ingredient and moiety. (*See id.* at 22 ("[T]he text of the provisions limits exclusivity to the 'conditions of approval' derived from 'new clinical investigations' . . . and not to a specific 'drug.'" (citations omitted)); *see also id.* at 21

("The focus on the scope of a first-in-time drug's exclusivity is appropriately on the 'conditions of approval' or 'change,' not the active moiety at issue.").)

Only if one does all this, is it even *remotely* conceivable to reach the conclusion that Congress meant for Aristada to be blocked under romanettes iii and iv based on Alkermes's reliance on investigations that were submitted to support Abilify Tablets (a drug whose exclusivity period has expired), given that Abilify Maintena and Aristada allegedly have the same conditions of approval and notwithstanding the differences in active moiety. (*Cf. id.* at 30 (heralding "[t]he plain language reading of the statute set forth by Otsuka" as consistent with clear congressional intent because it "reward[s] drug manufacturers, like Otsuka, for engaging in research of already approved drugs (*e.g.*, Abilify tablets) to create new products (*e.g.*, Abilify Maintena)").) And while Otsuka repeatedly, and perhaps even earnestly, asserts that this interpretation of the bar clauses was Congress's *obvious* intent, never before has this Court seen a more convoluted reading of a statute's text to support the contention that its meaning is plain! Otsuka also seemingly (unwittingly) *acknowledges* that romanette iii is ambiguous as it struggles to explain what it contends is the only proper reading of the statutory text. (*See, e.g., id.* at 24–25 (arguing that the term "such drug" in romanette iii is broad enough to "include[] in its scope [*both*] what FDA has interpreted to mean active moiety *and* the 'drug' in the 505(b)(1) application"(emphasis added)).) And it fails entirely to offer a developed, independent argument regarding romanette iv, presumably because, in Otsuka's view, success on that front rises and falls with the viability of its

romanette iii assertions. (*See, e.g.*, *id.* at 21 (treating "conditions of approval" and "change" as essentially equivalent).)[9]

In the instant morass of text and arguments, at least one thing is abundantly clear: even if Otsuka is correct that romanettes iii and iv *can* be read to bar Aristada under the reasoning Otsuka puts forward, nothing in Otsuka's briefs or oral argument persuades this Court that the FDA was *required* to read the statute in this fashion (i.e., that romanettes iii and iv unambiguously direct Otsuka's desired result). Thus, contrary to Otsuka's contentions, these statutory provisions cannot be deemed to provide a single, definitive answer to the key question (for *Chevron* Step One purposes): "What are the relevant criteria for determining the applicability of the three-year exclusivity period under romanettes iii and iv?" And it certainly cannot be said that Congress's

[9] A closer look at the exclusivity process generally—and specifically, the three-year exclusivity dynamic—only underscores the implausibility of Otsuka's statutory interpretation (as this Court understands it), which makes it all the more likely that romanettes iii and iv do not demand it. Per the eligibility clause, three-year exclusivity can occur only when a drug application that includes a particular active ingredient has been approved at some point in the past (which the Court will call T1); the Abilify Tablets application is the T1 application here. If, sometime later (at T2), a drug applicant submits a subsection 505(b) application for a drug that includes that (now previously approved) active ingredient, the eligibility clause establishes that the T2 drug application (Abilify Maintena here) can receive exclusivity *if* it contains reports of new clinical investigations essential to the application's approval that it conducted or sponsored. This much is not in dispute. *See* 21 U.S.C. § 355(c)(3)(E)(iii). When a later application like Aristada's comes on the scene (at T3), the question is whether that application is for the "conditions of approval of such drug in the approved subsection (b) application" for the purpose of the bar clause, *id.*, and answering *that* question requires identifying which conditions of approval matter: the conditions of approval of the drug in the T2 application or those of the drug in the T1 application? Notably, whatever else one thinks about romanettes iii and iv, their eligibility clauses parcel exclusivity out in the first instance based on the nature of the T2 drug application, and also, with respect to romanette iii, based on a look at the active ingredient of the T2 drug and the supporting clinical investigations. Yet, Otsuka's "unambiguous" statutory reading of the bar clause inexplicably unmoors the scope of the exclusivity bar from the trigger that created it. The strangeness of the view that the T1 drug application is determinative of the applicability of the exclusivity bar is made even stranger when one realizes that a T1 drug application like Abilify Tablets got its *own* exclusivity period when it was first approved; and, indeed, Abilify Tablets likely received five years of exclusivity under 21 U.S.C. § 355(c)(3)(E)(ii) because it contained a never-before-approved active ingredient. Otsuka does not explain why Congress would use romanettes iii and iv to, in effect, provide what amounts to yet another period of exclusivity based on the second-in-time applicant's reliance on a T1 drug that has already enjoyed such protection, and this Court sees no good reason why it would do so.

unambiguous response to that question is that the only things that matter are the second-in-time applicant's reliance on another drug and any similarity in the conditions of approval of the drug with exclusivity (or, for that matter, the drug upon which the applicant relied) and the drug in the second-in-time application, as Otsuka insists. This means that Otsuka has failed to demonstrate that its interpretation of romanette iii is the only viable reading of that provision, and its tag-along romanette iv contentions also necessarily fail.

Thus, Otsuka has not shown that "the statute unambiguously forecloses the [agency's] interpretation" in a manner that would preclude this Court's move to *Chevron*'s Step Two. *Vill. of Barrington*, 636 F.3d at 661 (citation omitted) (emphasis omitted); *see also Pharm. Research and Mfrs. of Am. v. FTC*, 790 F.3d 198, 207 (D.C. Cir. 2015) ("To prevail on its *Chevron* Step One argument, [the plaintiff] has to do better than concoct an interpretation purportedly based on the statute's context. [It] must show that the statute *unambiguously* forecloses the [agency's] interpretation." (internal quotation marks and citation omitted) (third alteration and emphasis in original)).[10]

[10] Notably, and for what it's worth, in addition to being essentially incomprehensible, Otsuka's view of romanettes iii and iv appears to undermine the balance that Congress struck in the Hatch-Waxman Amendments in at least one obvious way. *See Petit*, 675 F.3d at 782 (observing that considering "the problem Congress sought to solve" is critical at Step One (internal quotation marks and citation omitted)). The overriding goal of the amendments was to "balance two competing interests in the pharmaceutical industry: (1) inducing pioneering research and development of new drugs and (2) enabling competitors to bring low-cost, generic copies of those drugs to market[,]" *Takeda Pharm.*, 78 F. Supp. 3d at 68 (internal quotation marks and citation omitted); yet, Otsuka's reading would harm the first interest and do nothing for the second. Aristada contains a never-before-seen chemical entity (two, in fact); and indeed, it appears that the Aristada NDA received five years of marketing exclusivity precisely for that reason. (*See* FDA Decision at 20.) Yet Otsuka's statutory reading would not only delay Alkermes's access to those five years of exclusivity for its new-chemical-entity based drug, but it would at least arguably allow Otsuka to chain together aripiprazole-based supplements based on Abilify Maintena—or perhaps entirely new aripiprazole-based applications—and *indefinitely* delay Alkermes's access to the benefits of its *different* chemical entities (N-hydroxymethyl aripiprazole and aripiprazole

B. The FDA's Determination That Romanettes iii And iv Only Block Approval Of Subsequent Applications For New Drugs That Have The Same Active Moiety As The Drug With Exclusivity Survives Scrutiny At *Chevron* Step Two

Having concluded that romanettes iii and iv are ambiguous regarding the criteria that must be applied when the FDA determines whether or not a second-in-time NDA is barred by the exclusivity those provisions confer, this Court now turns to an evaluation of the reasonableness of the FDA's conclusion that only those second-in-time applications for drugs that have the same active moiety as a drug with exclusivity are barred. At *Chevron* Step Two, this Court *must* accept a reasonable agency construction of a statutory provision, even if it "differs from what the [C]ourt believes is the best statutory interpretation." *Brand X*, 545 U.S. at 980 (citation omitted). This is so because ambiguity in a statute may properly be considered to be implicit authorization from Congress to the agency to deliver a reasonable interpretation that resolves it, *see Van Hollen, Jr.*, 811 F.3d at 495, and the agency is "the authoritative interpreter (within the limits of reason)" of "an ambiguous statute [it] is charged with administering[.]" *Brand X*, 545 U.S. at 983. Thus, at this stage in the review process, this Court's only task is to ensure that the FDA's interpretation is a permissible construction of the text of the statute, *see Abbott Labs.*, 920 F.2d at 988 (explaining that the court must evaluate the "construction's 'fit' with the statutory language as well as its conformity to statutory purposes"), and that the FDA has satisfied the strictures of reasoned decision making in selecting that interpretation, *see Vill. of Barrington*, 636 F.3d at 660 ("At *Chevron* step two we defer to the agency's permissible interpretation, but only if the

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lauroxil). Again, if the statute actually required this result, the Court would have no choice but to enforce it. But this is one more nail in the coffin that encapsulates Otsuka's Step One averments.

agency has offered a reasoned explanation for why it chose that interpretation." (citation omitted)). For the reasons that follow, this Court concludes that the FDA's interpretation of the bar clauses in romanettes iii and iv is permitted by the statutory text and that the agency satisfactorily explained its choice.

1. The Text Of Romanette iii Permits The FDA's "Active Moiety" Interpretation, And The FDA Has Provided A Cogent Explanation For That Interpretation

The FDA has determined that the unclear phrase "conditions of approval of such drug in the subsection (b) application" in romanette iii should be read to block only those second-in-time applications that, as a threshold matter, seek marketing approval for a drug that has the same active moiety as the drug with exclusivity. As applied to the instant circumstances, for example, the FDA has concluded that "any approval of Aristada will not be an approval of 'such drug' (a drug containing the active moiety aripiprazole) and therefore will not be for the 'conditions of approval of such drug'" in the Abilify Maintena application. (FDA Decision at 21–22). Courts employ "all the tools of statutory interpretation" when determining permissibility, *Loving v. IRS*, 742 F.3d 1013, 1016 (D.C. Cir. 2014) (citation omitted); *PDK Labs. Inc. v. DEA*, 438 F.3d 1184, 1190 (D.C. Cir. 2006) (noting that "[e]ven at *Chevron*'s second step, we begin with the statute's language" (citing *Abbott Labs.*, 920 F.2d at 988)), and this Court finds that the text and structure of romanettes iii and iv permit the FDA's reading, for several reasons.

First of all, per its plain text, romanette iii's bar clause expressly prohibits approval of subsequent Section 505(b)(2) applications "for the conditions of approval of *such drug* in the approved subsection (b) application[.]" *See* 21 U.S.C. § 355(c)(3)(E)(iii) (emphasis added). It is permissible to read "such drug" as referring

back to the previous use of "drug" pursuant to the most natural reading of "such," *see Takeda Pharm.*, 78 F. Supp. 3d at 99, and the prior use of "drug" (in the eligibility clause) describes the drug product in the application that receives exclusivity. (*See* FDA Decision at 12 (reading "[t]he phrase 'such drug in the approved subsection (b) application' in the bar clause [to] refer[] to the earlier use of the term 'drug' in the eligibility clause").) Furthermore, the language of the bar clause clearly permits the agency's contention that the pertinent identifying characteristic of the drug that receives exclusivity is its active moiety. For approximately two decades now, the FDA has focused on the active moiety of a drug—i.e., "the molecule or ion, excluding [certain appended portions of the molecule,] responsible for the physiological or pharmacological action of the drug substance[,]" 1994 Rule, 59 Fed. Reg. at 50,368 (codified at 21 C.F.R. part 314)—to identify and distinguish different drugs, and Otsuka has not pointed to a characteristic that better defines a "drug" and, thus, better articulates the meaning of "such drug" as that phrase appears in romanette iii. Put another way, when a drug application is submitted for approval, the manufacturer must demonstrate that the substance it seeks to market "will have the effect it purports or is represented to have[,]" 21 U.S.C. § 355(d), and it is well established that the active moiety of a drug substance is the feature that makes the drug "go," insofar as it provides the drug substance's "physiological or pharmacological action[.]" 21 C.F.R. § 314.108(a). Thus, Congress's use of the phrase "such drug" is certainly amenable to an interpretation that relates to what the agency has long determined is a drug's distinguishing feature.[11]

[11] The fact that romanette iii's eligibility clause speaks of "active ingredient[s]" instead of active moieties, 21 U.S.C. § 355(c)(3)(E)(iii), is of no moment, as far as the bar clause is concerned. A

It is also clear to this Court that the FDA's interpretation is consistent with the structure and purpose of romanette iii and the relevant legislative history. Specifically, by providing a three-year period of marketing exclusivity under the specific circumstances romanette iii prescribes, Congress apparently intended to incentivize a particular *type* of effort on the part of drug manufacturers: the investments that are needed to demonstrate that a previously approved drug substance can be used in a new way. *See* 21 U.S.C. § 355(c)(3)(E)(iii); 130 Cong. Rec. 24,425 (1984) (statement of Rep. Waxman) ("[A] 3-year period of exclusive market life is afforded to *nonnew* chemical entities . . . which have undergone new clinical studies essential to FDA approval. This provision will encourage drugmakers to obtain FDA approval for significant therapeutic uses *of previously approved drugs*." (emphasis added)); (*see also* Pls.' Mem. at 18 (admitting that "[t]hree-year exclusivity was meant to incentivize drug manufacturers to invest in new clinical trials to demonstrate the safety and effectiveness for new uses of already approved drugs." (citations omitted)). Thus, it makes eminent sense for the FDA to conclude that the scope of the three-year-exclusivity benefit should relate to the particular drug substance that was studied in order to give rise to exclusivity in the first place; indeed, to find otherwise would upset the "careful balance" that Congress struck in the Hatch-Waxman Amendments insofar as it would

specific "congressional mandate in one section and silence in another often suggests not a prohibition but simply a decision not to mandate any solution in the second context, i.e., to leave the question to agency discretion[,]" *Van Hollen, Jr.*, 811 F.3d at 493–94 (internal quotation marks and citation omitted), and it cannot be disputed that a drug's active moiety is a highly salient drug characteristic that an expert agency might well deem relevant to the exclusivity analysis. Furthermore, there is no question that the FDA generally deems the active moiety of a drug to be the equivalent of that drug's active ingredient. *See, e.g.*, 1994 Rule, 59 Fed. Reg. at 50,358 (explaining the agency's longstanding view that "'active ingredient,' as used in the phrase 'active ingredient (including any salt or ester of the active ingredient),' means active moiety").

seemingly permit a drug manufacturer who made investments related to one particular drug substance to prevent the marketing of *other* drug products and substances that might be safe and effective as treatments for the same or similar conditions. (*See, e.g.*, FDA Decision at 27 & n.94.) Nothing in the statutory scheme suggests that Congress intended *that* result, and in fact, it appears that Congress strongly desired to affect the drug market in precisely the opposite manner. *See Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1568 (Fed. Cir. 1997); *see also Takeda Pharm.*, 78 F. Supp. 3d at 100 (explaining that Hatch-Waxman was designed both to "incentiviz[e] investment in the innovation of new drugs" and also to "encourag[e] the production of less-costly alternative drug products" (citation omitted)). Thus, an agency interpretation that views romanette iii's exclusivity as only extending to second-in-time applications for the marketing of drugs that are, in essence, the same as the drug that was previously studied (i.e., those that have the same active moiety) is entirely consistent with the way the statutory scheme was intended to operate and accords fully with the purposes animating Hatch-Waxman. *See AstraZeneca Pharm. LP v. FDA*, 872 F. Supp. 2d 60, 85 (D.D.C. 2012) (testing the FDA's statutory interpretation against Hatch-Waxman's "careful balance" to ascertain its reasonableness (citations omitted)), *aff'd*, 713 F.3d 1134 (D.C. Cir. 2013).

It is also clear that, in selecting this interpretation, the FDA plainly wielded its "expertise to produce a reasoned decision." *Vill. of Barrington*, 636 F.3d at 660 (citation omitted). Policy considerations may guide "an agency's choice among plausible meanings of a statute[,]" *Cent. Tex. Tel. Co-op, Inc. v. FCC*, 402 F.3d 205, 212 (D.C. Cir. 2005), and as the FDA has explained, employing active moiety as a

relevant criterion for determining whether a second-in-time application is barred promotes Hatch-Waxman's goals by protecting "against approval of drugs with the same active moiety for the same exclusivity-protected use[,]" while simultaneously encouraging competition by ensuring that exclusivity could "not block approval of drugs with different active moieties . . . that may have some advantages over previously approved active moieties[,]" (FDA Decision at 23–24 (footnote omitted)). Moreover, the FDA has noted that the active-moiety approach can "be applied consistently with scientific rigor across drug products." (*Id.* at 27.) In light of the just-discussed centrality of the active moiety of a drug to its usefulness, the FDA's interpretation is a quintessential—and quite cogent—policy-based resolution of statutory ambiguity. *See Vill. of Barrington*, 636 F.3d at 666.

2. The FDA's Interpretation Of Romanette iv—Which Is Partly Based On Its View Of The Scope Of The Exclusivity Conferred In Romanette iii—Is Permissible, Reasoned, And Rationally Related To The Goals Of The FDCA

At this point in time, the FDA's construction of romanette iv is the only live legal basis for Otsuka's claim that the FDA's approval of Aristada violates the exclusivity provisions of the FDCA. (*See* Compl. ¶¶ 51–59; *see also* Notice, ECF No. 36 (alerting Court that Abilify Maintena's romanette iii exclusivity has expired). In interpreting romanette iv, the FDA agrees with Otsuka that the "changes" in a supplement are adjustments to the conditions of approval of a preexisting NDA (*see* FDA Decision at 13; Otsuka's Citizen Petition, AR 000034); however, even prior to assessing Aristada's conditions of approval, the FDA determined that the exclusivity that attaches to Abilify Maintena's supplement did not preclude approval of Aristada because, in the FDA's view, a supplement's changes to the conditions of approval relate

to *a particular drug* (i.e., a product with a particular active moiety) and thus, a second-in-time application for a drug with a different active moiety than the initially approved drug was not blocked by romanette iv's exclusivity. (*See* FDA Decision at 13 ("[A] change approved in a supplement must be a change in conditions of approval for the same drug (active moiety) approved in the original NDA.").) Notably, the text of romanette iv provides fewer concrete hooks for interpretation than romanette iii, and as a result, to a large extent, the FDA's construction of the former is rooted in its conclusions about the latter. That is precisely why this Court considered it necessary to analyze the permissibility and cogency of the "active moiety" interpretation that the FDA has employed with respect to romanette iii as a precursor to its discussion of the FDA's interpretation of romanette iv. *See supra* Part III.B.1. And in light of that prior analysis, this Court easily concludes that the FDA's interpretation of romanette iv satisfies *Chevron*'s Step Two.

Specifically, as explained above, romanette iii plainly teaches that conditions of approval matter when the FDA determines whether a second-in-time application is barred by exclusivity, and although the phrase "conditions of approval" does not appear in romanette iv, there is no obvious reason why overlapping conditions of approval would be deemed significant when exclusivity is conferred to an application submitted under subsection (b) in the first instance, but *not* when exclusivity attaches to "a *supplement* to an application approved under subsection (b)[.]" 21 U.S.C. § 355(c)(3)(E)(iv) (emphasis added). Thus, as the parties here agree, it is permissible and proper to treat the supplement's "changes" as relating to the conditions of approval of the drug with exclusivity. (*See* FDA Decision at 13; Otsuka's Citizen Petition, AR

000034.) Moreover, to the extent that supplemental NDAs relate "to an application approved under subsection (b)[,]" 21 U.S.C. § 355(c)(3)(E)(iv), they necessarily augment an application that was previously approved for a drug with a particular active moiety. *Cf. AstraZeneca Pharm. LP.*, 713 F.3d at 1136 (discussing the supplement process). Accordingly, the ambiguous phrase "change approved in the supplement" permits the interpretation that the exclusivity granted to a supplement that alters the relevant conditions of approval of an approved drug application bars only second-in-time applications for products with the same active moiety. Such an interpretation is consistent with the previously noted principle that exclusivity is a reward for work on a particular drug substance, which is gleaned from the statutory structure and legislative history. *See, e.g.*, 130 Cong. Rec. 23,766 (1984) (statement of Sen. Hatch) (describing supplements as "restric[ting] coverage to only those alterations, like some changes in strength, indications, and so forth"). And, indeed, while there may be other, and potentially better, ways of reading romanette iv, the FDA was not required to pick the *best* interpretation; all that matters is that nothing in romanette iv *forecloses* the active-moiety limitation, and it is a restriction that makes sense in light of what we know about the statutory scheme and the way drugs work. *See NationsBank of N.C., N.A. v. Variable Annuity Life Ins. Co.*, 513 U.S. 251, 257 (1995) (explaining that, at Step Two, the agency's judgment receives "'controlling weight'" if it "fills a gap or defines a term in a way that is reasonable in light of the legislature's revealed design" (quoting *Chevron*, 467 U.S. at 844)).

This Court explained above why the FDA's romanette iii reasoning satisfied the requirements of reasoned decisionmaking, and the justifications provided there were

also offered to support the FDA's romanette iv reasoning. To begin with, the FDA is an expert agency charged with making precisely these sorts of highly technical determinations, and its interpretation of romanette iv is premised on "the agency's evaluations of scientific data within its area of expertise." *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 766 (D.C. Cir. 2010) (internal quotation marks and citation omitted). What is more, the FDA has seamlessly situated its decision within the history of the Hatch-Waxman Amendments, and, specifically, the problems that Congress sought to solve. That history tells the story of a focused legislative effort to better harmonize innovation and competition, *see Takeda Pharm.*, 78 F. Supp. 3d at 68—i.e., Congress unquestionably wanted to "provide incentives for new drug development," *ViroPharma*, 898 F. Supp. 2d at 7 (internal quotation marks and citation omitted), while at the same time preserving the market's unique ability to ensure that low-priced drugs are provided to the public, *see Teva Pharm., USA, Inc. v. Leavitt*, 548 F.3d 103, 107 (D.C. Cir. 2008); *Glaxo, Inc.*, 110 F.3d at 1568. As the FDA has noted, it was against that backdrop that marketing exclusivities were created (*see* FDA Decision at 4), and requiring that the exclusivity benefit be limited based on the active moieties of the relevant drugs—such that it is deemed to block only second-in-time drug applications that, in effect, concern the same drug—encourages innovation by guarding "against approval of drugs with the same active moiety for the same exclusivity-protected use" (*id.* at 23), and simultaneously promotes market competition by ensuring that this exclusivity "does not block approval of drugs with different active moieties . . . that may have some advantages over previously approved active moieties" (*id.* at 23–24 (footnote omitted)). To be sure, one might imagine a bigger (or smaller) exclusivity bar

than the "active moiety" approach permits, but, at the end of the day, the myriad ambiguities in the relevant statutory language makes clear to this Court that striking the desired balance between an innovator with an expansive exclusivity benefit (on the one hand) and a host of stifled future potential competitors (on the other) was a policy choice that Congress intended *the FDA* to make. *See Health Ins. Ass'n of Am., Inc. v. Shalala*, 23 F.3d 412, 416 (D.C. Cir. 1994) ("Resolution of an ambiguity in a statute, if it has consequences, inevitably requires the agency to consider competing policy objectives, and it is the reconciliation of such conflicts that is entitled to judicial deference." (internal quotation marks omitted) (quoting *Wagner Seed Co. v. Bush*, 946 F.2d 918, 923 (D.C. Cir. 1991))); *Ariz. Pub. Serv. Co. v. EPA*, 211 F.3d 1280, 1287 (D.C. Cir. 2000) ("[A]s long as the agency stays within [Congress'] delegation, it is free to make policy choices in interpreting the statute, and such interpretations are entitled to deference." (alterations in original) (internal quotation marks omitted) (quoting *Arent v. Shalala*, 70 F.3d 610, 615 (D.C. Cir. 1995))); *ViroPharma*, 898 F. Supp. 2d at 21 (upholding an FDA decision at Step Two where drug company failed to show that the interpretation was "anything other than a reasonable policy choice for the [FDA] to [have made]." (alterations in original) (internal quotation marks and citation omitted)).

3. Otsuka's Romanette iv Arguments (Such As They Are) Are Unavailing

Otsuka has trained all of its fire on the FDA's interpretation of romanette iii (*see supra* Part III.A.2) and makes little-to-no effort to mount an independent attack on the FDA's reading of romanette iv. Thus, only a small set of cross-over arguments is worth addressing here. With respect to Otsuka's contention that the FDA's active moiety

construction leads to "absurd" results under the circumstances presented in this case because Aristada ultimately converts in the body to aripiprazole, which is the active moiety of the Abilify line of drugs (Pls.' Reply at 27–28), it suffices to note that the complex scientific endeavor of determining whether or not the drug in the second-in-time application is actually too similar to the drug with exclusivity to be deemed innovative is precisely the kind of determination that Congress most certainly intended to be left to the FDA. *See Cmty. Care Found. v. Thompson*, 318 F.3d 219, 225 (D.C. Cir. 2003) (observing heightened deference when the agency's interpretation "concerns . . . a complex and highly technical regulatory program" (internal quotation marks and citation omitted)).

Otsuka's suggestion that the FDA's explanation for the "active moiety" interpretation inexplicably contradicts its past practice fares no better. (*See* Pls.' Mem. at 33–35 (pointing to statements the FDA made in a prior letter in response to a citizen petition submitted by Pfizer relating to its product Xalatan)); *see also King Broad. Co. v. FCC*, 860 F.2d 465, 470 (D.C. Cir. 1988) (finding that an agency acts arbitrarily and capriciously if it issues a decision "inconsistent with its prior analysis in similar situations without any acknowledgement of the fact, or cogent explanation as to why"). Several years ago, the FDA permitted the marketing of Allergan's Lumigan and Alcon's Travatan, over Pfizer's (non-exclusivity-based) objection. (*See* Letter from Janet Woodcock, MD, Director, CDER to Alessandra Ravetti, Pfizer ("Xalatan Letter"), AR 001508, 001518, 001533.) According to Otsuka, although the three drugs there all had different active moieties, the FDA nevertheless indicated that Lumigan and Travatan would have been blocked by a previously extant (but at that point expired) period of

exclusivity that had attached to a supplement to Pfizer's Xalatan. (*See* Pls.' Mem. at 33–34 (citing Xalatan Letter, AR 001532).) In contrast to Otsuka's suggestion that the FDA has acted arbitrarily and capriciously by approving Aristada despite this past policy statement, the FDA has expressly addressed the statements that it previously made under those markedly different circumstances, and it has explained both that the prior statements are not fairly attributable to the establishment of a contrary policy, and that, in any event, its current view represents the considered judgment of the agency about how broad the exclusivity benefit should be. (*See* FDA Decision at 25 n.87 (expressly grappling with the potential implications of the Xalatan letter, and concluding that, under the circumstances, the question of exclusivity's relationship to active moieties was simply not before the agency and the agency's statements did not represent the proper interpretation in light of "the statute, regulations, science, and policy").) An agency may change its mind on policy issues and legal interpretations without being accused of arbitrariness, so long as its decision is "adequately explained[,]" *Arkema Inc. v. EPA*, 618 F.3d 1, 6 (D.C. Cir. 2010); thus, when a party nonetheless claims that an agency has deviated impermissibly from past statements, courts in this jurisdiction have reviewed the agency's explanation only to ensure "minimal standards of rationality" in cases much like this one. *Sanofi-Aventis U.S. LLC v. FDA*, 733 F. Supp. 2d 162, 173 (D.D.C. 2010) (internal quotation marks omitted) (quoting *Small Refiner Lead Phase-Down Task Force v. EPA*, 705 F.2d 506, 521 (D.C. Cir. 1983)).

It seems that the real gravamen of Otsuka's complaint is the alleged unfairness of a statutory construction that permits "the true innovator that first engaged in the

necessary trials to prove the beneficial effects of treating patients with a long-acting formulation of aripiprazole" to be "penalized by the entry to market of a drug that referenced aripiprazole to shortcut the drug approval requirements[.]" (Pls.' Reply at 28 (footnote omitted); *see also* Pls.' Mem. at 27 (complaining about the "absurd[ity]" of permitting Alkermes to rely on investigations associated with Abilify Tablets and "at the same time" avoid the exclusivity associated with Abilify Maintena).) This may very well prove to be a bad policy choice, but for the reasons explained, it does not defy rationality, and that is especially so given that Otsuka's alternative reading is transparently orchestrated to extend the marketing exclusivity of the initial innovator drug in perpetuity (*see supra* note 10), which, in this Court's view, is an even more absurd result.

The bottom line is this: the FDA has made the permissible and reasonable choice to consider the exclusivity conferred by romanette iv to be cabined by the active moiety of the drug that triggers it, and the agency has provided an adequate explanation of how and why it decided that this was the place to draw the exclusivity boundary line. (*See, e.g.*, FDA Decision at 21–24, 27) (coupling the FDA's interpretive analysis of the role of "such drug" in understanding romanette iii (and by extension romanette iv) with its policy-based arguments); *see also id.* at 27 (asserting that the active-moiety approach "can be applied consistently with scientific rigor across drug products"). Otsuka has failed to demonstrate that Step Two of the *Chevron* analysis requires anything more.

C. The FDA's Interpretation Of Its Own Regulations To Conform With Its Reasonable Statutory Construction Is Not Plainly Erroneous Or Inconsistent With The Text Of The Applicable Regulations

The FDA's regulations regarding the three-year exclusivity benefit mirror romanettes iii and iv, and thus have a familiar structure. The regulation corresponding

to romanette iii, which appears at 21 C.F.R. § 314.108(b)(4), states (in relevant part) that:

> If an application: (i) Was submitted under section 505(b) of the act; (ii) Was approved after September 24, 1984; (iii) Was for a drug product that contains an active moiety that has been previously approved in another application under section 505(b) of the act; and (iv) Contained reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that were essential to approval of the application, the agency will not make effective for a period of 3 years after the date of approval of the application the approval of a 505(b)(2) application . . . for the conditions of approval of the original application[.]

21 C.F.R. § 314.108(b)(4)(i)–(iv) (hereinafter referred to as "subdivision (b)(4)"). The regulation implementing romanette iv appears in the next subdivision, at 21 C.F.R. § 314.108(b)(5); it provides:

> If a supplemental application: (i) Was approved after September 24, 1984; and (ii) Contained reports of new clinical investigations (other than bioavailability studies) that were conducted or sponsored by the applicant that were essential to approval of the supplemental application, the agency will not make effective for a period of 3 years after the date of approval of the supplemental application the approval of a 505(b)(2) application . . . for a change[.]
>
> 21 C.F.R. § 314.108(b)(5)(i)–(ii) ("subdivision (b)(5)").

The FDA has made clear that it views these regulations as dovetailing with the mandates of romanettes iii and iv and requiring the same result: that a second-in-time drug with a different active moiety is not barred by the three-year exclusivity period. (*See* Defs.' Mem. at 37; *see also* FDA Decision at 10–11 ("The statute *and regulations* for 3-year exclusivity describe which original NDAs and supplements (sNDAs) are eligible for [three-year] exclusivity and which are barred or blocked from approval by that exclusivity." (emphasis added)).) Otsuka argues here that the FDA somehow cannot do this due to (minor) wording differences between the text of the regulations and the statutes that implement them, and as a result of what Otsuka calls the overall "regulatory context."

(Pls.' Mem. at 37; *see also id.* at 36–39.) This Court finds Otsuka's argument wholly unpersuasive.

With respect to Otsuka's threshold contention that these regulations "unambiguously prevent FDA from approving a [Section] 505(b)(2) application for the conditions of approval of the original application or a change, irrespective of the active moieties[,]" and thus that the FDA's contrary interpretation is not entitled to *Auer* deference (*id.* at 36 (internal quotation marks omitted)), Otsuka fails to demonstrate that the text of these regulations is any clearer than the text of the statutes upon which the regulations are based. *See Christopher*, 132 S. Ct. at 2166 (explaining that *Auer* requires courts to defer to an agency's "fair and considered" interpretation of an ambiguous regulation unless the interpretation is "plainly erroneous or inconsistent with the regulation" (internal quotation marks and citations omitted)). Of course, it would be difficult for Otsuka to clear this hurdle, because the regulation has largely imported the same inherently ambiguous "conditions of approval" and "change" language that one finds in the statute, and the critical question of what it *means* for an application to be for the "conditions of approval" or "change" likewise remains unanswered in the regulatory context. Moreover, although Otsuka makes much of the fact that the bar clause of subdivision (b)(4) directs one's attention to "the conditions of approval *of the original application*"—in contrast to romanette iii's bar clause, which homes in on "such drug"—Otsuka never manages to explain why this distinction makes any difference, especially given that, as the FDA reads them, both provisions point to the same set of conditions: those that are associated with the drug application that has obtained exclusivity. (*See, e.g.*, Defs.' Mem. at 37.) And in this regard, the regulations

clearly permit the agency to employ the same reasoning that it applies when it interprets the statute, which means that "the conditions of approval of the original application" language is permissibly viewed as, in effect, incorporating the nature of the drug in the original application itself. (*See, e.g.*, Alkermes's Mem. at 39.) Thus, the FDA's view is entitled to deference because it is not "plainly erroneous or inconsistent with the regulation[,]" *Christopher*, 132 S. Ct. at 2166 (internal quotation marks and citation omitted), in any meaningful sense.

Undaunted, Otsuka points out that subdivision (b)(4) expressly mentions "active moiety," but only with respect to the drug in the first-in-time application, as a criterion for determining eligibility for three-year exclusivity. *See* 21 C.F.R. § 314.108(b)(4)(iii). Meanwhile, Otsuka says, the regulation that relates to five-year exclusivity explicitly limits the scope of its exclusivity based on the active moiety of the drug in the application with exclusivity, *see id.* § 314.108(b)(2).[12] According to Otsuka, this shows that the FDA knew how to use active moiety to cabin exclusivity when it wanted to, so the lack of any reference to active moiety in either of the regulatory bar clauses that relate to three-year exclusivity "unequivocally evidences" that active-moiety considerations have no place in defining the scope of that exclusivity period. (Pls.' Mem. at 37.)

[12] In pertinent part, the regulation that relates to five-year exclusivity provides:

> If a drug product that contains a new chemical entity was approved after September 24, 1984, in an application submitted under section 505(b) of the act, no person may submit a 505(b)(2) application . . . *for a drug product that contains the same active moiety* as in the new chemical entity for a period of 5 years from the date of approval of the first approved new drug application [with exceptions not relevant here].

21 C.F.R. § 314.108(b)(2) (emphasis added).

Otsuka's argument goes much too far for at least two reasons. First of all, it is clear to this Court that the FDA's use of "active moiety" in subdivision (b)(4)'s eligibility clause can be interpreted to leave precisely the opposite impression, insofar as the insertion of this language plainly underscores the agency's belief that the active moiety of the drug in the original application is related (perhaps inextricably) to the exclusivity period that is being conferred. Thus, instead of proving that active moiety makes no difference to the exclusivity inquiry (as Otsuka asserts), the express "active moiety" condition in subdivision (b)(4) arguably demonstrates that active moiety matters. Second, and even more important, it is not at all clear that the FDA references "active moiety" in the bar clause of the five-year exclusivity regulation yet omits it from the three-year exclusivity directives *because* the regulations consider that characteristic to have no bearing on the "conditions of approval" or "change" in those latter provisions. In this regard, Otsuka is relying on an *inference* that the FDA intended to indicate the irrelevance of active moiety to the scope of three-year exclusivity, and much more is needed to defeat the deference that is due to the FDA's interpretation of subdivisions (b)(4) and (b)(5), given their ambiguous language. *See Chase Bank U.S.A, N.A. v. McCoy*, 562 U.S. 195, 207 (2011) (finding regulation ambiguous where each party's interpretation was "plausible, and the text alone [did] not permit a more definitive reading"). For example, in contrast to Otsuka's view, the FDA's decision not to include an express "active moiety" limitation in the regulatory bar clauses of subdivisions (b)(4) and (b)(5) might mean that the scope of the three-year exclusivities does not turn *solely* on active moieties, unlike the five-year exclusivity grant. Thus, it cannot be said that the FDA's knowledge of how to use a phrase

necessarily means that failing to use that phrase in the pertinent context leads to only one possible interpretation; in other words, the text and structure of the five-year exclusivity regulation is simply too thin a reed upon which to rest Otsuka's argument for unambiguous text.

Nor can it be said that the FDA's interpretation of its regulations, which links the scope of the three-year exclusivities to the active moiety of the drug in the application that receives exclusivity, is "plainly erroneous or inconsistent with the regulation[.]" *Christopher*, 132 S. Ct. at 2166 (internal quotation marks and citation omitted). All that the Court has said before with respect to its analysis of romanettes iii and iv applies and leads inexorably to the conclusion that the FDA has not committed plain error or acted inconsistently with its regulations, and indeed, the fact that these regulations involve "a complex and highly technical regulatory program, in which the identification and classification of relevant criteria necessarily require significant expertise and entail the exercise of judgment grounded in policy concerns" makes deference to the FDA's interpretation "all the more warranted[.]" *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994) (internal quotation marks and citation omitted). These ambiguous regulations do not preclude the conclusion that an active-moiety overlap is needed in order for a second-in-time application to be "for" the "conditions of approval" of an earlier NDA regarding a drug, or "for" a "change approved" in a supplement regarding a drug with exclusivity. To the contrary, as already discussed, the use of active moiety in the eligibility clause of subdivision (b)(4) supports the FDA's interpretation, and the structure and purpose of the five-year exclusivity regulation actually furthers the FDA's view, because there is no logical reason that "the range of drugs blocked by exclusivity

for a less innovative change" would be "broader than the range of drugs that are blocked by exclusivity for a more innovative change[.]" (FDA Decision at 23.)[13]

In sum, this Court finds that the regulations that the FDA promulgated to implement the ambiguous provisions of the FDCA regarding the three-year period of exclusivity are themselves ambiguous, and thus permit the agency to select a reasonable resolution of the competing policy concerns about the scope of that exclusivity. *See Cent. Tex. Tel.*, 402 F.3d at 213. This Court has already recounted the FDA's discussion of its resolution, *see* Part III.B.2, and because there is no reason to second-guess the FDA's policy and scientific judgment here, the agency's interpretation must be given "controlling weight[.]" *High Plains Wireless, L.P. v. FCC*, 276 F.3d 599, 606 (D.C. Cir. 2002) (internal quotation marks and citation omitted).

D. Otsuka's Notice-And-Comment Claim Necessarily Fails Because It Relies On The Premise That The FDA Has Changed Its Regulations Regarding The Scope Of Exclusivity

Otsuka's final claim can be resolved in mercifully short order. Count Three of Otsuka's complaint contends that the FDA's decision to approve Aristada impermissibly evaded required notice-and-comment procedures. (*See* Compl. ¶¶ 65–74.) The central premise of this assertion is that the FDA's decision amounted to a "de facto" amendment of a duly promulgated regulation, insofar as it "changed significantly

[13] Otsuka repeatedly denies that it questions the validity of the FDA's five-year exclusivity regulation (*see* Pls.' Mem. at 39; Pls.' Reply at 38 n.15) and, in this regard, the Court takes Otsuka at its word. To the extent that Otsuka's reply brief hints that the five-year exclusivity regulation is illegitimate because the corresponding statute does not use the phrase "active moiety" and only purports to block applications "which refer[] to the drug for which the" application with exclusivity was submitted (Pls.' Reply at 30 (quoting 21 U.S.C. § 355(c)(3)(E)(ii))), this Court merely notes that Otsuka cannot have it both ways. If it intends to rely on the plain text of the five-year exclusivity regulation to bolster its argument that the FDA has misinterpreted the three-year exclusivity regulations at issue here—and it clearly does (*see* Pls.' Mem. at 37–38)—then it cannot simultaneously seek to undermine the five-year exclusivity criteria, and this is especially so when its subversive attack appears for the first time in its reply brief and, thus, would be waived in any event, *see Am. Wildlands v. Kempthorne*, 530 F.3d 991, 1001 (D.C. Cir. 2008).

[the regulations] by effectively adding language to—and amending—[them]." (Pls.' Mem. at 40; *see also* Compl. ¶¶ 65–74; Pls.' Reply at 44–46.) But Otsuka can only rely on that premise if the FDA's pre-decision regulations had an unambiguous meaning that the FDA "altered" when it decided that the Aristada NDA should be approved. *See Marseilles Land & Water Co. v. FERC*, 345 F.3d 916, 920–21 (D.C. Cir. 2003). Anything short of that renders the FDA's action a mere clarification or interpretation of the existing rules. *See Perez*, 135 S. Ct. at 1208 (explaining that "[o]ne would not normally say that a court 'amends' a statute when it interprets its text. So too can an agency 'interpret' a regulation without 'effectively amend[ing]' the underlying source of law" (second alteration in original)); *see also id.* at 1207 ("The act of 'amending,' . . . in both ordinary parlance and legal usage, has its own meaning separate and apart from the act of 'interpreting.'" (citation omitted)). Therefore, this Court's prior rejection of Otsuka's argument that the three-year exclusivity regulations have an unambiguous meaning that foreclosed the FDA's "active moiety" interpretation and consequent approval of Aristada (*see supra* Part III.C), also compels the rejection of Otsuka's contention that the FDA transgressed the APA by improperly "amending" an unambiguous regulation. Accordingly, the Court need not parse the lines between rules and adjudications or between interpretative and legislative rules; Otsuka offers no authority for treating the FDA's unremarkable resolution of the regulation's ambiguities as an action requiring notice and comment, and the Court has found none.

IV. CONCLUSION

This Court has resolved the instant dispute on the basis of indisputable first principles. It is well established that, when it enacted the FDCA, Congress intended for

marketing exclusivity to be a substantial reward for pharmaceutical companies that invest in the development of entirely new drugs or that study existing chemical compounds to demonstrate that they can be safe and effective when prescribed for use in a new way, and that exclusivity works as an incentive to innovate precisely because a drug manufacturer can make the substantial investments necessary to bring a new product to market, secure in the knowledge that the FDA will bar second-in-time products that could undermine the value of that investment. But it also must be acknowledged that providing such reassurances comes with a cost—it stifles innovation during the exclusivity period—and, thus, it is clear that Congress has broadly identified not only those circumstances under which the exclusivity benefit is to be conferred (the eligibility clause) but also the general description of the subsequent new drug applications that will be blocked by exclusivity (the bar clause), leaving it to the expert agency that administers this policy to determine the specific criteria that will properly balance these competing concerns. Otsuka maintains that the FDA has interpreted the statutory exclusivities in a manner that contradicts the text of the statute, conflicts with the agency's own regulations, and requires application of notice-and-comment procedures, but the principles established in *Chevron* and *Auer* demand that this Court give deference to the FDA's interpretation of the ambiguous terms of the statutory and regulatory provisions if the agency's construction is permissible and reasonable, and for the reasons explained in this Opinion, this Court has no doubt that both of these requirements are satisfied here. At bottom, and in clear contrast to the interpretation that Otsuka offers, the FDA's active-moiety comparison ensures that the scope of the exclusivity benefit actually relates to, and is in proportion to, the contribution that the

first-in-time manufacturer has made to the body of scientific knowledge that entitles it exclusivity to begin with, and as such, it is an eminently rational policy choice. Furthermore, given that the relevant statutory and regulatory provisions authorize this option, the FDA did not improperly amend or otherwise alter its regulations in contravention of the requirements of notice and comment when it selected this interpretation in the context of the instant case. Consequently, Otsuka has failed to sustain its claims that the FDA violated the APA when the agency viewed the scope of Otsuka's exclusivity benefit as limited and permitted approval of Alkermes's Aristada, which is a drug that indisputably has a different active moiety than Abilify Maintena.

Accordingly, and as set forth in the order accompanying this opinion, Otsuka's motion for summary judgment is **DENIED**, Defendants' and Intervenor-Defendants' motions for summary judgment are **GRANTED**, and **JUDGMENT WILL BE ENTERED IN DEFENDANTS' FAVOR**.

DATE: July 28, 2016

Ketanji Brown Jackson

KETANJI BROWN JACKSON
United States District Judge