IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

OTSUKA PHARMACEUTICAL CO., LTD, et al. Plaintiff, v. SYLVIA MATHEWS BURWELL, et al. Defendants, and ALKERMES, INC. et al., Intervenor-Defendants	Civil Action No. 15-1688

FEDERAL DEFENDANTS' MEMORANDUM IN OPPOSITION TO PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT, AND IN SUPPORT OF CROSS-MOTION FOR SUMMARY JUDGMENT

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INTRODUCTION

This case reflects the effort of plaintiffs Otsuka Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Development & Commercialization, Inc., and Otsuka American Pharmaceutical, Inc. ("Otsuka") to make unavailable an alternative therapy to a popular antipsychotic drug, Abilify Maintena (aripiprazole). Otsuka has approval and three years of exclusivity for certain conditions of use for Abilify Maintena, an injectable extended-release product indicated for treating schizophrenia. The active moiety (a relevant chemistry term for purposes of determining exclusivity) for Abilify Maintena is aripiprazole. Otsuka seeks to vacate the United States Food and Drug Administration's ("FDA") approval of a different drug, Aristada, which has a different chemical structure and a different active moiety, N-hydroxymethyl aripiprazole.

To obtain approval, Aristada's sponsor, Alkermes Inc., relied in part on FDA's findings of safety and efficacy for Abilify tablets, a different drug for which there is no relevant exclusivity period. Otsuka argues that Aristada is blocked from approval by Abilify Maintena's exclusivity because Aristada relied on findings from Abilify tablets and because the two drugs have overlapping conditions of approval. FDA concluded, however, that Otsuka's exclusivity for certain conditions of use for the active moiety in Abilify Maintena does not block approval of the different active moiety in Aristada. Further, Aristada is itself a new chemical entity entitled to its own 5-year exclusivity period. Otsuka's argument that its 3-year exclusivity period for Abilify Maintena should block approval of a different, novel active moiety is contrary to the express language of the structure-based exclusivity statute. And, if accepted, Otsuka's self-serving argument would greatly expand the scope of 3-year exclusivity, turn the purpose of the relevant Hatch-Waxman Amendments upside down, discourage innovation, and deprive consumers of important alternative therapies.

Accordingly, this Court should grant the federal defendants' motion for summary judgment, and deny plaintiff's motion.

I. STATUTORY AND REGULATORY BACKGROUND

Under the Federal Food, Drug, and Cosmetic Act ("FDCA"), pharmaceutical companies can use different pathways to seek approval of a drug, as described in relevant part below.

A. 505(b)(1) NDAs: Stand-Alone Approval Pathway

Section 505(b)(1) of the FDCA (21 U.S.C. § 355(b)(1))[1] requires that an application contain, among other things, "full reports of investigations" to show that the drug for which the applicant is seeking approval is safe and effective.[2] NDAs that are supported entirely by investigations either conducted by the applicant or to which the applicant has a right of reference are referred to as 505(b)(1) NDAs or stand-alone NDAs.

FDA will approve a 505(b)(1) NDA if it finds that the information and data provided by the applicant demonstrate that the drug product is safe and effective for the conditions prescribed, recommended, or suggested in the proposed labeling.[3] The sponsor must, among other things, provide substantial evidence that the drug product is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling.[4]

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[1] For ease of reference, this brief generally cites to Title 21 of the United States Code rather than to the FDCA, except for Section 505(b)(1) and 505(b)(2) NDAs, which are commonly referred to by their FDCA designation.

[2] *See* 21 U.S.C. § 355(b)(1)(A).

[3] *See, e.g.*, 21 U.S.C. §§ 355(b)(1), (c), & (d); 21 C.F.R. part 314.

[4] *See* 21 U.S.C. § 355(d)(5).

B. 505(b)(2) NDAs and ANDAs: Abbreviated Pathways

The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments)[5] amended the FDCA to add section 505(b)(2) (21 U.S.C. § 355(b)(2)) and 21 U.S.C. § 355(j), which provide abbreviated pathways for 505(b)(2) NDAs and Abbreviated New Drug Applications ("ANDAs"), respectively. The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure" with new incentives for drug development in the form of exclusivity and patent term extensions. AR 1281. These pathways permit sponsors to rely on what is already known about a previously approved drug.

Like a stand-alone NDA, a 505(b)(2) NDA must meet both the "full reports" requirement in 505(b)(1)(A) and the same safety and effectiveness standard as a 505(b)(1) NDA. Unlike a stand-alone NDA, in a 505(b)(2) NDA, some or all of the safety and/or effectiveness information relied upon for approval comes from investigations (1) "not conducted by or for the applicant" and (2) "for which the applicant has not obtained a right of reference or use."[6] Whereas a stand-alone 505(b)(1) NDA is supported entirely by studies that the sponsor owns or to which it has a right of reference, the 505(b)(2) applicant may rely on sources such as its own studies; published reports of studies to which the applicant has no right of reference; the Agency's findings of safety and/or effectiveness for one or more previously approved drugs (a "listed drug"); or a combination of these sources to support approval.[7]

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[5] PUB. L. NO. 98-417, 98 Stat. 1585 (1984).

[6] 21 U.S.C. § 355(b)(2).

[7] *See* AR 1340-1377 (Letter from Janet Woodcock, M.D., Director, CDER, FDA to Katherine M. Sanzo, Esq.; Lawrence S. Ganslaw, Esq., Morgan, Lewis & Bockius LLP; Jeffrey B. Chasnow, Esq., Pfizer Inc.; Stephan E. Lawton, Esq.; Gillian R. Woollett, Ph.D., Vice President Regulatory Affairs, Biotechnology Industry Organization; William R. Rakoczy, Esq., Lord, Bissell & Brook LLP (Oct. 14, 2003) ("505(b)(2) Citizen Petition Response")).

A 505(b)(2) application can be submitted for either a change to a previously approved drug or for a new chemical entity ("NCE"),[8] and may describe a drug product with substantial differences from a listed drug.[9] When a 505(b)(2) applicant seeks to rely on a finding of safety and effectiveness for a previously approved drug product, the applicant must establish that its basis for relying on a previous approval is scientifically justified. A 505(b)(2) applicant can "bridge"[10] its proposed product to the previously approved product by submitting, for example, studies that measure the relative bioavailability[11] of the two products or other appropriate scientific information.

As a trade-off for relying on FDA's finding of safety and effectiveness for another drug, a 505(b)(2) applicant must certify to patents for that listed drug, and may be subject to a 30-month stay of approval if it is sued for patent infringement. 21 U.S.C. §§ 355(b)(2)(A) & (c)(3)(C); *see also Takeda Pharms. USA v. Burwell*, 78 F. Supp. 3d 65, 100 (D.D.C. 2015) ("To ensure that both of these goals [of the Hatch-Waxman Amendments] are achieved, Congress constructed a system in which having to certify to patents and provide the patent owners with notice (protecting the innovator's work product) is the price that a new drug applicant pays for being able to rely on work already approved (promoting efficient drug development).").

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[8] "New chemical entity" is discussed *infra*, section I.C.

[9] 505(b)(2) Citizen Petition Response (AR 1342).

[10] A "bridge" in a 505(b)(2) application is information demonstrating sufficient similarity between the proposed product and the listed drug, or between the proposed product and a product described in published literature, to justify scientific reliance on certain existing information for approval of the 505(b)(2) NDA. *See* AR 1334-35 (FDA Draft Guidance, "Applications Covered by Section 505(b)(2)," http://www.fda.gov/downloads/Drugs/.../Guidances/ ucm079345.pdf ("1999 Draft Guidance")).

[11] Bioavailability generally refers to the rate and extent of absorption of a product in the body. *See, e.g.*, AR 1539 (FDA Draft Guidance, "Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations," http://www.fda.gov/downloads/ drugs/guidancecomplianceregulatory information/guidances/ucm389370.pdf (March 2014)).

C. 5-Year New Chemical Entity ("NCE") Exclusivity

The Hatch-Waxman Amendments also provide incentives for pharmaceutical innovation in the form of exclusivity to protect qualified drugs approved under section 505(b) from competition from certain 505(b)(2) applications and ANDAs for certain periods. Although 5-year exclusivity is not at issue in this case, it is important to understand FDA's interpretation of 5-year exclusivity and its relationship to the terms NCE and "active moiety" in order to understand FDA's interpretation of the relevant 3-year exclusivity provision.

A 5-year exclusivity period is provided for a drug "no active ingredient (including any ester or salt of the active ingredient)[12] of which has been approved in any other application under [21 U.S.C. § 355(b)]." 21 U.S.C. § 355(c)(3)(E)(ii). Congress expressly referred to this statute as protecting "new chemical entities." *See* AR 1285 (130 CONG. REC. at 22425 (Sept. 6, 1984)). Under FDA's long-standing implementing regulation, a drug that contains an NCE (described below) will qualify for 5 years of NCE exclusivity. 21 C.F.R. § 314.108(b)(2). If a drug does not contain an NCE, it will not be eligible for 5-year NCE exclusivity, but may be eligible for 3-year exclusivity. 21 U.S.C. § 355(c)(3)(E)(iii); 21 C.F.R. § 314.108(b)(4).

An Agency regulation defines "new chemical entity" to mean "a drug that contains no ***active moiety*** that has been approved by FDA in any other application submitted under section 505(b)." 21 C.F.R. § 314.108(a) (emphasis added). FDA adopted this "active moiety" approach to best give effect to Congressional intent to protect NCEs, and it is similar to how FDA defined

[12] An ester is (generally) an oxygen atom linked to a central (usually carbon) atom that is double bonded to an oxygen atom. *See* http://medical-dictionary.thefreedictionary.com/ester. A salt is a compound formed by the interaction of an acid and a base, the ionizable hydrogen atoms of the acid are replaced by the positive ion of the base. *See* http://medical-dictionary.thefreedictionary.com/salt.

"new molecular entity" at the time of the Hatch-Waxman Amendments. AR 1286-87 (54 Fed. Reg. at 28897-98 (July 10, 1989)). "Active moiety" is defined by regulation as:

> [T]he molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

Id.[13] In promulgating its regulation to exclude esters, salts, and noncovalent derivatives, FDA expressly referred to the legislative history of this provision, noting that "Congress . . . did not intend to confer significant periods of exclusivity on minor variations of previously approved chemical compounds." 54 Fed. Reg. 28,898 (citing CONG. REC. H9124 (Sept. 6, 1984) (statement of Representative Waxman); H. Rep. 857, Part I, 98th Cong., 2d Sess. 38 (1984)). Conversely, the regulation includes non-ester, covalent bonds, as FDA has long recognized that, "even minor covalent structural changes are capable of producing not only major changes in the activity of the drug but changes that are not readily predicted." AR 77 (citing FDA Petition Response, No. 1987P-0339 (July 26, 1989)).

Five-year NCE exclusivity generally prevents an applicant from submitting a 505(b)(2) NDA or ANDA that includes an active moiety protected by exclusivity for a 5-year period from the date of approval of the protected drug.[14] Five-year NCE exclusivity does not block submission or review of stand-alone 505(b)(1) NDAs or of applications that do not contain the protected active moiety. *See* 21 C.F.R. § 314.108(b)(2).

FDA's chemistry-based approach to defining active moiety for purposes of 5-year NCE exclusivity was upheld by the D.C. Circuit in *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 764

[13] "Covalent" bonds are formed when two atoms share a pair of electrons. *See* http://medical-dictionary.thefreedictionary.com/covalent.

[14] 21 U.S.C. §§ 355(c)(3)(E)(ii), (j)(5)(F)(ii).

(D.C. Cir. 2010). In *Actavis*, the plaintiff alleged FDA was required to identify the molecule responsible for the therapeutic effect at the site of drug action as a prerequisite for awarding NCE exclusivity. FDA argued the *Actavis* plaintiffs' interpretation of the statute was not dictated, or even supported, by the statutory language, and there was no indication that Congress intended FDA to conduct such an inquiry in determining a drug's NCE status. FDA further argued, because it may not always be possible to ascertain the molecule responsible for a drug's therapeutic effect at the site of action with any degree of scientific confidence, Actavis' approach, if adopted, would subject NCE decisions to constant challenges by sponsors offering competing views, resulting in inconsistency and uncertainty for the regulated industry.

The *Actavis* plaintiff asserted that the innovator drug should not get 5-year exclusivity because it was a prodrug[15] and immediately metabolized to a previously-approved active moiety in the body with the same activity. *Id.* FDA disagreed, applying its chemistry-based approach to determine that the innovator's non-ester, covalent modification of a previously approved active moiety qualified the drug as an NCE. *Id.* at 762. The court upheld this decision, finding the language of the statute ambiguous and upholding FDA's interpretation as reasonable. *Id.* at 764, 766. The Court rejected the *Actavis* plaintiff's argument that FDA should base its decision on how the drug is metabolized *in vivo*, observing that agencies may "employ bright-line rules for reasons of administrative convenience, so long as those rules fall within a zone of reasonableness and are reasonably explained," particularly because FDA could not always determine which

[15] Prodrugs are generally "[a] class of drugs, the pharmacologic action of which results from conversion by metabolic processes within the body (biotransformation)." Farlex Partner Medical Dictionary, *available at* http://medicaldictionary.thefreedictionary.com/prodrug. (AR 349, 1728-29).

chemical structure was responsible for the activity of the drug. *Id.* at 766 (quoting *Emily's List v. Fed. Election Comm'n*, 581 F.3d 1, 22 n.20 (D.C. Cir. 2002)).[16]

D. 3-Year Exclusivity

The Hatch-Waxman Amendments also provide for 3-year exclusivity for certain drugs that are not eligible for 5-year NCE exclusivity. *See* AR 1285 (130 CONG. REC. at 22425 (Sept. 6, 1984)) (referring to 3-year exclusivity for "nonnew chemical entities," in contrast to 5-year exclusivity for NCEs). The statute and regulations for 3-year exclusivity describe which original NDAs and supplements[17] are eligible for 3-exclusivity and which are barred or blocked from approval by that exclusivity.

For original NDAs, 21 U.S.C. § 355(c)(3)(E)(iii) states:[18]

> *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

[16] FDA's interpretation that "active ingredient" in the 5-year NCE provision means "active moiety" was recently questioned in the different context of a naturally-derived mixture. *See Amarin Pharms. Ireland Ltd v. FDA*, No. 14-cv-00324, 2015 WL 3407061 (D.D.C. May 28, 2015). The court held under the circumstances of that case, the statutory language required FDA to determine whether the active ingredient in Amarin's drug had been previously approved, not whether it contained a previously approved active moiety. That decision has no bearing on the outcome of this case because the two products that are relevant to this decision, Aristada and Abilify Maintena, have different active moieties (N-hydroxymethyl aripiprazole and aripiprazole, respectively) *and* different active ingredients (aripiprazole lauroxil and aripiprazole, respectively). *See* AR 349 n.32.

[17] Sponsors may conduct additional studies to seek approval for changes to their products, such as new indications or new safety information, by submitting a "supplement" to their original application. *See* 21 C.F.R. § 314.70(b)(2)(v)(A).

[18] A parallel provision applies 3-year exclusivity to ANDAs. *See* 21 U.S.C. § 355(j)(5)(F)(iii).

> 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.[19]

21 U.S.C. § 355(c)(3)(E)(iii) (emphases added).

The first clause (italicized above) describes the applications *eligible* for 3-year exclusivity. AR 351. Under this eligibility clause, a drug that is not eligible for 5-year NCE exclusivity (because it contains a previously approved active moiety) may be eligible for 3-year exclusivity if the drug's application includes new clinical investigations (other than bioavailability studies), essential to approval of the application, that were conducted or sponsored by or on behalf of the applicant. *Id.*

The second clause in section 505(c)(3)(E)(iii) (underlined above), describes which 505(b)(2) NDAs will be *barred* or blocked from approval by the 3-year exclusivity and thus establishes the scope of 3-year exclusivity. AR 352. The phrase "such drug in the approved subsection (b) application" in the bar clause refers to the earlier use of the term "drug" in the eligibility clause. *Id.* The "drug" in the eligibility clause refers to "a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application," that is, the drug that includes a previously approved active moiety. As FDA described in its decision, "FDA interprets this cross reference 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*." *Id.* (emphasis added).

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[19] *See also* 21 C.F.R. § 314.108(b)(4)(iv) (similarly stating that if an application submitted under 21 U.S.C. § 355(b) contains new clinical investigations that were essential to approval and conducted or sponsored by the applicant, 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 or an [ANDA] for the conditions of approval of the original application . . . .").

For supplements to approved NDAs, 21 U.S.C. § 355(c)(3)(E)(iv) states:

> *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 bioavailabilty [sic] 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] . . . .

21 U.S.C. § 355(c)(3)(E)(iv) (emphases added). FDA has taken a consistent approach to both original applications and supplements in determining eligibility and scope for 3-year exclusivity. AR 352. The eligibility clause (italicized above) corresponds to the eligibility clause in 21 U.S.C. § 355(c)(3)(E)(iii), except, among other things, the word "supplement" is substituted for the word "application" in 21 U.S.C. § 355(c)(3)(E)(iii). *Id.* A supplement may be eligible for 3-year exclusivity if it contains reports of new clinical investigations (other than bioavailability studies) essential to approval of the supplement that were conducted or sponsored by the applicant submitting the supplement. AR 352-53.

The bar clause of 21 U.S.C. § 355(c)(3)(E)(iv) (underlined above) does not refer to "such drug." Rather, it describes 3-year exclusivity as blocking approval of "a change approved in the supplement." AR 353. Under FDA's longstanding approach to NDAs and supplements, the "change" refers to a change in an aspect of the drug other than a change to the active moiety or active ingredient of the drug approved in the original NDA; sponsors may not file supplements for a different drug (different active ingredient or active moiety) than the drug approved in the original NDA. A change in active ingredient (or active moiety) would require an original, new drug application (not a supplement), and thus the supplement must necessarily be for a drug with

the same active moiety as the drug approved in the original NDA.[20] Accordingly, FDA interprets 21 U.S.C. § 355(c)(3)(E)(iv) to mean that, in order to be blocked by an approved supplement with 3-year exclusivity, a 505(b)(2) NDA must be for a drug with the same active moiety as the drug described in the supplement (and have the same change). Because the change approved in a supplement is always for the same active moiety as the drug approved in the original NDA being supplemented, exclusivity under 21 U.S.C. § 355(c)(3)(E)(iv) will always be for a drug with the same active moiety as the drug in the originally approved NDA. *Id.*

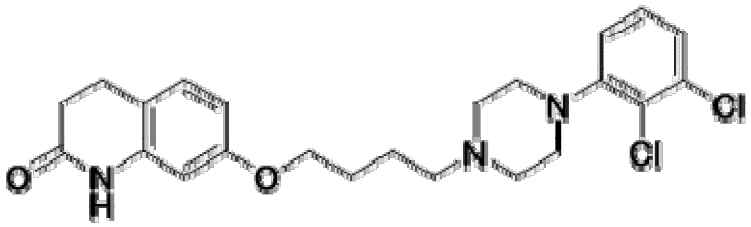
II. FACTUAL AND PROCEDURAL BACKGROUND

A. NDAs for Abilify (Aripiprazole) Products

Otsuka holds the NDA for Abilify (aripiprazole) tablets (NDA 021436), which FDA approved on November 15, 2002, as a 505(b)(1) NDA. AR 373-77. Abilify tablets received 5-year NCE exclusivity as the first approved drug with aripiprazole as its active moiety, as well as various 3-year exclusivity periods that are not relevant here and many of which have expired. AR 355 n.54; AR 619. Otsuka also holds the NDA 202971 for Abilify Maintena (aripiprazole) for extended-release injectable suspension, which FDA approved as a 505(b)(1) NDA on February 28, 2013. AR 487-91. Abilify Maintena is an atypical antipsychotic indicated for the treatment of schizophrenia. AR 543. It is administered monthly by intramuscular injection. *Id.*

[20] *Id.* (citing AR 1593 (Guidance for Industry, "Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees") (Dec. 2014) ("Every different active ingredient or combination of two or more different active ingredients should be submitted in a separate original application.")).

Aripiprazole is the active moiety for Abilify Maintena. AR 356. The chemical structure of aripiprazole is:



The Orange Book lists two 3-year exclusivity periods for Abilify Maintena, which expire on February 28, 2016 and December 5, 2017, respectively.[21] The first period relates to Abilify Maintena's original approval on February 28, 2013; the second relates to FDA's approval of a supplement for Abilify Maintena on December 5, 2014, which added information in the labeling on the results of a controlled clinical study treating adult patients with schizophrenia experiencing an acute relapse. *Id.*

B. Aristada

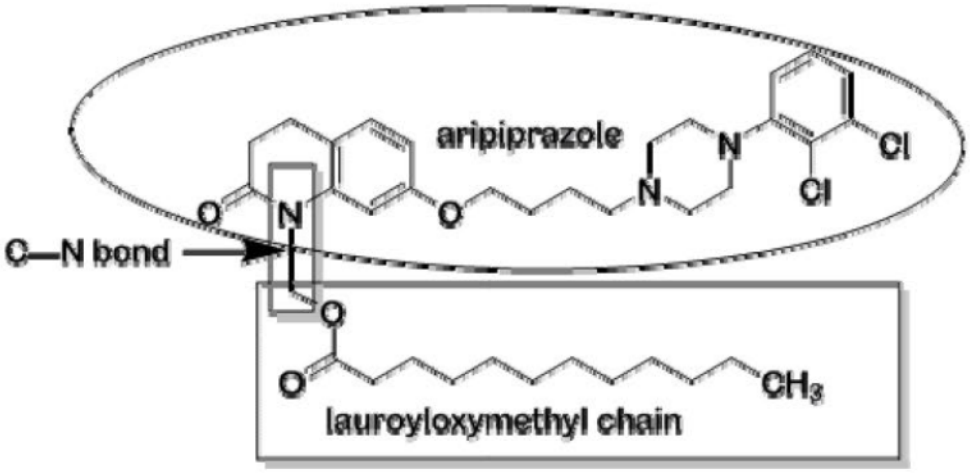
On October 5, 2015, FDA approved Alkermes' section 505(b)(2) NDA for Aristada (aripiprazole lauroxil) extended-release injectable suspension (NDA 207533). AR 1217-20. Aristada is an atypical antipsychotic indicated for the treatment of schizophrenia, to be administered every month or up to every six weeks (for its highest strength) by intramuscular injection.[22] AR 1221. For approval, the Aristada NDA relied, in part, on the Agency's finding of safety and effectiveness for the listed drug Abilify tablets (not Abilify Maintena), as well as studies conducted by Alkermes. AR 357. Accordingly, Alkermes certified to the listed patents

[21] *See* Orange Book, http://www.accessdata.fda.gov/scripts/ cder/ob/docs/patexclnew.cfm?Appl_No=202971&Product_No=001&table1=OB_Rx; *see also* AR 356; 599-606; AR 611-618.

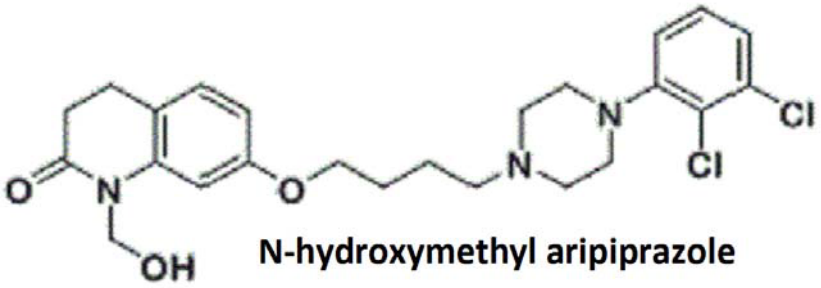
[22] Aristada is supplied as a suspension in a pre-filled syringe, in contrast to Abilify Maintena, which is marketed as a lyophilized powder that is mixed to form a suspension. The formulation characteristics of Aristada enable a longer dosing interval of up to every 6 weeks for its highest strength. AR 357 n.58

for Aristada tablets. AR 1205-06. Otsuka did not sue Alkermes for patent infringement based on these certifications within the 45-day period that would be necessary for a 30-month stay of approval under 21 U.S.C. § 355(c)(3)(C). *Id.*

Aristada contains the active ingredient aripiprazole lauroxil. AR 655. Aripiprazole lauroxil metabolizes in the body to (*i.e.*, is a prodrug of) N-hydroxymethyl aripiprazole, which in turn is a prodrug of aripiprazole. *Id.* The chemical structure of aripiprazole lauroxil is shown below, noting the difference from aripiprazole:



The active moiety of aripiprazole lauroxil is N-hydroxymethyl aripiprazole (shown below), which is aripiprazole lauroxil without the appended ester portion of the molecule. AR 670; *see also* 21 C.F.R. §314.108 (definition of "active moiety"). N-hydroxymethyl aripiprazole is aripiprazole modified with a hydroxymethyl group, with the carbon atom covalently attached to the nitrogen atom, as shown:



N-hydroxymethyl aripiprazole

N-hydroxymethyl aripiprazole has not been previously approved by FDA. AR 360. Therefore, Aristada contains an NCE entitled to 5-year NCE exclusivity, which will expire on October 5, 2020. *Id.; see also* AR 1210 (exclusivity summary).

C. Otsuka's Citizen Petitions

Otsuka submitted a citizen petition on September 9, 2014, requesting that FDA not accept Alkermes' application for filing, and arguing that a single adequate and well-controlled clinical trial would not be sufficient to satisfy the substantial evidence of effectiveness requirement in 505(b)(1)(A). AR 1-16. FDA denied that petition on February 3, 2015, without comment on whether FDA would take the requested actions. AR 21-24.

Otsuka submitted another petition on July 13, 2015, requesting that: (1) FDA delay approval of Alkermes' NDA until the expiration of the 3-year exclusivity periods for Abilify Maintena on December 5, 2017; or (2) refuse to approve the Alkermes NDA for failure to satisfy the substantial evidence of effectiveness requirement in 505(b)(1)(A). AR 25-44. With respect to 3-year exclusivity, Otsuka argued that during the exclusivity period, "FDA may not approve a second-in-time 505(b)(2) NDA that shares 'conditions of approval' with the first-in-time 505(b) drug." AR 34. According to Otsuka, "[a]s a matter of law, it is irrelevant to this analysis upon what drug the second-in-time 505(b) applicant relies." *Id.* Rather, "[t]he dispositive point is that

the conditions of approval for Abilify Maintena overlap with the conditions of approval for the Alkermes NDA." AR 33.

In a comprehensive 31-page decision, FDA denied that petition on October 5, 2015. AR 342-72. FDA rejected Otsuka's argument that 3-year exclusivity for Abilify Maintena blocked approval of Aristada. FDA interpreted the scope of exclusivity in sections 21 U.S.C. §§ 355(c)(3)(E)(iii) and (iv) as blocking drugs with the same single active moiety as the drug with 3-year exclusivity, but not blocking drugs that did not contain the same single active moiety. AR 361-37. Because Aristada has a different active moiety than Abilify Maintena, it is not blocked by Abilify Maintena's 3-year exclusivity. *Id.* FDA also rejected Otsuka's "overlapping conditions of approval" argument because it was overbroad, would be difficult to administer from a scientific and regulatory standpoint if it depended on the activity of the drug (as Otsuka suggested), and could result in a drug with exclusivity blocking approval of novel drugs with different active moieties or even different chemical classes of compounds. AR 367. By contrast, FDA's chemical-structure approach "can be applied consistently with scientific rigor across drug products." *Id.*

FDA also rejected Otsuka's argument that Alkermes should have been required to conduct two clinical trials, determining that Alkermes had provided adequate data and information to support approval of the drug based on, among other things, its own studies and reliance on FDA's finding of safety and effectiveness for Abilify tablets. AR 368-71.

D. Litigation

Otsuka sued FDA on October 15, 2015, seeking expedited review of FDA's decision. The parties agreed to a summary judgment briefing schedule.

ARGUMENT

III. STANDARD OF REVIEW

A court may grant a motion for summary judgment if the pleadings, the discovery and disclosure materials on file, and any affidavits show that there is no genuine issue as to any material fact and that the movant is entitled to judgment as a matter of law. Fed. R. Civ. P. 56(c). Summary judgment is "an appropriate procedure for resolving a challenge to a federal agency's administrative decision" when, as here, "review is based upon the administrative record." *Fund for Animals v. Babbit*, 903 F. Supp. 96, 105 (D.D.C. 1995) (citing *Richards v. INS*, 554 F.2d 1173, 1177 (D.C. Cir. 1977)). In such cases, the court's review is limited to the administrative record, *Fund for Animals*, 903 F. Supp. at 105 (citing *Camp v. Pitts*, 411 U.S. 138, 142 (1973)), and the agency is "entitled to summary judgment if the path of its reasoning is sufficiently discernable in light of the record." *Settles v. United States Parole Comm'n*, 429 F.3d 1098, 1108 (D.C. Cir. 2005); *see also* LCvR 7(h) (Comment) ("This provision recognizes that in cases where review is based on an administrative record the court is not called upon to determine whether there is a genuine issue of material fact, but rather to test the agency action against the administrative record.").

IV. FDA PROPERLY APPROVED ALKERMES' NDA FOR ARISTADA

A. *Chevron* Step One and Step Two Standards

This action challenges FDA's interpretation of statutory and regulatory provisions that FDA is charged with implementing. The Supreme Court's decision in *Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837 (1984), and its progeny set forth a two-step framework for reviewing an administrative agency's interpretation of its statute. Under *Chevron* step one: "First, always, is the question whether Congress has directly spoken to the precise

question at issue. If the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Id.* at 842-43. *Chevron* step two applies when Congress has not directly addressed the issue or has done so ambiguously. In that event, the Court may not "simply impose its own construction on the statute," but rather must determine whether the agency's construction is based on a permissible interpretation of the statute. *See id.* at 843, 843-44 n.11 (in case of ambiguity, the court must uphold the agency's interpretation if its construction is permissible under the statute; a court need not conclude that agency construction was the only one it permissibly could have adopted or even the reading the court would have reached); *see also Barnhart v. Walton*, 535 U.S. 212, 218 (2002) (reviewing court must decide: (1) whether the statute unambiguously forbids agency interpretation, and (2) whether the agency interpretation exceeds the bounds of the permissible).

Courts have repeatedly given *Chevron* deference to FDA's interpretation of the FDCA, as well as the agency's own implementing regulations. *See, e.g.*, *Actavis*, 625 F.3d at 764; *Novartis Pharms. Corp. v. Leavitt*, 435 F.3d 344, 349 (D.C. Cir. 2006); *Mylan Labs., Inc. v. Thompson*, 389 F.3d 1272, 1281 (D.C. Cir. 2004); *Purepac Pharm. Co. v. Thompson*, 354 F.3d 877, 883 (D.C. Cir. 2004); *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1319-20 (D.C. Cir. 1998) (citing *Auer v. Robbins*, 519 U.S. 452, 461 (1997)).

Chevron deference extends to administrative determinations that are not embodied in rulemaking or formal adjudication. *See Barnhart*, 535 U.S. at 221-22. In *Mylan Labs.*, 389 F.3d at 1279-80, for example, the D.C. Circuit extended *Chevron* deference to the agency's letter decision interpreting ANDA exclusivity provisions. The court explained that deference was appropriate because of "the complexity of the statutory regime . . . the [presence of] FDA's

expertise or the careful craft of the scheme it devised to reconcile the various statutory provisions." The D.C. Circuit has also granted deference to FDA's interpretations of the 5-year and 3-year exclusivity provisions. *See Actavis*, 625 F.3d at 764-66 (upholding FDA's use of active moiety definition to grant 5-year exclusivity to prodrug); *AstraZeneca Pharms. LP v. FDA*, 713 F.3d 1134, 1139-40 (D.C. Cir. 2013) (deferring to FDA's interpretation of the phrase "a change approved in the supplement" relating to 3-year exclusivity under 21 U.S.C. § 355(j)(5)(F)(iv)).

B. FDA's Interpretation Should Be Upheld Under Either *Chevron* Step One or Step Two

The FDCA confers broad authority to FDA to approve drugs that meet the statutory requirements for approval, and that are not blocked from approval by another drug's statutory exclusivity period. FDA has properly interpreted the 3-year exclusivity statute and determined that the 3-year exclusivities for Abilify Maintena do not block approval of Aristada, which has a different active moiety than Abilify Maintena.

1. FDA's Decision Is Consistent With The Statute Under *Chevron* Step One

Otsuka's first period of exclusivity relates to Abilify Maintena's original approval. As FDA explained in its decision, 21 U.S.C. § 355(c)(3)(E)(iii) bars approval of "such drug," which refers to the earlier use of the term "drug" in the eligibility clause. AR 352. The "drug" in the eligibility clause refers to "a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application," that is, the drug that includes a previously approved active moiety. *Id.* Thus, "FDA interprets this cross reference 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." *Id.* (emphasis added). This decision is fully consistent with the terms "drug" and "such drug" in the statute; FDA interprets these terms consistently to refer to a drug that includes the same previously approved active moiety. *Cf. Takeda*, 78 F. Supp. 3d at 98-9 ("Thus, in accordance with its plain meaning, the term "such drug" unambiguously refers back to 'the drug for which such investigations were conducted'" in 21 U.S.C. § 355(b)(2)(A) for purposes of 505(b)(2) patent certification requirements).

Otsuka's second period of exclusivity relates to FDA's approval of a supplement for Abilify Maintena. FDA's decision is consistent with 21 U.S.C. § 355(c)(3)(E)(iv), which bars FDA from approving other applications for "a change approved in the supplement." AR 352. FDA's decision gives proper effect to "a change approved in a supplement," as "supplement" is limited by the types of supplements that are permissible (*e.g.*, FDA will approve a supplement for a new indication, but not for a different active moiety). *Id.* Under FDA's policy, sponsors may not submit a supplement for a drug with a different active moiety than that in the original application; a change in active ingredient (or active moiety) would require an original, new drug application (not a supplement). AR 353.

Accordingly, sections 355(c)(3)(E)(iii) and (iv) both demonstrate Congress's clear intent that a drug must have the same active moiety as the drug in the originally-approved NDA in order to be blocked. *Id.*

2. Otsuka's Arguments Lack Merit

a. "Conditions of Approval of Such Drug" Refers to The Same "Drug"

Otsuka reads "such drug" out of the statute completely, arguing that "such drug" need not have the same active moiety as the antecedent "drug" with exclusivity. Pl.'s Br. at 14-15. Otsuka asserts that it is more appropriate to focus on "conditions of approval" than "such drug,"

and that FDA inverted the inquiry by changing the order of the phrases when describing them in its decision. Pl.'s Br. at 14 (citing AR 361). But FDA's decision fully evinces an understanding of the entire statutory text: "Thus, 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' for which Abilify Maintena received exclusivity." AR 361-62. The phrase "conditions of approval of such drug" contains a limitation to "such drug," and FDA is correct to focus on the actual words of the statute, rather than assume, as Otsuka does incorrectly, that Congress did not mean them. Moreover, the legislative history fully supports the structure-based approach that Congress took to 3-year exclusivity, which Congress described as attaching to "nonnew chemical entities," as those are described by reference to their structure within the statute. *See* AR 1285 (130 CONG. REC. at 22425 (Sept. 6, 1984)).[23]

Otsuka relies on *Veloxis Pharms., Inc. v. FDA*, 2015 U.S. Dist. LEXIS 77559, at *39 (June 12, 2015), for the principle that the statute is limited to "conditions of approval," not a specific drug. Pl.'s Br. at 15. But, as FDA explained in its decision letter, FDA did not decide this issue in *Veloxis* because both drugs in *Veloxis* had the same active moiety, which was a clear predicate of its decision: "Although not a subject of dispute in the context of the *Veloxis* Letter, it was clear that in interpreting the phrase 'conditions of approval of such drug in the subsection (b) application,' FDA considered the conditions of approval for tacrolimus, which was the active moiety of the two products at issue." AR 354.

[23] In addition to this active moiety analysis, FDA's decision described another aspect of the 3-year exclusivity inquiry, which focuses on the scope of the new clinical investigations that were essential to approval and conducted or sponsored by the applicant with exclusivity and informs the relevant "conditions of approval." AR 352. FDA did not undertake that analysis for Aristada, and thus a remand would be appropriate if this Court were to agree with Otsuka.

b. Section 505(b)(2) Does Not Help Otsuka

Whereas Otsuka previously argued that "overlap with the conditions of approval" was the "dispositive" part of the analysis, AR 33, Otsuka now asserts that "the question under the statute is whether the subsequent applicant (Alkermes) relied on an earlier drug's safety and/or effectiveness data to meet the drug approval requirements." Pl.'s Br. at 24. Otsuka argues that "FDA need only look to the 505(b)(2) application to see which drug the applicant relies on, and where, as here, that drug has an unexpired exclusivity for the same conditions of approval, FDA cannot grant final approval to the subsequent application pending the expiration of the exclusivity if the protected conditions of approval overlap." *Id.* Not only is Otsuka's argument incorrect,[24] it cannot help Otsuka here because—as Otsuka glosses over in its argument—Aristada relied on Abilify tablets (a drug with no relevant exclusivity period), not Abilify Maintena (the drug with exclusivity).

At best, Otsuka's arguments may be read as proposing that the "drug" with exclusivity should encompass not just the drug to which exclusivity attached but all applications for that drug in the same product line (even applications such as Abilify tablets for which there is no relevant exclusivity period), and should block a second in time 505(b)(2) application so long as the second-in-time 505(b)(2) application refers to one of the applications in the product line and there are overlapping conditions of approval. But the statute does not even have a reliance

[24] Otsuka's argument is not correct because the statute contains no such reliance limitation. As FDA recently determined in a different case, 3-year exclusivity may block approvals of 505(b)(2) drugs that do not rely on the drug with 3-year exclusivity. *See Veloxis Pharms., Inc. v. FDA*, 2015 U.S. Dist. LEXIS 77559, at *35-36 (June 12, 2015) (upholding FDA's decision). The *Veloxis* court found that the term "relied upon" in the latter portion of 21 U.S.C. §§ 355(c)(3)(E)(iii) and (iv) was not relevant to the exclusivity analysis. *Id.* at *27-30 (noting FDA's argument that the term is used to only to distinguish between 505(b)(1) and 505(b)(2) NDAs because it is included in the statutory provision as part of the lengthier definition of a 505(b)(2) NDA).

limitation,[25] let alone Otsuka's imagined, attenuated reliance theory on a drug without any applicable exclusivity period. These self-serving arguments are grounded in Otsuka's desired outcome, and are not found anywhere in the statutory text.

Otsuka also argues that 21 U.S.C. § 355(c)(3)(E)(iii) must be read in harmony with section 505(b)(2), and that "if 'drug' is broad enough in section 505(b)(2) to permit an applicant such as Alkermes to rely on information about a different active moiety for approval, then 'drug' in 505(c)(3)(E)(iii)&(iv) must also be read to include that same active moiety." *Id.* at 16. Thus, Otsuka argues that the word, "drug," in both sections, refers to both the active ingredient of the 505(b)(2) NDA, aripiprazole lauroxil (with the underlined language below, "[a]n application submitted under [505(b)(1)] for a drug"), *as well as* the active ingredient of the 505(b)(1) drug, aripiprazole (with the language shown in boldface below, "a drug for which the investigations described in [505(b)(1)(A)] and relied upon"). Pl.'s Br. at 17. This purported "plain language" argument based on Section 505(b)(2) misses the mark.

> Section 505(b)(2) describes an application in that section as follows:
>
> (2) An application submitted under paragraph (1) for **a drug for which the investigations described in clause (A) of such paragraph 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 from the person by or for whom the investigations were conducted shall also include--

21 U.S.C. § 355(b)(2) (emphases added). The single word "drug" in this section refers to the drug that is the subject of the 505(b)(2) application—*i.e.*, aripiprazole lauroxil. This "drug" is necessarily different in some respect from the drug that is being relied on; otherwise, the applicant would be filing an application for a duplicate drug under 21 U.S.C. § 355(j). In this case, the drugs have different active moieties, and the term "drug" cannot simultaneously refer to

[25] *See Veloxis Pharms., Inc. v. FDA*, 2015 U.S. Dist. LEXIS 77559, at *35-36 (June 12, 2015).

the drug that is the subject of the 505(b)(2) application and the different, previously-approved listed drug.

Otsuka cites no credible support for its proposition that two different drugs in two different applications are within the scope of the same use of a single term in this statutory provision.[26] Consistent with logic and standard principles of English usage, the clause beginning with "for which" refers back to the original subject of the sentence, "application submitted under paragraph (1) for a drug" (*i.e.*, the drug that is the subject of the 505(b)(2) NDA). Indeed, the term "application" is central to this provision, which defines a 505(b)(2) application and contains an additional reference back to the "application" when stating that it "shall also include . . . ."

FDA has long construed this instance of "drug" as referring only to the drug product that is the subject of the 505(b)(2) application. *See, e.g.*, 21 C.F.R. § 314.54(a) ("Any person seeking approval of a drug product that represents a modification of a listed drug . . . may . . . submit a 505(b)(2) application."); AR 1353 (505(b)(2) Citizen Petition Response) ("The 505(b)(2) process permits an applicant seeking approval for a drug product that differs from the approved drug product to obtain approval without conducting new studies to demonstrate to the Agency what has already been demonstrated."). FDA would have no conceivable reason to enlarge this single reference to the proposed "drug" for which a sponsor seeks approval in a 505(b)(2) application to encompass a different drug product that was already approved in a 505(b)(1) application.

Not only is Otsuka's suggested double definition illogical, unwieldy, and imprecise, such an approach is unnecessary to allow 505(b)(2) applicants to rely on information from different

[26] Otsuka cites *King v. Burwell*, 135 S. Ct. 2480, 2489-2490 (2015), which held that an "Exchange established by the State" could also include a federal exchange. Pl.'s Br. at 17. In that case, the Court concluded that federal and state exchanges were equivalent. *Id.* at 2489. Here, the active moieties aripiprazole and N-hydroxymethyl aripiprazole are not equivalent as a matter of science and law. *See Actavis*, 625 F.3 at 766; AR 670; *see also* 21 C.F.R. § 314.108(a) (definition of "active moiety").

previously-approved drugs. Section 505(b)(2) generally describes what such an application is—*i.e.*, one that relies on investigations for approval that the sponsor did not conduct or for which it did not obtain a right of reference—but does not purport to describe what types of investigations may be relied on. FDA has further fleshed out section 505(b)(2) through regulation and guidance. *See* AR 1328-29 (Draft 505(b)(2) Guidance); AR 1354 (505(b)(2) Citizen Petition Response) ("This provision does not limit the sources of studies on which 505(b)(2) applicants may rely."). A 505(b)(2) application may rely, for example, on FDA's finding of safety and efficacy for a listed drug or literature to obtain approval. AR 1328-29. Moreover, 505(b)(2) NDAs may rely on non-product specific published literature to establish safety and effectiveness. In those cases, the word "drug" in the statute cannot possibly refer to a 505(b)(1) listed drug, because there may be no listed drug upon which to rely. AR 1328. Thus, construing "drug" as referring solely to the drug product that seeks approval in a 505(b)(2) application avoids the internal inconsistency that Otsuka advocates, and further avoids placing restrictions on the types of information—in the absence of any statutory or regulatory directive to do so—on which an applicant could rely in a 505(b)(2) NDA.

Otsuka also argues that FDA's interpretation of "such drug" as being limited to the same active moiety "allows FDA, contrary to Congress's intent, to determine when a drug that has previously received three-year exclusivity will and will not actually be protected from the market entry of a 505(b)(2) NDA that has relied on its clinical investigations," and that FDA has "no such discretion." Pl.'s Br. at 18. On the contrary, FDA has been delegated authority to implement the FDCA and interpret its organic statute,[27] and has faithfully applied the express

[27] *See* 21 U.S.C. § 371(a) (granting FDA general authority to issue binding, substantive regulations); *Chevron*, 467 U.S. at 842-844 (discussing deference to agency interpretation of statutes).

terms of the statute in this case. FDA's implementation of this statute is not "cherry pick[ing]," as Otsuka contends, Pl.'s Br. at 20, but involves a scientifically rigorous active moiety determination that can be applied evenhandedly across all drug products, is grounded in the actual language of the statute, and does not depend on a reliance limitation that is absent in the statute. AR 367.

Nor is it correct for Otsuka to say that this case has the "absurd" result that "a 505(b)(2) can rely on another drug to meet the approval requirements and, at the same time, avoid that drug's exclusivity." Pl.'s Br. at 20. As much as Otsuka would like to avoid this fact, Aristada did not rely on the drug with exclusivity, Abilify Maintena, for approval; it relied on a drug with no remaining relevant exclusivity, Abilify tablets. It is not "absurd" for Congress to create structure-based exclusivity provisions with the intention to provide awards of exclusivity to both NCEs and nonnew chemical entities for the clinical studies they have conducted. By contrast, section 505(b)(2) has its own patent-based scheme of protection for drugs relied upon that Otsuka did not pursue in this case. Moreover, as this Court recognized in *Takeda*, applicants who rely on FDA's finding of safety and effectiveness for another drug under 505(b)(2) must bridge any differences between those drugs, such as by conducting their own studies, which Alkermes did. *See Takeda*, 78 F. Supp. 3d at 95 ("FDA has decided to leave it up to the drug sponsor to determine whether the sponsor would like to do less work and rely on a very similar drug, or do more work and rely on a dissimilar drug."). Alkermes has already paid the price of reliance under the 505(b)(2) statute by conducting additional studies and certifying to applicable patents, and, as explained above, is not also subject to the 3-year exclusivity of a drug with a different active moiety.

3. FDA's Interpretation is Reasonable Under *Chevron* Step Two.

Even if the statute were found to be ambiguous, FDA's interpretation is fully permissible under *Chevron* step two. *See AstraZeneca Pharms. LP v. FDA*, 713 F.3d 1134 (D.C. Cir. 2013) (holding that disputed terms in the 3-year exclusivity statute, including "a change approved in the supplement," were "permeated by ambiguities that, under *Chevron*, leave discretion in the FDA to adopt reasonable interpretations").

a. FDA's Interpretation Furthers the Goals of the Hatch-Waxman Amendments

Congress provided for two relevant types of non-patent-based protections: 5-year exclusivity for new chemical entities (for a "drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved"); and 3-year exclusivity for "nonnew" chemical entities (for a "drug, which includes an active ingredient (including any ester or salt of the active ingredient that has been approved"). *See* AR 1285 (130 CONG. REC. at 22425 (Sept. 6, 1984)). FDA's interpretation reasonably limits the scope of 3-year exclusivity to block approval of drugs with the same previously approved active moiety as the drug with exclusivity.

For 21 U.S.C. § 355(c)(3)(E)(iii), FDA's interpretation is grounded directly in the text (*i.e.*, "conditions of approval of such drug" refers back to the same "drug"); to the extent there is any ambiguity, this interpretation is wholly reasonable. AR 352. For 21 U.S.C. § 355(c)(3)(E)(iv), which is limited to "a change approved in the supplement" rather than being expressly tied to the antecedent drug, the statute does not address what types of changes can be approved in a supplement and therefore what types of applications would be blocked from approval. AR 353. For this statute, FDA has applied its policy that it does not approve supplements for changes in active moieties, which would require an original new drug application. *Id.* Thus, FDA interprets this statute such that the 505(b)(2) NDA must be for a

drug with the same active moiety as the drug in the originally approved NDA in order to be blocked. AR 353. This interpretation is consistent with FDA's structure-based interpretation of 21 U.S.C. § 355(c)(3)(E)(iii), and is entitled to this Court's full deference. *See Barnhart*, 535 U.S. at 218 (deferring to agency's construction of ambiguous statute unless it exceeds the bounds of the permissible).

By contrast, Otsuka's proposed interpretation would broaden 3-year exclusivity to block any drug with overlapping conditions of approval when there is attenuated reliance on some undefined concept of "drug," regardless of chemical structure, and would extend the scope of 3-year exclusivity well beyond that of 5-year exclusivity, which is limited to blocking drugs with the same active moiety. AR 362-63. Thus, under Otsuka's theory, Otsuka's 5-year exclusivity for Abilify tablets (if it were unexpired) would not block Aristada (per *Actavis* because it contains a different active moiety), *see* 21 C.F.R. § 314.108(b)(2), but Otsuka's 3-year exclusivity for Abilify Maintena would, simply because Otsuka purports that they share overlapping conditions of approval. This would be the case despite the fact that Aristada relied on a Abilify tablets for approval (and despite the fact that Abilify tablets did not have any relevant remaining exclusivity).

FDA's interpretation gives full effect to the text of the statute ("conditions of approval of such drug") and is consistent with the goals of the Hatch-Waxman Amendments to provide an appropriate scope of protection to the innovator drug, while still encouraging innovation by not blocking approval of drugs with different active moieties "that may have some advantages over previously approved active moieties." AR 363-64.

Otsuka argues that FDA's interpretation ignores the Hatch-Waxman tradeoff; it believes that Aristada's reliance on a different drug containing aripiprazole under 505(b)(2) means that

Aristada must also be subject to exclusivity for Abilify Maintena. Pl.'s Br. at 25-26. But the Hatch-Waxman Amendments provided a number of trade-offs between innovator and generic or 505(b)(2) drugs, including the trade-off expressly within the text of 505(b)(2) pertaining to patent certifications: the applicant relying on the listed drug must certify to patents for that same listed drug (and only for that drug). *See Takeda*, 78 F. Supp. 3d at 100 ("having to certify to patents and provide the patent owners with notice (protecting the innovator's work product) is the price that a new drug applicant pays for being able to rely on work already approved (promoting efficient drug development)").

Aristada provided those certifications here, but Otsuka did not sue and obtain a 30-month stay of approval. AR 1206-07. Rather, Otsuka seeks to block competition under the different, non-patent based protections in the Hatch-Waxman Amendments, which Congress granted to either NCEs or nonnew chemical entities, *i.e.*, on the basis of chemical structure.

Otsuka also argues that "three-year exclusivity is not to be undermined by meaningless technical changes and game playing, for doing so thwarts congressional intent to incentivize innovation." Pl.'s Br. at 20-21; *see also id*. at 22 ("Instead, FDA's decision allows a drug that represents absolutely no meaningful therapeutic advance to rely on an innovator drug and avoid that innovator drug's exclusivity."). Thus, although Otsuka is apparently not challenging FDA's scientific determination that Aristada has a different active moiety than Abilify Maintena, Pl.'s Br. at 9 n.7, Otsuka believes that FDA's reliance on this active moiety distinction is not valid for purposes of the exclusivity statute because not all differences in active moieties are meaningful.[28]

[28] Otsuka nevertheless spends several introductory pages of its brief casting scientific doubt on the decision it states that it does not challenge, primarily by pointing to press statements by Alkermes' CEO and by asserting that FDA "abruptly changed its mind" about the active moiety prior to approval. Pl.'s Br. at 3-7. The cited press statements do not help Otsuka. In context, the CEO was generally referring to the action of the aripiprazole portion of Aristada after it is

The D.C. Circuit upheld FDA's bright-line, chemical-structure approach to determining active moieties for purposes of 5-year exclusivity in *Actavis*. *Actavis*, 625 F.3 at 766 ("We are hard pressed to second-guess the FDA's view, especially since it 'rests on the agency's evaluation of scientific data within its area of expertise.'") (internal citations omitted). The plaintiff argued that the prodrug in that case should not get 5-year exclusivity because the true "active" portion of the drug in the body was the same as the previously approved drug. But the D.C. Circuit affirmed FDA's approach to evaluate the chemical structure of the prodrug form of the drug (*i.e.*, before it is administered and metabolized in the body), taking note of FDA's explanation that it is difficult to determine "precisely which molecule, or portion of a molecule, is responsible for a drug's effects." *Id.* So too here: the 5-year and 3-year exclusivity provisions each rely on FDA's active moiety definition, which is based on the principle that covalent, non-ester modifications are, "on the whole, distinct from other types of derivative drugs." *Id.* at 765. As FDA described in its decision, "in many cases, it may not be possible from a scientific perspective to identify all of the metabolites and their relative activity at the time of drug approval." AR 367. Thus, "FDA has adopted an approach focusing on the drug's chemical structure that can be applied consistently with scientific rigor across drug products." *Id.* This approach, as in *Actavis*, is reasonable and should be upheld.

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metabolized in the body; he was not undertaking FDA's regulatory and scientific determination of "active moiety" for purposes of determining exclusivity. Nor did FDA do an about-face on its active moiety determination; the record shows that some of the reviews loosely and incorrectly referred to aripiprazole as the active moiety, but the actual documentation of FDA's active moiety decision is at AR 665-671. *See* AR 1133. More importantly, Otsuka does not even attempt to point to any infirmity in FDA's decision, which explained that "aripiprazole is attached to its hydroxymethyl group by a covalent C-N [carbon-nitrogen] bond." AR 670. This covalent, non-ester modification of aripiprazole qualifies Aristada as containing a different active moiety under 21 C.F.R. § 314.108(a); *see also Actavis*, 625 F.3d at 766.

Moreover, Otsuka's approach would broaden 3-year exclusivity to cover, for example, all drugs with an overlap in the conditions of approval (and with some undefined notion of reliance), such as all drugs indicated to treat headaches or cancer, regardless of differences (even big differences) in chemical structure. AR 367. This outcome would seriously "hinder the availability of therapeutic alternatives and discourage or delay the development of innovative new drugs." *Id.*

b. FDA's Decision Is Consistent With Xalatan

Otsuka attempts to make much out of FDA's Xalatan Citizen Petition Response, a letter decision that is far from being on all fours with the instant facts and issues. *See* Pl.'s Br. at 26-27. In the Xalatan matter, FDA decided three issues raised in the petition: (1) whether FDA's approval of a supplement to an NDA was a taking of the first sponsor's confidential information; (2) whether there was substantial evidence supporting that approval; and (3) whether it was arbitrary and capricious to approve the supplemental application in the absence of particular clinical data because the first sponsor was required to submit such data. AR 1517-18. FDA made statements in that decision suggesting that the first sponsor's 3-year exclusivity period would have blocked approval of the second 505(b)(2) application. AR 1532. As Otsuka notes, that application had a different active moiety. Pl.'s Br. at 26-27. But, as FDA explained in the Aristada decision, "the Xalatan Citizen Petition response is not relevant precedent" because the issue was moot, *i.e.*, "FDA did not need to determine whether 3-year exclusivity for one active moiety would block approval of a supplemental 505(b)(2) NDA for a different active moiety because the later-in-time 505(b)(2) supplement was submitted after the expiration of 3-year exclusivity for the first-in-time NDA supplement." AR 365 n.87. Although FDA made certain conclusory statements in the Xalatan response regarding the scope of Xalatan's 3-year

exclusivity in a factually different context, the exclusivity issue was not squarely before the Agency. FDA's Aristada decision explains that now that the question has been presented to the Agency, it has fully considered the statute, regulations, science, and policy implications regarding 3-year exclusivity as it applies to different active moieties. *Id.*

Otsuka argues that FDA's explanation is inadequate because FDA gave "no reasoned basis" for its changed approach. Pl.'s Br. at 27. To the contrary, FDA explained why it was not bound by the statements in the Xalatan Citizen Petition response. AR 365 n.87. Otsuka fails to identify any reason why FDA's explanation is inadequate, or even substantively address it at all. Pl.'s Br. at 27. FDA's explanation easily passes muster under the deferential standard of review. *See Sanofi-Aventis US v. FDA*, 733 F. Supp. 2d at 171-73 (D.D.C. 2010) (accepting FDA's explanation regarding its past decisions as conforming to "certain minimal standards of rationality") (citing *Small Refiner Lead Phase-Down Task Force v. EPA*, 705 F.2d 506, 21 (D.C. Cir. 1983)).

C. FDA's Decision Is Consistent With Its Regulation

Otsuka also argues that FDA's decision violates its own regulation, 21 C.F.R. § 314.108(b)(4)&(b)(5). Pl.'s Mem. at 28. The primary basis for this challenge appears to be that the regulation pertaining to 3-year exclusivity for approval of an original NDA, § 314.108(b)(4), does not use the term "such drug" or refer to "active moiety." *Id.* at 29-30; *compare* § 314.108(b)(4) *with* 21 U.S.C. § 355(c)(3)(E)(iii). Otsuka, in effect, argues that this lack of an express chemical-structural limitation in the bar clause of the regulation should somehow supersede the express reference to "such drug" in the statute and that FDA is prohibited from applying its regulation in a manner consistent with that statutory limitation. FDA, however, reasonably interpreted the relevant statutory language "such drug" as referring to

a "drug" having the same active moiety. FDA noted in its decision that its regulation, § 314.108(b)(4) is "similar[]" to the statute. AR 351 n.39. *See Pauley v. Bethenergy Mines*, 501 U.S. 680, 706 (1991) ("An interpretation that harmonizes an agency's regulations with their authorizing statute is presumptively reasonable."); *see also Sec'y of Labor, Mine Safety & Health Admin. v. W. Fuels-Utah, Inc*., 900 F.2d 318, 320 (D.C. Cir. 1990) ("[A] regulation must be interpreted so as to harmonize with and further and not to conflict with the objective of the statute it implements.").

FDA's decision in no way "violates" the applicable regulations. Pl.'s Br. at 28. The bar clause in 21 C.F.R. § 314.108(b)(4) extends to "conditions of approval of the original application." The term "original application" may reasonably be tied to the active moiety of the drug in the original application, particularly given the importance of active moiety to the identity of the drug with exclusivity. *See* 21 C.F.R. §314.108(b)(4)(iii) (requiring the drug with exclusivity to be "for a drug product that contains an active moiety that has been previously approved"). Similarly, the bar clause in 21 C.F.R. § 314.108(b)(4) extends exclusivity to "a change." In the context of the statute, this "change" should not be construed more broadly than the "change approved in the supplement," and FDA has reasonably interpreted the exclusivity for such supplements to not extend beyond the active moiety of the originally approved drug, because supplements cannot be approved for a different active moiety than that approved in the original NDA. AR 353.

Otsuka also argues that FDA formally interpreted the "such drug" clause broadly and without regard to active moieties, citing the preambles to the proposed and final rule. Pl.'s Br. at 29. The breadth that FDA described in the preamble to the proposed rule, however, referred to the broader active moiety approach that FDA adopted (as opposed to a specific drug product

approach that FDA also considered), and not, as Otsuka argues here, breadth that would expand the scope of 3-year exclusivity beyond that of 5-year exclusivity. *See* 54 Fed. Reg. at 28,897 ("FDA does not believe that . . . Congress intended the protection offered by the exclusivity for changes in approved drugs to be broader than the protection offered by exclusivity for new chemical entities."). But under Otsuka's theory, 3-year exclusivity would be broader than 5-year exclusivity: Otsuka's five-year exclusivity for Abilify tablets (if it were unexpired) would not block Aristada (per *Actavis*) because they have different active moieties, *see* 21 C.F.R. §314.108(b)(2), but Otsuka's three-year exclusivity for Abilify Maintena would, simply because Otsuka purports that they share exclusivity protected conditions of approval and Aristada relied on a different drug application for aripiprazole for approval (even if that application did not have any relevant exclusivity).

D. FDA Does Not Need to Engage in Rulemaking to Approve Drug Applications

Otsuka argues, unconvincingly, that FDA's decision violates rulemaking requirements because FDA's decision allegedly amends the current rule to add an identical active moiety limitation without undertaking notice-and-comment rulemaking. Pl.'s Br. at 33.[29] First and foremost, Otsuka's assertion that FDA has proposed or issued a "new" rule lacks merit. FDA has reasonably interpreted and applied the statute to address the specific factual circumstances at issue, but this does not make its decision a new "rule." FDA's decision takes a

[29] Instead of focusing on the actual text of FDA's regulations, Otsuka proposes its own purportedly controlling "categorical" rule as follows: "The statutory provisions and regulations prohibited a 505(b)(2) that relied on a previously approved drug from avoiding that drug's exclusivity in all instances." Pl.'s Br. at 33 (citing *Veloxis*, 2015 U.S. Dist. LEXIS 77559, at *33-34)). Otsuka's argument that FDA amended that rule to "creat[e] an exception that does not appear in the statute or regulatory text," rings especially hollow because the "rule" Otsuka proposes does not appear in the statute or regulation. *See* Pl.'s Br. at 33.

position that is consistent with both the statute and the regulation; no additional procedure is required. *See* Section I.C., *supra*.

It is well within FDA's discretion to make approval decisions through administrative adjudications rather than through less-formal and less flexible rulemaking proceedings. *See SEC v. Chenery Corp.*, 332 U.S. 194, 202-03 (1947) ("There is thus a very definite place for the case-by-case evolution of statutory standards."). FDA's citizen petition response interpreting and applying 21 U.S.C. § 355(c)(3)(E) relates to its decision whether to approve Alkermes' NDA and is unquestionably an informal adjudication. Such orders may in fact "establish broad legal principles." *Central Tex. Tel. Coop. Inc. v. FCC*, 402 F.3d 205, 210 (D.C. Cir. 2005). FDA regularly issues responses to citizen petitions or letter decisions responding to inquiries. These responses interpret existing law within the context of those adjudications; courts have noted these approvingly in several instances. *See, e.g.*, *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 776 (D.C. Cir. 2010); *Apotex, Inc. v. FDA*, 226 Fed. Appx. 4, 5 (D.C. Cir. 2007) ("[T]he district judge's opinion, which grants *Chevron* deference to the FDA's statutory interpretation of 21 U.S.C. § 355(j)(5)(B)(iv) embodied in FDA approval letters (*i.e.*, informal adjudications), is supported by the Supreme Court's post-Mead decision in *Barnhart v. Walton*, [535 U.S. 212, 222, (2002)], as well as our own decision in *Mylan Laboratories, Inc. v. Thompson*, [389 F.3d 1272, 1279-80 (D.C. Cir. 2004)]"); *Novartis Pharms. Corp. v. Leavitt*, 435 F.3d 344, 351-52 (D.C. Cir. 2006) (deferring to FDA's interpretation of a statute without notice-and-comment rulemaking); *Mylan Labs., Inc. v. Thompson*, 389 F.3d 1272, 1279-80 (D.C. Cir. 2004) (extending *Chevron* deference to the agency's interpretation of ANDA exclusivity provisions that was expressed in a letter decision).

Otsuka cites cases requiring notice-and-comment rulemaking in circumstances unlike those here. FDA has not adopted a position inconsistent with its existing regulation. *See* Pl.'s Br. at 36 (citing *Shalala v. Guernsey Memorial Hosp.*, 514 U.S. 87, 100 (1995) (reversing the Sixth Circuit's holding that a decision by HHS "effects a substantive change in the regulations [and is] void by reason of the agency's failure to comply with the Administrative Procedure Act in adopting it."). Rather, FDA's decision is consistent with both its existing regulation and the statute. *See* Section I.C., *supra*. Nor has FDA: created a new regulatory scheme, separate and apart from its existing regulatory scheme; s*ee Mendoza v. Perez*, 754 F.3d 1002, 1023 (D.C. Cir. 2014) (analyzing agency "Training and Employment Guidance Letters" establishing special procedures for "the certification process for cattleherders," "employers engaged in sheepherding and goatherding operations," and "employers seeking H-2A certification in these occupations"); abandoned a "long standing interpretation," *see Am. Fed. of Gov't Employees, AFL-CIO, Local 3090 v. Fed. Labor Relations Auth.*, 777 F.2d 751, 759 (D.C. Cir. 1985); or repealed an existing rule, *see Tunik v. MSPB*, 704 F.3d 1326, 1345 (Fed. Cir. 2005). The Supreme Court instructs that agencies need not use notice-and-comment procedures when issuing a new interpretation of a regulation, even if that interpretation deviates significantly from an interpretation the agency has previously adopted (which FDA's interpretation here does not do). *Perez v. Mortg. Bankers Ass'n*, 135 S. Ct. 1199, 1203 (2015) (overturning rule in *Paralyzed Veterans of Am. v. D.C. Arena L.P.*, 117 F. 3d 579 (D.C. Cir. 1997)). The Court stated: "Beyond the APA's minimum requirements, courts lack authority 'to impose upon [an] agency its own notion of which procedures are 'best' or most likely to further some vague, undefined public good.'" *Id.* at 1207. No additional process is required here.

Not only is there no legal requirement for notice-and-comment rulemaking in this case, there is also no practical justification for such a requirement. Otsuka complains that it did not have "an opportunity to comment on FDA's proposed new regulatory approach." Pl.'s Br. at 40. To the contrary, Otsuka was well aware of the existing statutory text and argued that FDA should not impose a "same active moiety" requirement based on "conditions of approval of such drug" referring back to the original "drug." AR 39 (conceding that the "provision suggests that there must be a relationship between 'such drug in the [first-in-time 505(b) application]' and the drug in the subsequent 505(b)(2) application' for it to be barred from approval"). FDA is well aware of the policy underlying notice-and-comment rulemaking, but such justification is absent here. *See Pension Benefit Guar. Corp. v. LTV Corp.*, 496 U.S. 633, 655-56 (1990) ("The determination in this case, however, was lawfully made by informal adjudication, the minimal requirements for which are set forth in § 555 of the APA, and do not include such elements. A failure to provide them where the Due Process Clause itself does not require them . . . is therefore not unlawful.").

CONCLUSION

For the foregoing reasons, Otsuka's motion for summary judgment should be denied, and the federal defendants' motion granted.

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Respectfully submitted,

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