UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

OTSUKA PHARMACEUTICAL CO., LTD., *et al.*,	)	
Plaintiffs,	)	Civil Action No. 1:15-cv-1688-KBJ
-v.-	)	
SYLVIA MATHEWS BURWELL, *et al.*,	)	
Defendants	)	
ALKERMES, INC., *et al.*	)	
Intervenor-Defendants.	)	

MEMORANDUM OF POINTS AND AUTHORITIES BY INTERVENOR-DEFENDANTS ALKERMES, INC. AND ALKERMES PHARMA IRELAND LIMITED IN SUPPORT OF THEIR MOTION FOR SUMMARY JUDGMENT AND IN OPPOSITION TO PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

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Intervenor-Defendants Alkermes, Inc. and Alkermes Pharma Ireland Limited (collectively, "Alkermes") respectfully submit this memorandum of points and authorities in support of their motion for summary judgment and in opposition to the motion for summary judgment [Dkt. 24] filed by Plaintiffs Otsuka Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Development & Commercialization, Inc., and Otsuka America Pharmaceutical, Inc. (collectively, "Otsuka").

INTRODUCTION

Alkermes invented a new drug, ARISTADA, whose active ingredient (and "active moiety") have never been used in any other drug. There is no dispute that aripiprazole lauroxil is a new chemical entity and its active moiety is N-hydroxymethyl aripiprazole. ARISTADA's key innovation is that the molecule aripiprazole lauroxil provides a unique form of extended relief to schizophrenia patients. Alkermes studied its innovative drug in its own clinical trials and met all the requirements for the federal Food and Drug Administration ("FDA") to approve ARISTADA as safe and effective. The question in this case is whether Otsuka can block that approval merely because it has certain rights to an injectable form of a *different* drug, aripiprazole, that also treats schizophrenia.

The rights Otsuka seeks to invoke were a reward for conducting new clinical studies on an existing drug, aripiprazole. Otsuka's exclusive rights are limited to the new uses developed for the drug Otsuka actually studied, whereas Alkermes' drug ARISTADA uses a different active moiety. As FDA reasonably concluded, the Federal Food, Drug, and Cosmetic Act ("FDCA") does not give Otsuka a monopoly on schizophrenia treatments generally, or on injectable schizophrenia treatments specifically.

Otsuka's main argument is that it must be able to block ARISTADA because, even though the two drugs use different active moieties, Alkermes' submission to FDA relied in part

on FDA's 2002 approval of aripiprazole *tablets*—a product that Otsuka also happens to own, but on which any relevant exclusivity has long since expired. Otsuka asserts that, due to ARISTADA's partial reliance on findings for aripiprazole tablets, an exclusivity that Otsuka has for its separate aripiprazole injection product somehow blocks approval of Alkermes' non-aripiprazole product. FDA correctly rejected Otsuka's argument, and to overcome the agency's conclusion, Otsuka must show that its position is unambiguously compelled by the statute. But the text only allows Otsuka to block a competitor seeking approval for the same new "conditions of approval *of such drug*" or for the same "change approved in the supplement"—that is, Otsuka's rights are only to the particular new study of injectable aripiprazole that Otsuka conducted. Neither the text of the FDCA, nor its structure, nor its legislative history suggests in any way that Otsuka has the right to block products that rely *partially* on FDA's previous consideration of a *different*, much older aripiprazole product. To the contrary: Congress created the "reliance" pathway in Section 505(b)(2) of the FDCA so that new drugs could be brought to market while building on studies that FDA had already reviewed and approved (here, the pre-2002 studies of aripiprazole *tablets*). Re-doing those studies would serve no purpose—and re-running them in human subjects, some of whom would receive a placebo, would pose ethical questions. To the extent the results of those earlier studies are novel and inventive, they can be protected by patents, and Otsuka could have blocked ARISTADA's approval based on its patents *if* Otsuka had a valid argument that Alkermes infringed those patents. It made no such argument. Instead, Otsuka insists that, just because Otsuka conducted a study *of injectable aripiprazole*, Alkermes cannot win approval of even a *non-aripiprazole product*, unless Alkermes re-does 13-year-old studies of *oral aripiprazole*. FDA properly found no basis in the statute for the extraordinarily broad form of exclusivity Otsuka is demanding.

FDA's decision is also eminently reasonable as an interpretation of FDA's existing regulations, and, contrary to Otsuka's dramatic characterization, it does not "amend" those regulations in a way requiring notice and comment. To the contrary, it is the same type of agency interpretation of existing law and regulations to which this Court regularly defers. The Court should do the same here.

STATEMENT OF FACTS FROM THE ADMINISTRATIVE RECORD

I. ARISTADA Is a New Drug, Not an Aripiprazole Drug Like Otsuka's Products

This is a case about two different drugs. Otsuka no longer disputes FDA's expert finding that ARISTADA is a different drug than Abilify Maintena in every legally relevant sense of the word "drug."[1] Whether measured as "drug product," "drug substance," "active ingredient," or "active moiety," the drugs are different:

Definition	ARISTADA	Abilify Maintena
Drug product "means a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more ingredients." 21 C.F.R. § 314.3(b).	Aripiprazole lauroxil extended-release injectable suspension (FDA 000356)	Aripiprazole extended-release injectable suspension (FDA 000356)
Drug substance "means an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates use[d] in the synthesis of such ingredient." 21 C.F.R. § 314.3(b).	Aripiprazole lauroxil (FDA 000364)	Aripiprazole (FDA 000364)
Active ingredient is used interchangeably with "drug substance." FDA 000348 n.27; *see also* 21 C.F.R. § 210.3(b)(7).	Aripiprazole lauroxil (FDA 000357)	Aripiprazole (FDA 000356)
Active moiety "means the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the	N-hydroxymethyl aripiprazole (FDA 000359-60)	Aripiprazole (FDA 000356)

[1] 21 U.S.C. § 321(g)(1).

molecule, responsible for the physiological or pharmacological action of the drug substance." 21 C.F.R. § 314.108(a).		

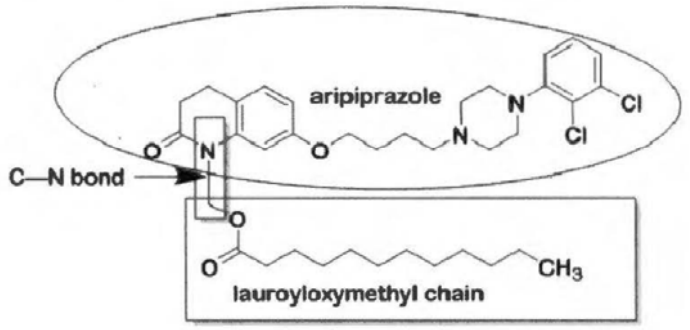
FDA awarded ARISTADA its own five-year exclusivity period as a New Chemical Entity ("NCE") in recognition of its novelty. FDA 000360; *see also* 21 U.S.C. § 355(c)(3)(E)(ii); 21 C.F.R. § 314.108(b)(2). FDA also concluded that ARISTADA's active moiety, N-hydroxymethyl aripiprazole, is new because, after any portions of ARISTADA that cause it to be a salt or ester, and other non-covalent bonds, are removed, the remaining molecule is N-hydroxymethyl aripiprazole, which has never been approved in any other application. FDA 000359.

After spending nearly six pages attempting to blur these clear lines,[2] Otsuka clarified that it is not challenging FDA's determinations on any of these points. Dkt. 24-1, at 9 n.7. Indeed, Otsuka cannot challenge FDA's determinations without retracting statements it made and certified as true to FDA, *e.g.*, that "aripiprazole lauroxil is a New Chemical Entity ('NCE') according to an FDA bright-line rule" and that ARISTADA contains "a new active moiety not contained in any previously-approved drug product." FDA 000001, 002.

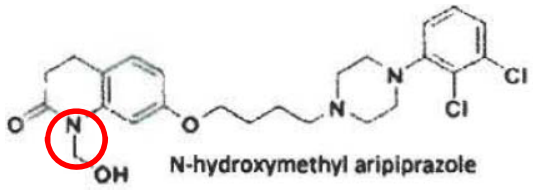
The differences between the drugs are apparent in the unique chemical structure of ARISTADA's active ingredient, aripiprazole lauroxil. Figure 1 shows the entire aripiprazole lauroxil molecule:

[2] For these purposes, Otsuka relied on gratuitous statements by reviewers not tasked with making an active moiety determination and that FDA stated did not speak for the agency, as the active moiety determination is made in a detailed memo by the Associate Director of Science. *See* FDA 000665-71; *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1321 (D.C. Cir. 1997) (deferring to final action, rather than intermediate statements by agency staff because, "were [the court] to hold otherwise, [it] would effectively empower any individual employee not just to veto the views of the agency head, but to preclude any deference to the agency at all, since [the court] would have no basis for deciding to whose view we should defer"). Otsuka also relied on two statements (from 2013) made by Alkermes' CEO at healthcare conferences that are legally irrelevant to FDA's appropriate and unchallenged determination that the active moiety in ARISTADA is N-hydroxymethyl aripiprazole.

Figure 1: Aripiprazole Lauroxil Showing Differences From Aripiprazole



FDA 000357. One part—and only one part—of that molecule (the part within the oval diagram) is essentially the same as the aripiprazole molecule. But when a patient is administered ARISTADA, which contains aripiprazole lauroxil in the syringe, aripiprazole itself emerges only through a series of steps in the body, as an eventual metabolite of aripiprazole lauroxil. First the body breaks an ester bond to form N-hydroxymethyl aripiprazole. Then—the key step for FDA's purposes—the body breaks a *non-ester covalent bond* to release aripiprazole. The following excerpt from Figure 3 shows N-hydroxymethyl aripiprazole, and the circle (added for this brief) highlights the covalent bond:



FDA 000359. This covalent bond distinguishes ARISTADA's active moiety from Abilify Maintena's and, indeed, from that of any other drug ever approved. "[I]t has been FDA's longstanding experience 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. Because of their potential significance, FDA has always identified changes in covalent structure, including minor changes, … as sufficient to create a new 'active moiety' and thereby to create a new chemical entity." FDA 001493 (quoting 1989 citizen petition response); *see also* FDA

000004. Such a structural difference represents a "major innovation" above existing drugs on the market. *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 765 (D.C. Cir. 2010) (describing prodrugs containing this kind of non-ester covalent bond as "major innovations").

As FDA explained (and the D.C. Circuit upheld) in *Actavis Elizabeth*, a drug's metabolites (like the aripiprazole metabolite in ARISTADA) that are released only after breaking a non-ester covalent bond are legally irrelevant to the classification of a drug for therapeutic or exclusivity purposes. *Id.* at 763 (analyzing NCE exclusivity). Otsuka agrees.[3] Instead, FDA looks to the structure of the drug as it exists before the body breaks that covalent bond: "the active moiety of a molecule with a non-ester covalent bond is the entire molecule, even if the molecule includes a covalent bond to a molecule that was itself previously an active moiety." *Id.* That is precisely the analysis FDA followed here to determine that ARISTADA is a new drug containing a new active moiety, and why FDA awarded ARISTADA five-year marketing exclusivity for containing an NCE. FDA 000356-60.[4]

II. ARISTADA's Chemical Differences From Otsuka's Product Represent a Clinical Innovation

ARISTADA represents a significant advancement in the treatment of schizophrenia. Its use of aripiprazole lauroxil as the active ingredient rather than aripiprazole makes each dose last longer and allows for longer grace periods after missed doses, giving patients needed flexibility. And, unlike a generic drug, ARISTADA and Abilify Maintena are not therapeutically

[3] FDA 000009 (Otsuka: "Under FDA's bright-line rule, it is irrelevant that aripiprazole lauroxil 'ultimately' 'convert[s]' into aripiprazole when determining whether the active moiety is aripiprazole lauroxil or aripiprazole. The deciding factor is the chemical structure prior to bioconversion, and, specifically, whether there are covalent structural modifications.").

[4] Classifying drugs using a metabolite-based approach—like the one urged by the plaintiff and rejected by FDA (and the court) in *Actavis*—would improperly disregard portions of a drug molecule that "should be deemed responsible for the drug's activity, which can include its 'distribution within the body, its metabolism, its excretion, or its toxicity.'" *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 764 (D.C. Cir. 2010). It also would pose great administrative difficulties, such as "'determining precisely which molecule, or portion of the molecule, is responsible for the drug's effects.'" *Id.* at 766. Indeed, that difficulty would be present in this case, where the metabolite aripiprazole breaks down further into another active metabolite, dehydro-aripiprazole. FDA000367.

substitutable,[5] precisely because of their chemical differences.[6] Indeed, as explained below, those differences give ARISTADA features that patients seek out and that Abilify Maintena lacks, illustrating just how unfounded Otsuka's repeated attempts to deride ARISTADA as a "copycat" really are.

Schizophrenia is "a severely debilitating mental illness that affects approximately 1% of the world's population." FDA 001169 (FDA REMS Review). Historically, schizophrenia was treated with antipsychotics (like haloperidol), but those drugs treated only a portion of schizophrenia symptoms and had a relatively high incidence of side effects. *Id.* A second class of antipsychotics (called "atypical antipsychotics") was developed, which target additional receptors in the brain and tend to treat more symptoms with a lower incidence of side effects. *Id.* The long-acting injectable ("LAI") form of atypical antipsychotics is an "important option" for patients, "appear[ing] to improve adherence" over self-administered daily tablets and reduce the risk of overdose. *Id.* There are over a dozen kinds of atypical antipsychotics in tablet form, but before the introduction of ARISTADA, only five LAIs were available (Risperdal Consta®, Invega Sustenna®, Invega Trinza™, Abilify Maintena®, and Zyprexa Relprevv®). *Id.* Prior to ARISTADA's approval, FDA reviewers noted that "[t]here is a need for an LAI treatment option that could provide greater flexibility in dosing and dose intervals to better suit specific patient needs as well as additional convenience and ease of use with reduced risk for medication errors." *Id.*

[5] FDA makes determinations of therapeutic equivalence, assigning products an "AB" rating if they are equivalent. *See Serono Labs*, 158 F.3d at 1317. Most generic drugs are "AB" rated to the brand-name drug, meaning under most state laws that they can be substituted for the brand. Some 505(b)(2) drugs can obtain an "AB" rating, but ARISTADA is not "AB" rated to Abilify Maintena.

[6] Otsuka asserts without support that "FDA first found the drugs were the same for safety and efficacy, and then different for exclusivity purposes," Dkt. 24-1, at 8, but that is not true and not supported by a single record cite. FDA's prior findings that aripiprazole oral tablets were safe and effective lent support to ARISTADA's approval, but Alkermes conducted additional clinical studies, including bridging studies, to show why its own drug, aripiprazole lauroxil, is safe and effective to treat schizophrenia. FDA 000368-71.

ARISTADA responds to this identified need, giving patients a new treatment option for schizophrenia in long-acting injectable form and providing flexibility in dosing (and in missed doses) that is otherwise unavailable to patients. In addition to providing a new active ingredient (aripiprazole lauroxil) to patients, ARISTADA can be administered to patients every four or six weeks (depending on strength of dose) and has relatively forgiving grace periods for missed doses (which also vary depending on strength of dose).[7] By contrast, Abilify Maintena (which contains a different active ingredient, aripiprazole) may only be dosed every four weeks, and has relatively shorter grace periods for missed doses.

III. Alkermes Sought Approval for ARISTADA as a New Drug, Not a Generic Drug, and Conducted Its Own Clinical Work on the Innovative Aspects of Its Drug Without Re-Establishing What FDA Already Knew

ARISTADA is the result of seven years of work by Alkermes to formulate, study, obtain approvals for, manufacture, and market the drug. It is not a "copycat" drug in any sense of the word. In fact, Alkermes first met with FDA regarding ARISTADA's development in 2010, *three years before* FDA approved Abilify Maintena. FDA 000072. ARISTADA is a new drug approved pursuant to a New Drug Application ("NDA").

Alkermes utilized an FDA approval pathway outlined in Section 505(b)(2) of the FDCA, 21 U.S.C. § 355(b)(2) (often called a "505(b)(2)" approval). Alkermes filed an NDA, and thus was required to show that ARISTADA is safe and effective in its own right (whereas an

[7] ARISTADA, like other long-acting injectable atypical antipsychotics, requires a ramp-up period for new patients introduced to the drug. During the initial dosing period, a patient takes an immediate-release therapy for the first three weeks. FDA 001223-24. After the initial period, the patient can simply receive the injection on a monthly basis (or, with the highest dose, up to every six weeks). *Id.* As with other long-acting injectable atypical antipsychotics, if a scheduled injection is received too late (i.e., too long after the prior injection), the patient must again repeat the ramp-up protocol, or a revised version of it. ARISTADA, however, has an extended "grace period," allowing patients to avoid repeating the ramp-up protocol if they receive a late injection within a certain amount of time of the missed injection. The highest two doses of ARISTADA allow for a grace period of up to four weeks beyond the recommended monthly dosing schedule, and the lowest dose of ARISTADA permits up to a two-week grace period. *Id.* The extended grace period feature is extremely important for the population living with schizophrenia as it may reduce the need for oral supplementation in a patient population where compliance with daily dosing often presents challenges and where lack of compliance can contribute to relapse.

Abbreviated New Drug Application ("ANDA") to market a *generic* drug shows only that the drug is the "same" as an already-approved drug). Proceeding under Section 505(b)(2) allows an applicant to show safety and effectiveness by relying, in part or in whole, on findings of safety and effectiveness that FDA has made for other drugs. *See Takeda Pharm., U.S.A., Inc. v. Burwell*, 78 F. Supp. 3d 65, 71-72 (D.D.C. 2015), *appeal filed*, No. 15-5021 (D.C. Cir. filed Jan. 26, 2015). If relying only in part on others' findings, "the applicant can supplement with studies of its own." *Id.* at 72.

That is exactly what Alkermes did here. Alkermes relied in part on FDA's findings of safety and effectiveness of an old drug, oral aripiprazole tablets (Abilify, NDA No. 021436, approved in 2002), which were "well established." FDA 000357, 368. Alkermes did not rely on any findings FDA made as to Abilify Maintena (NDA No. 202971, approved in 2013). To demonstrate the safety and effectiveness of its new drug aripiprazole lauroxil, Alkermes also conducted its own clinical studies (a Phase 3 clinical study involving 623 patients and four Phase 1 pharmacokinetic clinical studies). FDA 000368-69. These Phase 3 and Phase 1 studies "established the scientific bridge between" ARISTADA and Abilify oral tablets, "demonstrat[ing] that the basis for reliance on the listed drug was justified." FDA 000369. FDA determined that "[t]he studies conducted by Alkermes, together with the Agency's finding of safety and effectiveness for Abilify Tablets, support the conclusion that Aristada is safe and effective under the conditions of use described in the Aristada labeling." FDA 000370. Although Otsuka filed two Citizen Petitions challenging FDA's ability to make this scientific determination, Otsuka does not challenge here FDA's reasoned and fully supported conclusion that ARISTADA is safe and effective.

IV. FDA Lawfully Concluded That the FDCA Does Not Compel It To Apply Abilify Maintena's Marketing Exclusivity To ARISTADA, a Different Drug Containing a Different Active Moiety

Alkermes submitted its NDA for ARISTADA to FDA on August 22, 2014. Otsuka began its campaign to block ARISTADA's approval weeks later by filing a Citizen Petition urging FDA to refuse to even accept ARISTADA's NDA for filing. Otsuka claimed aripiprazole lauroxil is too different scientifically from aripiprazole to rely, even in part, on FDA's findings that aripiprazole oral tablets are effective to treat schizophrenia. *See* FDA 000001-18. Despite Otsuka's submission, FDA accepted the ARISTADA NDA for filing on October 22, 2014.

Undeterred, Otsuka filed another Citizen Petition on July 13, 2015. As before, Otsuka argued that ARISTADA is too different from aripiprazole to rely on FDA's findings for aripiprazole oral tablets, even if only in part, to show ARISTADA's efficacy, and that accordingly ARISTADA should be required to conduct another clinical trial. FDA 000025-44. Otsuka also added a second argument to its July 2015 Citizen Petition. Otsuka argued that the three-year new clinical study exclusivities that FDA awarded to Otsuka's Abilify Maintena on February 28, 2013 (expiration February 28, 2016) and December 5, 2014 (expiration December 5, 2017) should block ARISTADA's approval until the expiration of Abilify Maintena's second exclusivity on December 5, 2017. *Id.*

On October 5, 2015, FDA issued its decision denying Otsuka's Citizen Petition in its entirety. FDA's decision is embodied in a carefully detailed, 31-page memorandum. FDA rejected Otsuka's argument that ARISTADA is too different from Abilify for Alkermes to rely on any Abilify data, and Otsuka does not raise it again in this action. FDA 000368-71. FDA also rejected Otsuka's argument that its three-year exclusivities on Abilify Maintena block approval of ARISTADA. FDA 000342-67. That decision is the one Otsuka continues to challenge in this lawsuit.

FDA first explained that the FDCA provides a five-year exclusivity for new chemical entities, and—for applications for drugs that do not contain NCEs—the FDCA provides three years of exclusivity for conducting certain clinical studies on older chemical entities. FDA 000347. Thus, a threshold determination for whether an application can obtain five- or three-year exclusivity, FDA noted, is whether an application for a drug contains an NCE or not. *Id.* The FDCA makes an application eligible for NCE exclusivity if it is "for a drug,[8] no active ingredient (including any ester or salt of the active ingredient) [that] has been approved in any other application." 21 U.S.C. § 355(c)(3)(E)(ii).[9] An application for a drug that does not contain an NCE can be eligible for three-year exclusivity in certain situations. *Id.* §§ 355(c)(3)(iii), (iv). FDA has determined that the dividing line between an NCE and a non-new chemical entity is whether an application contains an "active moiety that has been approved by FDA" in another application. 21 C.F.R. § 314.108(a); FDA 000347-48.[10] And, as noted above, FDA defines "active moiety" as the molecule excluding portions that cause it to be an ester, salt, or other noncovalent derivative of the molecule. 21 C.F.R. § 314.108(a); FDA 000348. When an application contains an NCE, exclusivity attaches to the new active moiety in the drug product, blocking any 505(b)(2) or ANDA application that contains that active moiety. FDA 000350.

FDA next explained that three-year exclusivity is more limited and only blocks applications containing drugs with the same active moiety *and* the same "conditions of approval"

[8] In 2014, to provide NCE exclusivity to drug products that contain more than one drug substance—one of which could qualify as an NCE, and one of which could not—FDA changed its interpretation of "drug" in the NCE eligibility clause to mean "drug substance" rather than the "drug product." FDA 000347-48 & n.25; FDA 000364 & n.83.

[9] Abilify oral tablets were awarded NCE exclusivity for aripiprazole, but it has long since expired.

[10] As FDA notes, a recent District of Columbia district court decision questioned whether this phrase should appropriately be defined as active moiety or active ingredient in the context of a drug with more than one active moiety. FDA 000349 n.32; *see Amarin Pharm. Ir. Ltd. v. FDA*, No. 14-cv-324, 2015 WL 3407061 (D.D.C. May 28, 2015). Abilify Maintena has only one active moiety (aripiprazole), and, whether the phrase means "active ingredient" or "active moiety" the answer is the same for exclusivity purposes. ARISTADA and Abilify Maintena have different active ingredients and different active moieties. FDA 000349 n.32.

(or, in the case of clause (iv), the same "change approved in the supplement"). FDA 000350-54; 360-67. FDA arrived at this conclusion by closely scrutinizing the statute. FDA explained that the first subordinate clause of 21 U.S.C. § 355(c)(3)(E)(iii)[11] is often called the "eligibility clause." It allows an NDA to claim marketing exclusivity if it is for "a drug which includes an active ingredient" (defined by FDA as active moiety) "that has been approved in another application" and was supported by a certain kind of new clinical study essential to the NDA's approval. FDA 000351. FDA emphasized that the "eligibility clause" describes an "application . . . for a drug, which includes" a previously-approved active moiety, and that the active moiety cannot be divorced from what makes an application eligible for exclusivity. FDA 000361.

FDA then analyzed the text of the "bar clause," which describes the scope of the three-year exclusivity and involves "two aspects." FDA 000352. Because the "bar clause" blocks approval of 505(b)(2) applications only for "conditions of approval of such drug in the approved subsection (b) application," FDA concluded that, for a 505(b)(2) application to be barred by the new clinical study exclusivity of a previously approved drug product, the new application must be for both (1) the "conditions of approval" *and* (2) "such drug,"—that is, the drug in the previously approved application. *Id.* Because FDA had already determined (by its reading of the "eligibility clause") that the "drug" in the application with exclusivity means the drug

[11] 21 U.S.C. § 355(c)(3)(E)(iii):

> **[eligibility clause]** 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, [**bar clause**] 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 [**condition**] 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.

substance with its active moiety, FDA reasonably determined that when the "bar clause" cross-references "such drug" it too means the drug with that active moiety. *Id.*[12]

The new clinical study exclusivity provided by 21 U.S.C. § 355(c)(3)(E)(iv) is worded slightly differently because it provides exclusivity to *supplements* to NDAs, as opposed to original NDAs.[13] *Id.* Thus, it bars 505(b)(2)s for a "change approved in the supplement" instead of for "conditions of approval of such drug in the approved subsection (b) application." FDA takes a "consistent approach" to both three-year exclusivity provisions. FDA 000353. As FDA noted, a "supplement" may only be submitted to amend the "same drug" so any exclusivity awarded under clause (iv) necessarily also extends only so far as that drug. *Id.*; *see also ViroPharma, Inc. v. Hamburg*, 898 F. Supp. 2d 1, 21 (D.D.C. 2012) ("[T]he general exclusivity period provided in § 355(j)(5)(F)(iv) . . . is itself limited to that which is 'new' about the given drug.").

FDA then applied this analysis to the case at bar. The approved application, Abilify Maintena, is for a drug containing the active moiety aripiprazole, for which certain clinical studies were conducted, and which earned certain three-year exclusivities as a result. FDA 000361. The first will expire on February 28, 2016, and is listed as a "new dosage form"; the

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[12] There is a third clause (identified *supra* n.11 and *infra* n.13 as a "condition") that states what kind of application can be blocked by the exclusivity. There are parallel three-year exclusivity provisions in subsections (c) and (j). The "condition" clause in subsection (c) exclusivity identifies 505(b)(2) applications as those that can be blocked by exclusivity; subsection (j) identifies ANDAs. *See* FDA 000351 & n.38; 21 U.S.C. §§ 355(j)(5)(F)(iii), (iv).

[13] 21 U.S.C. § 355(c)(3)(E)(iv):

> [**eligibility clause**] If a supplement to an application submitted under subsection (b) of this section for a drug is approved after September 24, 1984, and if the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, [**bar clause**] 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 application under subsection (b) of this section [**condition]** 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.

second will expire on December 5, 2017, and is listed as "addition of the results of a controlled clinical study treating adult patients with schizophrenia experiencing an acute relapse," *Approved Drug Products with Therapeutic Equivalence Evaluations*, U.S. Dep't of Health & Human Servs., Office of Generic Drugs (35th ed. 2015) [*hereinafter Orange Book*], *available at* http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=202971&TABLE1=OB_Rx.[14] FDA 000361. However, FDA explained, *both* exclusivities are for "a drug *containing the active moiety aripiprazole*." FDA 000361 (emphasis added). ARISTADA does not contain the active moiety aripiprazole. *Id.* Its active moiety is N-hydroxymethyl aripiprazole. *Id.* FDA determined, based on this analysis, the facts of which are not in dispute, *see* Dkt. 24-1, at 9 n.7, that Otsuka's claim of exclusivity fails. FDA 000361. Abilify Maintena and ARISTADA are different drugs with different active moieties; thus, any new clinical study exclusivity held by Abilify Maintena cannot block ARISTADA.

Based on its conclusions that Otsuka's exclusivities for aripiprazole do not apply to Alkermes' ARISTADA product, and that Alkermes had satisfied all other relevant requirements, FDA approved ARISTADA for sale in the United States. ARISTADA has now been on the market for two months and schizophrenia patients have begun to receive treatments with this new drug.

ARGUMENT

I. FDA's Decision That New Clinical Drug Exclusivity Does Not Extend Beyond Drugs That Share an Active Moiety Is Controlling Under *Chevron*, and FDA Permissibly Concluded That Otsuka's Exclusivities Do Not Block Approval of ARISTADA

Otsuka asserts that FDA contravened the clear text of 21 U.S.C. §§ 355(c)(3)(E)(iii) and (iv) by refusing to extend new clinical study exclusivity beyond its natural boundary, the drug

[14] These shorthand notations naming the exclusivities are not binding as to the scope of the exclusivities. Only FDA has the authority to determine their scope. *See Veloxis Pharm., Inc. v. FDA*, No. 14-2126, 2015 WL 3750672, at *12 (D.D.C. June 12, 2015); *ViroPharma, Inc. v. Hamburg*, 898 F. Supp. 2d 1, 22 (D.D.C. 2012).

Otsuka actually studied to earn the exclusivity in the first place. FDA's decision rests on a straightforward reading of the FDCA's text and certainly is reasonable under *Chevron*. Indeed, it is a much more faithful reading of the text than the convoluted reading Otsuka proposes.

Under the Administrative Procedure Act ("APA"), this Court may not vacate FDA's decision unless it is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). Otsuka cannot ask this Court "to substitute its judgment for that of the agency." *Apotex Inc. v. FDA*, 414 F. Supp. 2d 61, 66 (D.D.C. 2006), *aff'd*, 226 F. App'x 4 (D.C. Cir. 2007). "That is, it is not enough for the agency decision to be incorrect—as long as the agency decision has some rational basis, the court is bound to uphold it." *Id.*

Chevron's familiar two-step framework for reviewing FDA's interpretation of the FDCA applies in this case. At step one, Otsuka must show that "Congress has directly spoken to the precise question at issue,"—that is, the contours of the "bar clause" of new clinical study exclusivity. *Mylan Labs., Inc. v. Thompson*, 389 F.3d 1272, 1280 (D.C. Cir. 2004) (citation, internal quotation marks, and modifications omitted). It cannot do so. Courts routinely find that the scope of marketing exclusivities in the FDCA is ambiguous in some respect. *See, e.g.*, *AstraZeneca Pharm. LP v. FDA*, 872 F. Supp. 2d 60, 81 (D.D.C. 2012), *aff'd*, 713 F.3d 1134 (D.C. Cir. 2013). Otsuka's tortured construction is not even a permissible reading of the statute; it certainly is not unambiguously *compelled* by the text. The most Otsuka could show is that the relevant statutory language "is silent or ambiguous with respect to a specific issue," in which case the Court would proceed to *Chevron*'s second step.

At step two, a court must evaluate "whether the agency's position rests on a 'permissible construction of the statute,'" *Pharm. Research and Mfrs. of Am. v. Thompson*, 362 F.3d 817, 823 (D.C. Cir. 2004) (citation and modifications omitted), and must "defer to the agency's

interpretation as long as it is 'based on a permissible construction of the statute,'" *Bluewater Network v. EPA*, 372 F.3d 404, 410 (D.C. Cir. 2004) (quoting *Chevron, U.S.A., Inc. v. Natural Resources Def. Council*, 467 U.S. 837, 843 (1984)). So long as the agency's interpretation is reasonable, it must be upheld, even if there are "other reasonable, or even more reasonable, views." *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1321 (D.C. Cir. 1998). Otsuka has failed to show FDA's interpretation is anything less than eminently reasonable. Accordingly, Otsuka's challenge to the approval of ARISTADA must be rejected.

A. The Statute Does Not Give New Clinical Study Exclusivity the Scope Otsuka Seeks

1. The Text of 21 U.S.C. §§ 355(c)(3)(E)(iii) and (iv) Does Not Compel FDA To Apply New Clinical Study Exclusivity Across Active Moieties

The *Chevron* analysis starts (and in this case, also ends) with the text at issue, namely, 21 U.S.C. §§ 355(c)(3)(E)(iii) and (iv). *Apotex Inc.*, 414 F. Supp. 2d at 67 ("Under *Chevron*'s familiar framework, the plain language of Hatch-Waxman is the starting point for the Court's analysis."); *Otsuka Pharm. Co. v. Burwell*, No. GJH-15-852, 2015 WL 3442013, at *8 (D. Md. May 27, 2015) ("[T]he Court begins its *Chevron* step one inquiry into Congress's intent, as it must, from 'the fundamental canon that statutory interpretation begins with the language of the statute itself.'" (citing *Butler v. West*, 164 F.3d 634, 639 (D.C. Cir. 1999))). Tellingly, Otsuka spends just one paragraph in its 40-page memorandum on its textual analysis of these exclusivity provisions, reverting quickly to policy, separate statutory provisions, and completely non-probative legislative history. The highly abbreviated (and rather difficult to parse) explication Otsuka does offer, falls far short of demonstrating that its interpretation is *unambiguously* correct, as it must to prevail under *Chevron*'s first step.

The text at issue is the "bar clause" of new clinical study exclusivity, and the question is what precisely it bars. Otsuka argues the clause can bar any 505(b)(2) application that relied on

findings of safety and efficacy from an approved NDA, regardless of whether the 505(b)(2) application and the approved NDA are for the same drug. As detailed above, FDA has reasonably determined from the statutory text that the exclusivity does not turn on reliance, but instead on whether the two drugs share an active moiety and conditions of approval (or a change approved in the supplement). By itself, this reasonable construction of the language that is contrary to Otsuka's position shows that the statute does not *compel* Otsuka's reading. But as we show below, the text cannot even support Otsuka's interpretation.

Otsuka starts its textual analysis from a strained and implausible reading of "such drug." Otsuka says the phrase "such drug in the approved subsection (b) application" does not only refer back to the drug with exclusivity mentioned earlier in the provision, but must also refer to another drug entirely, the one (or more) drugs whose findings of safety and efficacy the 505(b)(2) applicant relied upon (even if only in part) for approval. Dkt. 24-1, at 17-18. Otsuka argues that the phrase "such drug in the approved subsection (b) application" in the "bar clause" of 21 U.S.C. § 355(c)(3)(E)(iii), somehow unambiguously refers to something "*later* in the sentence." Dkt. 24-1, at 17 (emphasis added). It is unclear what Otsuka hopes to achieve with this implausible reading, as "drug" does not appear later in the sentence. Otsuka asserts that "such drug" means the drug "referred to earlier in the sentence . . . *and* the drug in the first-in-time 505(b)(1) application," *id.*, but, just as "drug" does not appear after the "bar clause," neither does "the drug in the first-in-time 505(b)(1) application." In any event, not only is Otsuka's interpretation far from compelled, but, as this Court has recognized, the word "such" "nearly always operates as a reference back to something previously discussed." *Takeda Pharm.*, 78 F. Supp. 3d at 99.[15] Here, FDA followed exactly that approach. FDA reasonably found that "such

[15] *See also United States v. Chi Tong Kuok*, 671 F.3d 931, 945 n.8 (9th Cir. 2012) ("'Such' in this context means 'of the sort or degree previously indicated or implied.'" (quoting Webster's Third New International Dictionary 2283

drug" references the "drug" previously described in the eligibility clause.

Otsuka, to support its counter-textual reading of "such drug" as signaling something to come, provides two inapt citations. It first cites a 1989 case from the Northern District of Illinois that discusses the phrase "such as," and then cites Merriam-Webster's Collegiate Dictionary, which also defines "such as." Dkt. 24-1, at 17. "Such as" has a different meaning than "such"—generally denoting an example or list to come rather than referencing an item previously discussed. Moreover, for "such drug" to have two meanings (the "drug" referenced earlier in the provision *and* the drug on whose findings the 505(b)(2) applicant relied), the definite article in the phrase "such drug in **the** approved subsection (b) application," 21 U.S.C. § 355(c)(3)(E)(iii), would have to become an indefinite article, making the phrase "such drug in **an** approved subsection (b) application." Rather than compelled, Otsuka's reading is foreclosed.

Otsuka's next textual argument is to read the phrase "of such drug" out of the statute. Otsuka makes the remarkable assertion that "the text of the provisions limits exclusivity to the 'conditions of approval' derived from 'new clinical investigations,' . . . and not to a specific drug." Dkt. 24-1, at 15 (citations omitted); *see also id.* at 14 ("Exclusivity under these provisions applies to 'conditions of approval' and 'a change,' not to particular active moieties."). But which conditions of approval get exclusivity? The "conditions of approval *of such drug.*" Any valid reading of the statute must endeavor to give effect to every word in a statute to the extent possible, and FDA properly did so here. Otsuka's reading, by contrast, does not, making it impermissible. *See Mich. Citizens for an Indep. Press v. Thornburgh*, 868 F.2d 1285, 1293 (D.C. Cir. 1989) (noting courts should strive "to give effect, if possible, to every word Congress used," and that failure to do so can constitute "an effective repeal of part of the statute,"

(2002))); *Nieves v. United States*, 160 F.2d 11, 12 (D.C. Cir. 1947) ("The word 'such' is restrictive in its effect and obviously relates to an antecedent.").

"frustrat[ing] the intent of Congress" (internal quotation marks and citations omitted)).

At times, Otsuka reluctantly acknowledges the statute includes the limiting language "such drug" and "approved in the supplement" but offers no reason why FDA should be compelled to read it out of the "bar clause." Otsuka merely asserts, without support, that FDA errs by "placing the focus on 'such drug' rather than, appropriately, on the 'conditions of approval' or 'change.'" Dkt. 24-1, at 14; *see also id.* ("The focus on the scope of a first-in-time drug's exclusivity is appropriately on 'conditions of approval' or 'change,' not the active moiety at issue."). But "of such drug" restricts the scope of "conditions of approval," and the latter cannot be read without the former. Otsuka does not explain the difference between FDA merely giving effect to the phrase "of such drug" and allegedly placing too much "focus" on it, but, in any event, Otsuka gives no reason why such a loose concept as "focus" can provide a basis to compel agency action under step one.

Of course, to prevail under step one, Otsuka must show that *its* reading of the statute—including that the "drug" whose exclusivities can purportedly block approval of a 505(b)(2) drug—is clear, unambiguous, and compelled by the FDCA. It has failed to do so. Moreover, Otsuka's attempt to arrive at a so-called compelled reading of the text of the new clinical study exclusivity provisions runs contrary to the wealth of case law holding that the FDCA's exclusivity provisions are ambiguous in many respects. In fact, another court in this Circuit has already held that "key phrases" in the parallel, nearly-identical new clinical study exclusivity applicable against ANDAs (at 21 U.S.C. § 355(j)(5)(F)(iv)) "are undefined and their meaning disputed"—including what kinds of changes can qualify as a "change approved in the supplement." *AstraZeneca*, 872 F. Supp. 2d at 81 (D.D.C. 2012). In addition, *Veloxis*, upon which Otsuka places primary reliance, also recognized that the scope of section 355(c)(3)(E)(iii),

including the key phrase "conditions of approval," is ambiguous and must be analyzed under *Chevron* step two. *Veloxis Pharm., Inc. v. FDA*, No. 14-cv-2126, 2015 WL 3750672, at *12 (D.D.C. June 12, 2015) (noting that both parties conceded the ambiguity).[16] Acknowledging some (though not all) of this contrary authority in a footnote, Otsuka merely asserts, without a single citation in support, that its motion "can, and should, be decided under *Chevron* step one." Dkt. 24-1, at 13 n.12. New clinical study exclusivity does not become clear and unambiguous based on the mere say-so of Otsuka.

2. The Structure of the FDCA Does Not Compel FDA To Apply New Clinical Study Exclusivity Across Active Moieties

The Court need not go any further—Otsuka's preferred reading of the bar clause is certainly not compelled and in all likelihood is foreclosed by the text of sections 355(c)(3)(E)(iii) and (iv). But if one were to entertain the idea that "the conditions of approval of such drug" *must* include the conditions of approval of *a different drug*, Otsuka would still need to show that the statute inexorably requires 505(b)(2) drugs to be blocked by drugs on whose findings they relied. Otsuka attempts to do so by alluding to the "structure" of the FDCA, arguing that two provisions—21 U.S.C. § 355(b)(2) (establishing the 505(b)(2) pathway for product approval) and

[16] Many other marketing exclusivity provisions in the FDCA have likewise been held ambiguous in some respect. *See, e.g.*, *Actavis*, 625 F.3d at 764 (holding 21 U.S.C. § 355(j)(5)(F)(ii), which provides five years of exclusivity to drugs "no active ingredient (including any ester or salt of the active ingredient) of which" has been approved in a prior new drug application, is ambiguous); *Nat'l Pharm. Alliance v. Henney*, 47 F. Supp. 2d 37, 39 (D.D.C. 1999) (holding that the six-month pediatric exclusivity provisions at 21 U.S.C. § 355a are ambiguous due to ambiguity of the term "drug"); *Baker Norton Pharm., Inc. v. FDA*, 132 F. Supp. 2d 30, 33 (D.D.C. 2001) (holding that 21 U.S.C. § 360cc(a), which provides seven years of exclusivity for a drug designated under Orphan Drug Act as a drug indicated "for a rare disease or condition," is ambiguous because the word "drug" is ambiguous); *Otsuka Pharm. Co. v. Burwell*, No. GJH-15-852, 2015 WL 3442013, at *12 (D. Md. May 27, 2015) (holding that orphan drug exclusivity provisions are ambiguous under *Chevron* step one in light of labeling provisions codified at 21 U.S.C. § 355a(o)); *Mylan Pharm., Inc. v. Sebelius*, 856 F. Supp. 2d 196, 209 (D.D.C. 2012) (holding that section 505(j)(5)(B)(iv) of the FDCA, which provides 180 days of exclusivity to the first ANDA applicant for a drug, provides "absolutely no guidance or limitations" regarding whether the first ANDA applicant and the NDA-holder must be adverse for the ANDA applicant to claim the 180-day exclusivity period, and finding FDA's interpretation of the provision reasonable under *Chevron* step two); *Apotex Inc. v. FDA*, 414 F. Supp. 2d 61, 66 (D.D.C. 2006), *aff'd* 226 F. App'x 4 (D.C. Cir. 2007) (holding that section 505(j)(5)(B)(iv) of the FDCA, which provides 180 days of exclusivity to the first ANDA applicant for a drug, "is silent regarding the issue of how many exclusivity periods may arise in connection with a single drug product. . . . and hence is ambiguous under *Chevron* step one").

21 U.S.C. § 355(c)(3)(E)(iii) and (iv) (establishing new clinical study exclusivity)—must be read together. *See* Dkt. 24-1, at 15. But all adding section 355(b)(2) into the analysis does is show that if Congress wanted to add a concept of reliance into new clinical study exclusivity, it had the words at its disposal to do so—but it did not use them in the exclusivity provisions.

Otsuka's basic premise is that the 505(b)(2) pathway must require a trade-off, or quid pro quo—if a 505(b)(2) drug relies on findings from another drug, in Otsuka's view, that 505(b)(2) application must be blocked by its exclusivities. The primary problem with Otsuka's argument is that 21 U.S.C. § 355(b)(2) *does in fact* include a trade-off—just not the one Otsuka seeks. To rely on a previously approved drug in a 505(b)(2) application, the applicant must "certify" to any and all patents listed in FDA's *Orange Book* for the relied-upon drug.[17] *See* 21 U.S.C. § 355(b)(2)(A) (requiring the (b)(2) applicant to certify that it will not infringe the relied-upon drug's patent rights, if any); *Takeda Pharm.*, 78 F. Supp. 3d at 89-90 (quoting FDA Citizen Petition response stating that, as a condition of referencing another drug, a 505(b)(2) applicant "must identify in its application the drug product or products *on which it relies* and certify to any relevant patents for those drug products"). Alkermes submitted certifications to Otsuka's listed patents for Abilify oral tablets; if Otsuka had a basis for suing Alkermes for patent infringement, it had forty-five days to file suit, which would then trigger a 30-month block on Alkermes' approval. 21 U.S.C. §§ 355(b)(3), (c)(3)(C). Otsuka filed no such lawsuit, so it got no 30-month stay. Otsuka cannot now manufacture a patent suit in the guise of a marketing exclusivity.

There is no marketing exclusivity trade-off in section 355(b)(2) itself. Rather, marketing exclusivity contains its own trade-off: a drug company that develops a new use or indication for

[17] That is precisely why Alkermes certified to the patents listed by the drug (Abilify tablets) whose findings of safety and efficacy it relied upon, in part, for ARISTADA's approval.

an already-approved drug gets three years of exclusivity, but *only* for the new "conditions of approval of such drug" or the "change approved in the supplement."

Congress's choice to speak clearly on the patent trade-off but remain silent on any alleged marketing exclusivity trade-off argues strongly against trying to imply one. *See Catawba Cnty., N.C. v. EPA*, 571 F.3d 20, 37 (D.C. Cir. 2009) ("When interpreting statutes that govern agency action, we have consistently recognized that a 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." (citations and internal quotation marks omitted)). Certainly, it was at least *permissible* for FDA to decline to graft a marketing-exclusivity trade-off onto the statute.

Section 355(b)(2) also provides another textual clue that argues against Otsuka's counter-textual reading of new clinical study exclusivity. Otsuka argues that the "such drug" in new clinical study exclusivity must be broad enough to encompass the "drug" relied upon in section 355(b)(2). But section 355(b)(2) uses language in several places to indicate the drug relied upon, yet this kind of language does not appear in the bar clause of the new clinical study exclusivity provision. For example, section 355(b)(2)(A) calls the referenced drug "the drug for which such investigations were conducted"; *see also* 21 U.S.C. § 355(b)(2)(B) ("the drug for which investigations described in paragraph (1)(A) were conducted"). If Congress had intended to make clear that the marketing exclusivity of referenced drugs can block 505(b)(2) applications even if they do not contain a drug product with the same active moiety, it could have written section 355(c)(3)(E)(iii) to make that clear: instead of barring 505(b)(2) drug approvals for "conditions of approval of such drug in the approved subsection (b) application," it could have

barred 505(b)(2) drug approvals for "conditions of approval of such drug for which investigations described in subsection (b)(1)(A) were conducted."

Otsuka attempts to draw much from the fact that sections 355(c)(3)(E)(iii) and (iv) and section 355(b)(2) use nearly the same language to describe what a 505(b)(2) application is. But that does not lead inexorably (or even presumptively) to the conclusion that approval of 505(b)(2) applications must be blocked by any exclusivities of drugs they rely upon for approval, regardless of whether they include the same drug, *i.e.*, same active moiety. The nearly identical language in these provisions[18] merely identifies what a 505(b)(2) application is. Sections 355(c)(3)(E)(iii) and (iv) include this language to indicate that a 505(b)(2) applicant can be blocked by an existing new clinical study exclusivity (as opposed to a 505(b)(1) application, which is not blocked, or an ANDA, which has its own parallel new clinical study exclusivity provisions at 21 U.S.C. §§ 355(j)(5)(F)(iii), (iv)). The FDCA uses this same language in each of the two preceding clauses to identify a 505(b)(2) application. *See, e.g.*, 21 U.S.C. §§ 355(c)(3)(E)(i), (ii).

3. Legislative History Does Not Compel FDA To Apply New Clinical Study Exclusivity Across Active Moieties

In contrast to the little space afforded to its textual argument, Otsuka's discourse on the legislative history pre-dating the passage of the Hatch-Waxman amendments is lengthy (covering approximately ten pages). However, that history paints with a broad brush and never makes the point Otsuka seeks to compel (application of new clinical study exclusivity to altogether different drugs). Therefore, it does not aid Otsuka's argument.

[18] *See* 21 U.S.C. §§ 355(b)(2), (c)(3)(E)(iii), (iv) (a drug for which "the investigations described in clause (A) of [§ 355(b)(1)] 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").

Otsuka's legislative history argument focuses on the idea that the Hatch-Waxman Amendments to the FDCA balanced competing goals: encouraging the development of lower-cost drugs (by way of streamlined approval procedures and incentives to challenge patents) and maintaining incentives for pharmaceutical companies to continue to develop new therapies. Alkermes does not dispute that Congress balanced several goals in the FDCA. But that fact, by itself, does nothing to resolve the specific dispute before the court.

Moreover, FDA appropriately balanced those goals in its decision and, in any event, a court may not substitute its policy judgment for an agency's. *See Mich. Citizens*, 868 F.2d at 1293 (courts "are not now after *Chevron*—if [they] ever were—permitted to accept such an argument" that the agency "put too much weight on [one] policy"). The "paradigm situation *Chevron* addressed" is when an agency "is called upon to balance two legislative policies in tension." *Id.* "If the agency's choice 'represents a reasonable accommodation of conflicting policies that were committed to the agency's care by the statute, we should not disturb it unless it appears from the statute or its legislative history that the accommodation is not one that Congress would have sanctioned.'" *Id*. (quoting *Chevron*, 467 U.S. at 845).

Otsuka argues that the three-year exclusivity provisions were intended to incentivize pharmaceutical companies to invest in new clinical trials on old drugs and that FDA's decision inappropriately de-incentivizes such investment. Dkt. 24-1, at 11-12. Alkermes does not dispute that Congress intended to incentivize certain clinical studies by providing these exclusivities; indeed, incentivizing research and development is the impetus for all marketing exclusivities provided to pharmaceutical products. But the devil is in the details, and the legislative history provides absolutely no detail on the breadth of that three-year exclusivity—*i.e.*, what kinds of

applications it would block. Those details are provided in the text itself, to which (as explained above) Otsuka's motion pays very little heed.

Otsuka's legislative history argument also inappropriately prioritizes its view of "innovation" to the exclusion of all other considerations by Congress in the FDCA, some of which conflict with an overly broad approach to exclusivity. *See AstraZeneca*, 872 F. Supp. 2d at 89 (rejecting NDA holder's attempt to expand its new clinical study exclusivity, noting that while it was "correct to point out that Congress provided exclusivity rights 'as an incentive for pioneer companies to engage in expensive clinical research,'" expanding it as requested "would disrupt the 'careful balance' Congress crafted"). Otsuka has been rewarded for its innovation and will continue to be rewarded for those innovations; Otsuka has eleven listed patents and two existing marketing exclusivities for Abilify Maintena.[19] Its marketing exclusivities are enforceable against 505(b)(2) and ANDA applicants that share its active moiety, aripiprazole, and end there. And that exclusivity apparently is working; Otsuka currently faces no generic competition for Abilify Maintena and instead competes only against other LAIs that feature different active ingredients (and active moieties). This is the extent of the exclusivity Congress provided; nothing more.

As would be expected with respect to a statute that balances competing goals, there is more to the story than the part Otsuka tells with its voluminous but selective string cites of congressional statements about the innovation impetus for three-year new clinical study

[19] Otsuka has made over $100 billion in revenue on its Abilify tablets in just the past eight years, and even more since it began selling Abilify in 2002. *Otsuka Pharm. Co., Ltd. v. Torrent Pharm. Ltd.*, 99 F. Supp. 3d 461, 507 (D.N.J. 2015) ("Otsuka's aripiprazole exclusivity has generated, in the last eight years alone, over $100 billion in revenue."). It has been given fifteen marketing exclusivities, and it has listed ten patents over the life of its drug, some of which have not yet expired. Those patents and exclusivities provided it with sole control of the aripiprazole oral tablet market for over twelve years, until generic Abilify tablets were approved earlier this year.

exclusivity.[20] Otsuka cites nothing to support the idea that Congress was awarding new clinical study exclusivity to block drugs that the applicant with new clinical study exclusivity *never actually studied*.

Otsuka asserts that "Alkermes may only avoid the effect of Otsuka's three-year aripiprazole exclusivity if it forgoes reliance on aripiprazole and files a full 505(b)(1) application," FDA 000294, but such an outcome—in addition to having no textual basis—would frustrate Congress's stated purpose of including the 505(b)(2) approval pathway—to avoid "unnecessary," "wasteful," and potentially "unethical" retesting designed to re-prove a finding FDA already made. *See* H.R. Rep. No. 98-857, at 16 (June 21, 1984) ("FDA considers such retesting to be unnecessary and wasteful because the drug has already been determined to be safe and effective. Moreover, such retesting is unethical because it requires that some sick patients take placebos and be denied treatment known to be effective."). Under Otsuka's theory, to avoid a delay of several years in the approval of Alkermes' unquestionably new drug ARISTADA, Alkermes would have been required to undertake duplicative, lengthy, and wasteful clinical studies, rather than rely on the body of scientific findings FDA has amassed on the old drug, oral aripiprazole. That outcome is just what Congress intended to avoid by permitting 505(b)(2) applications.

Congress could and did reasonably decide not to extend new clinical study exclusivity to block other drugs when balancing the competing objectives addressed by the statute. Neither of Hatch-Waxman's competing goals (promoting innovation and streamlining access to generic

[20] Otsuka merely repeats some of the same congressional statements throughout the brief, and they are all by just two legislators, Representative Waxman and Senator Hatch. *See* Dkt. 24-1, at 11-12, 15.

Otsuka also relies heavily on another case involving the breadth of new clinical study exclusivity on a 505(b)(2) applicant, *Veloxis*, to support its legislative history argument. But Otsuka uses this case merely to rehash the same generalized statements about the competing goals of Hatch-Waxman that do nothing to further Otsuka's arguments about how broadly new clinical study exclusivity may be applied.

drugs) necessarily encompassed preventing competition between different drugs, each of which represents an innovation for patients, and Congress was free to land on the accommodation it did. Notably, none of the congressional statements Otsuka repeats throughout its brief suggests that a goal of the new clinical study exclusivity provisions was preventing competition between two innovative drugs. ARISTADA is an innovative drug. Otsuka does not contest FDA's expert determination that it is a new drug entitled to new chemical entity exclusivity. ARISTADA does not compete against Abilify Maintena as a generic drug; it is not therapeutically substitutable. Otsuka is attempting to assert exclusivity against ARISTADA to prevent legitimate competition; that was not what Congress intended when it enacted the Hatch-Waxman Amendments.

Otsuka also suggests that an earlier version of the 1984 Amendments, which was not adopted, "make[s] clear that the scope of exclusivity is not determined by identical active moieties," relying on the following language: "the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted effective before the expiration of three years." Dkt. 24-1, at 20 n.17. If anything, this unenacted bill shows Congress knew how to link referencing a drug to exclusivity if it wanted to. The fact that it chose not to do so in the law it ultimately passed weighs further against Otsuka's theory. In any event, the D.C. Circuit has cautioned against relying too heavily on unenacted statutory language, particularly in the *Chevron* context. *See, e.g.*, *W. Fuels-Utah, Inc. v. Lujan*, 895 F.2d 780, 786 (D.C. Cir. 1990).

4. Alkermes' Reliance, as a Factual Matter, Does Not Compel FDA To Apply New Clinical Study Exclusivity Across Active Moieties

Even if a reliance/block trade-off could be implied despite the lack of any text creating it, that would still not result in any exclusivities held by Abilify Maintena blocking ARISTADA. That is because ARISTADA's NDA did not reference findings *about Abilify Maintena*. It

referenced findings about Abilify tablets, *which have no exclusivity left for treatment of schizophrenia*.

Otsuka offers no reason why, even if it were correct on its reliance/block trade-off theory, reliance on one drug (Abilify) could lead to *another drug* (Abilify Maintena) blocking approval of the 505(b)(2) application.[21] If anything, Otsuka's argument is a corollary to one argued by another NDA holder in *Takeda*. In *Takeda*, the NDA holder argued that the 505(b)(2) applicant, although it did not reference the NDA holder's drug for approval, should have been required to certify to its patents because it shared the same drug substance as the drug the 505(b)(2) applicant relied upon. This Court held that the statute unambiguously requires only that a 505(b)(2) applicant certify to the patents listed by the reference drug product—and not another drug product. 78 F. Supp. 3d at 97. Otsuka now asks for a rule that a 505(b)(2) applicant's reliance on findings from one drug product (Abilify tablets) means that it is blocked by exclusivities held by any other drug product related to the first drug product in some manner (whether due to drug substance, active moiety, or active ingredient—the precise rule is unclear). Otsuka's reading has even less basis in text than the rule urged by the NDA applicant in *Takeda* and should be rejected as well.

If Otsuka is correct, and the "drug" relied upon must be considered to be the same drug whose exclusivity can bar a 505(b)(2) drug's approval, its interpretation would have far-reaching consequences. It would mean that three-year new clinical study exclusivity, though shorter in length and protecting a more narrow innovation than five-year new chemical entity exclusivity,

[21] *Veloxis* is not the silver bullet that Otsuka claims it is. *Veloxis* does not stand for the proposition that a 505(b)(2) application can rely on findings from one drug and *that reliance on that drug* can make it subject to the exclusivity held by any other drug product containing that drug. *Veloxis* held that FDA permissibly interpreted the new clinical study exclusivity provisions to mean that reliance is *not* a factor in determining whether one drug's exclusivity can block approval of a 505(b)(2) application. *Veloxis*, 2015 WL 3750672, at *8-11. The exclusivity analysis turns instead on whether the drugs have overlapping conditions of use, *id.* at *11, and whether they contain the same active moiety, FDA 000366, precisely what is *not* the case here.

would apply to bar a broader class of drugs—not just those with the same active moiety, but also those with different active moieties. It would also mean that, in addition to Congress's express interest in balancing the interests of innovator drugs against those of lower-cost generics through the Hatch-Waxman amendments, Congress was furthering an un-expressed desire to balance interests between innovator drugs (and that it put its thumb on old innovator drugs instead of new ones). The statute does not bear this interpretation.

5. Otsuka Has Identified No Absurd Results That Would Compel Its Counter-textual Reading

Otsuka argues FDA should be compelled to apply new clinical study exclusivity to different drugs because, it asserts, any other interpretation "leads to the absurd result that an NCE 505(b)(2) is never subject to any non-patent exclusivity." Dkt. 24-1, at 18 n.16. A litigant relying on absurdity to overcome the plain text faces a high bar, *United States v. Cook*, 594 F.3d 883, 890-91 (D.C. Cir. 2010), and a result is not "absurd" just because Otsuka dislikes it. Here, the result is precisely in line with what Congress intended when it sought to balance incentivizing innovation and bringing lower-cost drugs to the market. An NCE 505(b)(2) is an innovation—a new chemical entity. It makes sense that, where an NCE's approval is not blocked by any patents, Congress would not want that approval delayed by a narrower three-year new clinical study exclusivity for a different drug. *See* FDA 000039 n.85 ("[A 505(b)(2) application] for a new chemical entity would not be subject to any patent protection or exclusivity accorded a previously approved drug, because, by definition, there will be no applicable previously approved drug." (citing Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, 28,890 (July 10, 1989))).

For all of these reasons, Otsuka has failed to show that there is a clear and unambiguous interpretation of the statutory provisions that compels the reading it advances. Therefore, Otsuka cannot prevail in its challenge under *Chevron* step one.

B. FDA's Decision That New Clinical Study Exclusivity Applies Only to Drugs That Share an Active Moiety Is a Reasonable Interpretation of the Statute and Owed Substantial Deference

Otsuka's challenge under *Chevron* step two fares no better. FDA's considered response to Otsuka's July 2015 Citizen Petition, which it issued only after the submission of over three hundred pages of briefing and exhibits, is due substantial deference. *See Mylan Labs., Inc.*, 389 F.3d at 1279-80 (deferring to FDA decision "expressed in letters to the parties," reasoning that Congress intended for courts to defer to the agency's interpretation of the FDCA when resolving exclusivity disputes through letter decisions because "[t]here is no denying the complexity of the statutory regime under which the FDA operates, the FDA's expertise or the careful craft of the scheme it devised to reconcile the various statutory provisions"); *see also AstraZeneca*, 713 F.3d at 1137-38; *ViroPharma*, 898 F. Supp. 2d 13; *Barr Labs., Inc. v. Thompson*, 238 F. Supp. 2d 236, 245-50 (D.D.C. 2002). Otsuka provides no basis for finding that FDA has impermissibly construed the FDCA's new clinical study exclusivity. *See Bluewater Network*, 372 F.3d at 410 (quoting *Chevron*, 467 U.S. at 843) (courts must "defer to the agency's interpretation as long as it is 'based on a permissible construction of the statute'").

1. FDA Has Reasonably Construed Sections 355(c)(3)(E)(iii) and (iv) and Its Implementing Regulations To Apply New Clinical Study Exclusivity Only to Drugs That Share an Active Moiety

FDA reasonably interprets the phrase "conditions of approval of such drug in the approved subsection (b) application," 21 U.S.C. § 355(c)(3)(E)(iii), to mean that other 505(b)(2) drugs that share the "conditions of approval" and "drug" (meaning its active moiety) in the approved NDA, can be blocked by the NDA's new clinical study exclusivity. And FDA likewise

interprets the phrase "change approved in the supplement," 21 U.S.C. § 355(c)(3)(E)(iv), to be no broader than its sister provision in section 355(c)(3)(E)(iii). As explained above, FDA's interpretation is consistent with the text, structure, and purpose of the statute—and is far more plausible than the competing interpretation that Otsuka proffers, which ignores key statutory language ("such drug") while inserting other language (a "reliance" requirement) that Congress did not use. Certainly, Otsuka has not shown that FDA's preferred reading is "arbitrary, capricious, or manifestly contrary to the statute." *Chevron*, 467 U.S. at 844.

Otsuka also asserts that FDA violated its own regulations when it approved ARISTADA despite Abilify Maintena's new clinical study exclusivities. But an agency's interpretation of its own regulations is "*controlling* unless plainly erroneous or inconsistent with the regulation." *Auer v. Robbins*, 519 U.S. 452, 461 (1997) (emphasis added, citation and internal quotation marks omitted); *accord Serono Labs.*, 158 F.3d at 1320. This standard requires an "even greater degree of deference" than that provided under *Chevron. Consarc Corp. v. U.S. Treas. Dep't, Office of Foreign Assets Control*, 71 F.3d 909, 915 (D.C. Cir. 1995).

FDA appropriately applied the regulations it promulgated to implement sections 355(c)(3)(E)(iii) and (iv) and (j)(5)(F)(iii) and (iv) when it approved ARISTADA. Those regulations appear at 21 C.F.R. §§ 314.108(b)(4) and (b)(5):

> 21 C.F.R. § 314.108(b)(4): When "an application" was approved and "was for a drug product that contains an active moiety that has been previously approved in another application and . . . 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 . . . the approval of a 505(b)(2) application or an [ANDA] for the conditions of approval of the original application . . . ."
>
> 21 C.F.R. § 314.108(b)(5): When a "supplemental application" was approved and "contained reports of new clinical investigations (other than bioavailability studies) 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 . . . the approval of a 505(b)(2) application or an [ANDA] for a change . . .

approved in the supplemental new drug application."

FDA's regulations are entirely consistent with FDA's interpretation of the statutory provisions they implement. Just like the statute, they set forth an application's eligibility for exclusivity, and then what that exclusivity will bar. 21 C.F.R. § 314.108(b)(4) makes an "application" "for a drug product" eligible for exclusivity if it "contains an [old] active moiety" and "contained reports of [certain] new clinical investigations" "essential to the approval of the application." That exclusivity bars 505(b)(2) applications and ANDAs for the "conditions of approval *of the original application*." *Id.* (emphasis added). Just as in the statute, the pertinent question is, which "original application"? And just like in the statute, FDA interprets it as the one referenced earlier in the provision—the one for a specific drug product with a specific active moiety that completed a specific clinical study and obtained a specific approval as a result (here, Abilify Maintena).

21 C.F.R. § 314.108(b)(5) is also consistent with FDA's interpretation of the statute it implements. The regulation applies to "supplemental applications," and bars approval of 505(b)(2) applications and ANDAs for "a change approved in the supplemental application" (language that tracks 21 U.S.C. § 355(c)(3)(E)(iv)). FDA applies the regulation just as it interprets the statute, as only barring applications for a change approved in the supplemental application, which was a change to a drug product containing a certain active moiety.

When FDA proposed these rules in 1989 pursuant to notice-and-comment rulemaking, it gave fair notice of the interpretation at issue here. FDA made clear that it "does not believe that Congress intended the exclusivity provisions to operate inconsistently, or 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." FDA 001286. The regulation

covering NCE exclusivity, which FDA promulgated with the rules for new clinical study exclusivity, provides:

> 21 C.F.R. § 314.108(b)(2): When "a drug product that contains a new chemical entity . . . no person may submit a 505(b)(2) application or abbreviated new drug application under section 505(j) of the act 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 . . . ."

FDA's NCE regulation plainly links exclusivity to a drug's active moiety. FDA's application of new clinical study exclusivity here is consistent with NCE exclusivity (linking exclusivity to a drug's active moiety), just as FDA announced in 1989 that it would be.

2. FDA's Interpretation Is Well In Line With the Statute's Language and Purpose

Otsuka asserts that "FDA's decisions frustrate the policy goals of the Hatch-Waxman Amendments," Dkt. 24-1, at 25-26, but its argument merely re-asserts and re-hashes the same legislative history argument it made to argue its statutory reading is compelled by the FDCA. It fares no better under the lens of *Chevron*'s second step. FDA's decision preserves the incentive to innovate in two ways: (1) by preserving Abilify Maintena's exclusivities as to other drugs that share its active moiety, and (2) by rewarding Alkermes' innovation in creating a new chemical entity by approving ARISTADA without delay. Its decision also best carries out the policy goals of the 505(b)(2) approval pathway: (1) avoiding repetitive and unnecessary clinical trials, and (2) promoting efficiency by allowing FDA to rely on findings it has already made on a drug.

3. FDA's Decision Is Consistent With Its Approach to Marketing Exclusivities

FDA's decision that new clinical study exclusivity is limited to the drug studied is consistent with FDA's approach to other marketing exclusivities, including five-year NCE exclusivity. FDA reasonably explained in its Citizen Petition response that five-year NCE exclusivity, which blocks submission of other drugs with that same chemical entity, "was

intended to reward the types of changes that Congress believed likely to be the most innovative." FDA 000363. Thus, FDA reasoned, "the range of drugs blocked by exclusivity for a less innovative change (i.e., those changes covered by 3-year exclusivity)" should not be "broader than the range of drugs that are blocked by exclusivity for a more innovative change (i.e., those protected by 5-year exclusivity)." *Id.* Tethering exclusivity to the active moiety in the approved drug in both NCE exclusivity and new clinical study exclusivity effectuates that end.

FDA also reasoned that it would "be inconsistent for the scope of exclusivity for studies that are essential to the approval of a supplement to an NDA to be broader than the scope of exclusivity for studies that are essential to the approval of an original NDA." *Id.* Thus also tethering exclusivity to the active moiety in the approved "change" in the supplement achieves that end.

FDA's decision to decline to apply new clinical study exclusivity across active moieties is also consistent with its approach to other marketing exclusivities in the FDCA. For example, the FDCA limits seven-year orphan drug exclusivity to "such drug for such disease or condition." 21 U.S.C. § 360cc(a). A Maryland district court recently rejected an attempt by Otsuka to expand this orphan drug exclusivity beyond its reasonable bounds. *Otsuka Pharm. Co.*, 2015 WL 3442013, at *11 (noting Otsuka's position "def[ied] logic"). Rejecting Otsuka's premise that Congress intended a seven-year orphan drug exclusivity it gave to "such drug for such disease," 21 U.S.C. § 360cc(a), to block that drug for *other diseases*, the court looked to language of the statute itself, which FDA appropriately applied to "such drug for such disease." *Id.* at *13. The court deferred to FDA's eminently reasonable conclusion that orphan drug exclusivity does not extend beyond "such disease." *Id.* at *14. Otsuka attempts the flipside of

that argument here—that the "such drug" in new clinical study exclusivity actually extends beyond "such drug." It too "defies logic." *See id.* at *11.

Contrary to Otsuka's argument, Dkt. 24-1, at 26-27, FDA's Citizen Petition response to arguments raised by Pfizer, the manufacturer of Xalatan, does not bar the approach FDA took to Otsuka's Citizen Petition. As FDA explained, Pfizer sought an FDA decision on completely different issues. FDA 000365 n.87. In 2006, Pfizer submitted a Citizen Petition urging FDA not to approve certain 505(b)(2) applications because (1) a 505(b)(2) applicant's reliance on findings of safety and efficacy of Xalatan would constitute a "taking" and violation of the Trade Secrets Act; (2) findings from Xalatan did not provide substantial evidence establishing the safety and efficacy of the 505(b)(2) drug; and (3) FDA should require the 505(b)(2) applicant to conduct additional clinical trials. FDA 001517-18. As FDA noted, Pfizer *did not* seek a decision from FDA on the scope of its new clinical study exclusivity, or argue that any exclusivity it had applied to the 505(b)(2) drug. FDA 000365 n.87. FDA's statement about exclusivity was gratuitous and, in any event, moot at the time it was made because, at the time FDA issued its Citizen Petition response in 2010, any potential exclusivity held by Xalatan had expired. As FDA appropriately explained, now that it has been squarely presented with the issue of whether one drug's new clinical study exclusivity can block that of another drug with a different active moiety, it thoroughly analyzed the relevant text and came to a reasoned conclusion that the answer is no. *Id.*

Just as it did here by limiting new clinical study exclusivity to the active moiety studied in the application, FDA regularly refuses to extend marketing exclusivity any more broadly than Congress intended. FDA has limited the drug Diprivan's new clinical study exclusivity to "the 'change approved in the supplement,'" *i.e.*, the inactive ingredient (a preservative) actually

studied, and not to drugs containing other preservatives not studied. *See Zeneca Inc. v. Shalala*, No. CIV.A WMN-99-307, 1999 WL 728104, at *12 (D. Md. Aug. 11, 1999) (rejecting challenge to FDA's approval of an ANDA as arbitrary and capricious in alleged violation of NDA's exclusivity rights under 21 U.S.C. § 355(j)(5)(F)(iv)), *aff'd*, 213 F.3d 161 (4th Cir. 2000). FDA has also refused to extend Seroquel's new clinical study exclusivity to an informational table included in its labeling that did not result from the clinical studies that gave rise to its exclusivity. *AstraZeneca*, 872 F. Supp. 2d at 85 (deferring to FDA's conclusion that the "statute to require a 'nexus between the subject of the new clinical investigations and the changes to the product that the investigations support'"); *see also ViroPharma*, 898 F. Supp. 2d at 21 ("FDA was within its discretion to apply a limiting principle so that Hatch–Waxman's exclusivity provisions do not apply to *all* approved changes that are 'new'. . . . [T]he general exclusivity period provided in § 355(j)(5)(F)(iv) . . . is itself limited to that which is 'new' about the given drug.").

Veloxis presents the flipside of the situation presented in this case, and also supports FDA's decision in this case. In *Veloxis*, the 505(b)(2) application and NDA with new clinical study exclusivity contained the same active moiety, tacrolimus. FDA 000354. And although the 505(b)(2) applicant *did not rely* on findings from the NDA holder's drug, the 505(b)(2) drug was still blocked (*in part*) by the NDA holder's exclusivities because it contained the same active moiety as, and shared certain "conditions of approval" with, the NDA. *Id.*; *see also Veloxis*, 2015 WL 3750672 at *11. There, FDA made clear that "[r]eliance is not a prerequisite for exclusivity under the unambiguous statutory text." Federal Defendants' Br. in Support of Summ. J., Dkt. 61, at 38, *Veloxis*, No. 14-cv-2126 (D.D.C. July 24, 2015); *see also id.* at 38 ("The phrase 'relied upon' *does not*, as Veloxis asserts, mean that reliance is required to trigger exclusivity."). FDA acted there, as it did here, completely in line with that analysis; reliance was and is not the

trigger for exclusivity.

II. FDA's Interpretation of 21 C.F.R. § 314.108(b) Is Not a Legislative Rule

Otsuka claims that FDA's interpretation of its exclusivity rules, 21 C.F.R. §§ 314.108(b)(4) and 314.108(b)(5), required notice and comment under the APA because that interpretation supposedly created new legislative rules. This argument is meritless. As FDA correctly explained (in the course of rejecting Otsuka's separate and now abandoned legislative-rule argument),[22] the agency's approval of ARISTADA and corresponding denial of Otsuka's Citizen Petition were an "informal adjudication that does not require rulemaking." FDA 000371. Interpretations and clarifications of existing statutes and regulations offered in the course of informal adjudications do not need to go through notice-and-comment review. The fact that such an interpretation may serve as a "precedent" in future adjudications—because reasoned decision-making requires agencies to engage with prior decisions—does not transform the agency's adjudicative order into a "rule" as defined by the APA, 5 U.S.C. § 551(4). And to the extent the reasoning in an FDA decision letter adjudicating an exclusivity dispute could somehow be considered a "rule," FDA at most provided an interpretive rule (not a legislative one) because it did no more than clarify how FDA construes existing statutes and regulations. The Court should accordingly reject Otsuka's argument that FDA's application of the FDCA and its exclusivity regulations constituted legislative rulemaking that requires notice and comment.

A. FDA's Decision Was an Adjudication, Not a Rulemaking

"Agencies enjoy broad discretion to choose the form of their proceedings." *Global Crossing Telecomms., Inc. v. FCC*, 605 F. App'x 4, 5 (D.C. Cir. 2015) (per curiam). Agencies can (and often do) interpret statutes and implement regulations in adjudicatory proceedings. *See*

[22] In contending that the ARISTADA NDA could not be approved without at least two adequate and well-controlled clinical trials, Otsuka claimed any deviation from the purportedly "settled interpretations regarding the necessity of two AWCTs" would constitute a legislative rule. FDA 000043.

Conference Grp. LLC v. FCC, 720 F.3d 957, 965 (D.C. Cir. 2013) (observing that an FCC order was "neither a legislative nor an interpretative rule" but "[r]ather . . . simply an interpretation given in the course of an informal adjudication"). Nor does the fact that the reasoning of an order "rendered in an adjudication 'may affect agency policy and have general prospective application'" transform the agency's adjudicatory order "into a rulemaking subject to APA section 553 notice and comment." *Id.* "[T]he nature of adjudication is that similarly situated non-parties may be affected by the policy or precedent applied, or even merely announced in dicta, to those before the tribunal." *Goodman v. FCC*, 182 F.3d 987, 994 (D.C. Cir. 1999) (citation omitted)).

Here, FDA's application of the FDCA and its codified regulations in resolving a specific dispute was "simply an interpretation given in the course of an informal adjudication." *Conference Grp.*, 720 F.3d at 965. FDA regularly issues similar interpretive decisions in precisely this manner, and courts defer to the agency's efforts—deferring, for example, to letter decisions issued to the interested parties, which "reasonably resolve[] ambiguity" in the relevant statutes and regulations and arise in a particular "factual situation." *Mylan Labs.*, 389 F.3d at 1280, 1284; *see ViroPharm*, 898 F. Supp. 2d at 17-18. Indeed, given the nature of the complex regulatory scheme under which the agency operates, it would be completely unreasonable to require FDA to delay approval of drugs it has already found are safe and effective—and deprive the public of access to those drugs—in order to go through a lengthy rulemaking process resolving interstitial interpretive questions that might only apply to a handful of NDAs. Neither the FDCA nor the APA condemns FDA to such inefficiency.

Otsuka nevertheless claims that its case is unique, and that FDA's letter decision to approve Alkermes' NDA "went well beyond an 'adjudication' by amending a current (and

properly promulgated) rule and applying it retroactively," thereby "setting forth an 'interpretation' of its statute, regulations, science, and policy, not just adjudicating a particular case." Dkt. 24-1, at 37. But agencies frequently (and lawfully) announce new interpretations and policies in the course of adjudications, and those interpretations may be applied retroactively, *Consol. Freightways v. NLRB*, 892 F.2d 1052, 1058 (D.C. Cir. 1989), so long as there is no unfair surprise, *see Otis Elevator Co. v. Sec'y of Labor*, 762 F.3d 116, 125 (D.C. Cir. 2014) (deferring to the Secretary of Labor's interpretation of Occupational Safety and Health Act regulations rendered in an adjudication and also acknowledging presence of fair notice). And for all of the reasons Otsuka's substantive arbitrary-and-capricious challenge fails in this case, there was no unfair surprise: Otsuka "has not identified any pattern of contrary practice by [FDA] or contrary interpretations by the [agency]." *Otis Elevator*, 762 F.3d at 125.

B. Even If FDA's Interpretations Could Be Called "Rules," They Are Not Legislative Rules

Even if FDA's letter decision could be understood to promulgate a "rule" as the APA uses that term, any such rule would be interpretive (rather than legislative), and interpretive rules do not require notice-and-comment. *See* 5 U.S.C. § 553(b)(A). An interpretive rule, which Otsuka never bothers to define, "advise[s] the public of the agency's construction of the statutes and rules which it administers." *Perez v. Mortg. Bankers Ass'n*, 135 S. Ct. 1199, 1204 (2015) (citation and internal quotation marks omitted).

Here, FDA's letter decision simply explained how it interpreted FDCA provisions and regulations pertaining to marketing exclusivity. FDA provided an explanation as to the meaning of the phrases "conditions of approval of such drug" and "a change approved in the supplement." FDA 000352-354. Presented with the question of how to apply terms that had not been specifically defined by either the FDCA or the implementing regulations, FDA clarified their

scope in order to determine drug exclusivity here. In doing so, FDA did not "adopt[] a new position inconsistent with" existing regulations or otherwise enact a "substantive change in the law." *Shalala v. Guernsey Memorial Hosp.*, 514 U.S. 87, 100 (1995). Its actions were therefore at most "[i]nterpretive rules" and exempt from notice and comment. *Id.* at 99-100.

Otsuka incorrectly suggests that, because FDA's interpretations did not repeat the exact wording of the regulations, they are "inconsistent" with the promulgated regulations and therefore must be treated as legislative rules. Dkt. 24-1, at 26-27, 36. The D.C. Circuit has long rejected this approach, which would rob interpretive rules of any utility. Under Otsuka's approach, "no rule could pass as an interpretation . . . unless it were confined to parroting the rule or replacing the original vagueness with another." *Am. Mining Cong. v. Mine Safety & Health Admin.* 995 F.2d 1106, 1112 (D.C. Cir. 1993). Instead, the D.C. Circuit has held that agencies are free to supply "crisper and more detailed lines than the authority being interpreted" without triggering an obligation to go through time-consuming, notice-and-comment rulemaking. *Id*. That is precisely what FDA did here, and the Court should accordingly reject Otsuka's procedural APA challenge even if FDA's informal adjudication somehow announced a rule.

III. If the Court Finds an APA Violation, the Facts of This Case Counsel in Favor of Remand Without Vacatur

Even if this Court were to find FDA's decision violates the APA in some manner, that finding would not establish that Otsuka is entitled to block Alkermes' approval. Rather, the scope of Otsuka's exclusivity would have to be determined by the agency on remand, and Otsuka has not shown any basis for vacating Alkermes' approval pending the outcome of that remand.

This Court has the equitable discretion to remand without vacating FDA's approval of ARISTADA. *See Allied-Signal, Inc. v. U.S. Nuclear Regulatory Comm'n*, 988 F.2d 146, 150-51 (D.C. Cir. 1993). Courts must look to both "the seriousness of the order's deficiencies (and thus

the extent of doubt whether the agency chose correctly) and the disruptive consequences of an interim change that may itself be changed." *Id.* Where there is little doubt that the agency's decision will ultimately be upheld, or vacatur in the interim period would cause serious disruption, the court should decline to vacate the agency's decision on remand. *See Williston Basin Interstate Pipeline Co. v. FERC*, 519 F.3d 497, 504 (D.C. Cir. 2008); *Sprint Commc'ns Co. v. FCC*, 274 F.3d 549, 556 (D.C. Cir. 2001); *Int'l Union, United Mine Workers v. FMSHA*, 920 F.2d 960, 966-67 (D.C. Cir. 1990). Here both conditions are met.

First, there is a strong possibility that on remand, FDA would determine that any exclusivity held by Abilify Maintena does not block ARISTADA. Because FDA found that Otsuka's claim of exclusivity failed at the threshold inquiry (because the products do not share an active moiety), FDA has not yet carried out all steps of its exclusivity analysis.[23] As an initial matter, the exclusivity that Otsuka repeatedly asserts should block ARISTADA—its "new dosage form" exclusivity, will expire shortly, on February 28, 2016. And FDA has not yet determined whether, and to what extent, the "change" approved in Abilify Maintena's supplement on December 5, 2014, was eligible for exclusivity (which expires December 5, 2017) as both "new" and "essential" to the supplement's approval. Nor has FDA determined whether the "change," which added labeling language regarding a clinical study utilizing aripiprazole on acutely-relapsed patients, overlaps with ARISTADA's labeling. Both are matters to which the agency must apply its expertise in the first instance. *See Veloxis*, 2015 WL 3750672, at *12 (deferring to FDA's scientific determination of the scope of marketing exclusivity); *ViroPharma*,

[23] FDA also might reasonably conclude, on remand, that if the drug whose findings a 505(b)(2) application references for approval has any relevance to the extent to which approval of that 505(b)(2) can be blocked by another NDA's exclusivities, a 505(b)(2) application cannot be blocked by exclusivities of a drug product on whose findings it did not rely and with which it does not share an active moiety. This reading would be entirely consistent with *Veloxis*, where the NDA whose exclusivities blocked certain conditions of approval of a 505(b)(2), shared the same active moiety. *Veloxis*, 2015 WL 3750672, at *4 (noting that both Astagraf XL, the reference-listed drug, and Envarsus XR, the 505(b)(2) applicant drug, were tacrolimus formulations); *see also* FDA 000366.

898 F. Supp. 2d at 22 (same). Studies are not "essential" to a supplement's approval if, for example, other pre-existing information in the NDA could have supported the "change." *ViroPharma*, 898 F. Supp. 2d at 22. Once these prerequisites are met, the identified "change" would only block other drugs if the other drugs include that "change" in their labeling. *Id.* at 7. Thus, generic drugs and 505(b)(2) drugs are often approved despite highly specific marketing exclusivities for drugs with the same active moiety because the generic drugs and 505(b)(2) drugs "carve out" the specific exclusivity from their labeling. *See, e.g.*, *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996) (upholding FDA's interpretation that an ANDA product is not blocked by three-year exclusivity if its label carves out the indication for which the exclusivity was granted); *Otsuka Pharm. Co.*, 2015 WL 3442013, at *14. And though *Orange Book* descriptions of exclusivities are not controlling on FDA, it is notable that the notation for Abilify Maintena's exclusivity that expires December 5, 2017 is quite narrow, listed as "addition of the results of a controlled clinical study treating adult patients with schizophrenia experiencing an acute relapse." FDA 000361. ARISTADA should not be blocked by Abilify Maintena's exclusivity, which appears at most to cover the publication of the results of its own study on an extended-release formulation of aripiprazole.

Second, vacatur here would have severely disruptive effects on those patients who are currently taking ARISTADA. *See Defenders of Wildlife v. Jackson*, 791 F. Supp. 2d 96, 115 (D.D.C. 2011) (remanding without vacatur because vacatur would result in, *inter alia*, "serious adverse implications for public health and the environment" and "farmers in Colorado, Kansas, Nebraska, Oklahoma, Texas, and Wyoming would be unable to use" the product); *see also A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1492 (D.C. Cir. 1995) (remanding without vacatur because removing drug from market "would prove disruptive to Philips Roxane, which has relied

on [the approval] in good faith" and "nothing in the record suggests that significant harm would result from allowing the approval to remain in effect pending the agency's further explanation"). Schizophrenia can be a debilitating disease when symptoms are uncontrolled. Its symptoms can be severe, involving hallucinations, psychosis, delusions, lack of emotion, energy, and motivation, and, when uncontrolled, the outcomes can be even more severe, involving illicit drug use, alcoholism, homelessness, and suicide. ARISTADA is effective in treating schizophrenia symptoms and provides benefits to patients not otherwise available, such as flexibility to go up to six weeks between treatments, and a relatively forgiving grace period for missed doses.[24] FDA 001223-24. Removing ARISTADA from the market could adversely impact those patients currently on ARISTADA, unnecessarily subjecting them to acute outbreaks of symptoms they otherwise would not experience. *See* Peter F. Buckley & Christoph U. Correll, *Strategies for Dosing and Switching Antipsychotics for Optimal Clinical Management*, 69 J. Clin. Psychiatry 4, 14 (2008), Decl. of Sarah K. Frederick, Exh. 1. ("With few exceptions, abrupt switching of antipsychotics is neither advisable nor necessary."). This potential harm to patients counsels strongly against vacating FDA's approval of a drug not due to any issue of safety or efficacy, but because of a narrow marketing exclusivity claimed by a different drug.

CONCLUSION

For the foregoing reasons, Alkermes respectfully requests that the Court grant its motion for summary judgment and deny Otsuka's.

[24] Abilify Maintena's labeling, by contrast, only permits dosing every four weeks and has relatively shorter grace periods for missed doses. FDA 000545-46.

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