IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

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

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MEMORANDUM IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

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INTRODUCTION

Plaintiffs Otsuka Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Development & Commercialization, Inc., and Otsuka America Pharmaceutical, Inc. ("Otsuka") challenge the lawfulness of final agency actions of the defendant United States Food and Drug Administration ("FDA"). Specifically, Otsuka challenges FDA's denial of Otsuka's Citizen Petition and FDA's final approval of the New Drug Application ("NDA") submitted by the intervenor-defendant Alkermes, Inc. ("Alkermes")[1] for aripiprazole lauroxil (Aristada®). A.R. 342-72, 1217-80. For the reasons set forth in this memorandum, FDA's decisions are unlawful and should be reversed and vacated.

The Hatch-Waxman Amendments to the federal Food, Drug and Cosmetic Act ("FDCA"), *see* Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. 98-417, 98 Stat. 1585 (1984), are at the core of this case. Those amendments were intended to incentivize innovation and get cheaper drugs to the public more quickly. One way the Hatch-Waxman Amendments achieved these twin goals was by creating a shortcut pathway to the FDCA's burdensome and costly full drug approval process, allowing drug manufacturers to meet the approval requirements by submitting an NDA that relies on FDA's determinations of safety or effectiveness for a previously approved drug. This very substantial Hatch-Waxman benefit—the right to shortcut the standalone NDA process and to rely on the studies of a previously approved drug in the absence of a license to do so—comes, however, with the corresponding Hatch-Waxman tradeoff of the applicant's being subject to the exclusivity rights of the previously approved drug on which the applicant relies. Here, Alkermes undeniably took advantage of the benefit of the shortcut; however, FDA unlawfully allowed Alkermes to avoid the tradeoff and come to market

[1] Alkermes Pharma Ireland Limited is also an intervenor-defendant in this action and with Alkermes, Inc., is collectively referred to as Alkermes.

despite, and in violation of, Otsuka's earned exclusivity for the approved conditions of use of Abilify Maintena®.

Otsuka challenges FDA's decisions on three separate grounds. First, FDA's actions violate the plain text of the three-year exclusivity provisions in Sections 505(c)(3)(E)(iii)&(iv) of the FDCA. Second, FDA's actions violate the agency's regulations interpreting the exclusivity provisions in 21 C.F.R. § 314.108(b)(4)&(b)(5). Third, in its decision denying Otsuka's citizen petition, FDA engaged in unlawful rulemaking by *de facto* promulgating a "rule" as defined by the Administrative Procedure Act ("APA") without following the APA's mandatory notice-and-comment rulemaking procedures.

STATEMENT OF FACTS FROM THE ADMINISTRATIVE RECORD[2]

I. Otsuka's NDAs And Related Exclusivity Rights

Otsuka holds an approved NDA for Abilify®, an atypical antipsychotic of aripiprazole indicated for the treatment of schizophrenia and other uses. A.R. 373-486. Abilify tablets are administered once-daily. *Id.* 403-86. On February 28, 2013, FDA approved Otsuka's NDA for Abilify Maintena, a long-acting injectable of aripiprazole for the treatment of schizophrenia in maintaining symptom control in stabilized patients. *Id.* 487-542. On December 5, 2014, FDA approved a supplemental New Drug Application ("sNDA") for Abilify Maintena that was supported by clinical trial data demonstrating the efficacy of the long-acting injectable of aripiprazole in acutely relapsing patients. *Id.* 607-18, 543-98.

Abilify Maintena was a significant advance over the Abilify tablet. The long-acting injectable provided patients with schizophrenia a quite different and, for many, a much improved treatment option. A once-monthly dosage is administered more easily than a daily tablet (a doctor

[2] Pursuant to Local Rule 7(h)(2), Otsuka is not submitting a separate "statement of material facts as to which the moving party contends there is no genuine issue."

need only see a patient once every 30 days to ensure treatment for the next 30 days), thus decreasing the risk of missing a dosage and preventing the disease from relapsing or progressing. *See id.* 1169. Because of Otsuka's investment in developing further uses of aripiprazole to treat schizophrenia, Otsuka received three-year marketing exclusivity covering long-acting aripiprazole for the conditions of use of treatment of schizophrenia in maintenance patients under Section 505(c)(3)(E)(iii) (Feb. 2013 NDA) and acutely relapsing patients under Section 505(c)(3)(E)(iv) (Dec. 2014 sNDA). *Id.* 599-606, 611-18. The latter of these exclusivities does not expire until December 2017. *Id.* 356.

II. The Alkermes NDA

On August 22, 2014, Alkermes submitted an NDA to FDA under Section 505(b)(2) for Aristada (aripiprazole lauroxil). *Id.* 1217. Following the announcement of its 505(b)(2) NDA, Alkermes repeatedly and aggressively hyped its product as simply a prodrug[3] of aripiprazole, with the active moiety of aripiprazole. *See, e.g.*, Richard Pops, Chairman and CEO, Alkermes' CEO Presents at Goldman Sachs Healthcare Conference (June 11, 2013) ("[T]he active moiety is aripiprazole."); Richard Pops, Chairman and CEO, Alkermes CEO Presents at Citi Global Healthcare Conference (Feb. 25, 2013) ("Once in the body this more complicated molecule . . . clips down to Aripiprazole, for the active moiety in the blood stream of these patients for the month and time is Aripiprazole, and that way we can build off of a huge clinical foundation of safety and efficacy of this molecule."); Jim Frates, Senior VP and CFO, Alkermes' Management Presents at Deutsche Bank 38th Annual dbAccess Health Care Conference (May 29, 2013) ("[W]hat we are

[3] Prodrugs are "'[a] class of drugs, the pharmacologic action of which results from conversion by metabolic processes within the body (biotransformation).'" A.R. 349. They "are themselves pharmacologically inactive compounds that are converted into biologically active substances in a variety of ways, including by hydrolysis of ester or amide linkages, or by other metabolic processes." *Actavis Elizabeth LLC v. FDA*, 689 F. Supp. 2d 174, 176 n.3 (D.D.C.), *aff'd*, 625 F.3d 760 (D.C. Cir. 2010).

trying to do is deliver Aripiprazole, native Aripiprazole, over the course of a month."); Richard Pops, Chairman and CEO, Alkermes' CEO Presents at Bank of America Merrill Lynch Smid Cap Conference (May 8, 2013) ("Our product is a prodrug, the prodrug of Aripiprazole designed specifically to be an injectable product once a month. Once it's injected, it fits comfortably in the muscle for a long period of time and it [metabolizes] and releases Aripiprazole."); *see also* James Frates, CFO, Alkermes' Management Presents at Credit Suisse 2012 Healthcare Conference (Nov. 14, 2012) ("[O]ne of the questions we don't have to answer in the clinical program [for Aristada] is whether [Otsuka's drug] ABILIFY actually treats schizophrenia.").[4]

FDA agreed with Alkermes's assessment until September 28, 2015—seven days before FDA approved Aristada and denied Otsuka's petition. Prior to that, FDA, like Alkermes, found repeatedly that the active moiety of aripiprazole lauroxil was aripiprazole. A.R. 784 (Apr. 20 clinical pharmacology review) ("[T]he efficacy contribution only from the IM injection (i.e. aripiprazole lauroxil without any oral aripiprazole) was additionally confirmed using the following rationales: . . . by comparing ***aripiprazole exposure (i.e. the active moiety)*** on day 85 vs. day 29."); 1038 (Apr. 30 pharmacology/toxicology NDA/BLA review and evaluation) ("Following intramuscular injection, aripiprazole lauroxil is converted to the ***active moiety, aripiprazole***."); 1117 ("After intramuscular administration, aripiprazole lauroxil is converted to the ***active moiety, aripiprazole***. . . . Exposure levels to the ***active moiety, aripiprazole***, and the main aripiprazole metabolite, dehydro-aripiprazole . . . ."); 1131 (Aug. 13 tertiary pharmacology/toxicology review) ("This NDA relied, in part, on the Agency's finding of safety for aripiprazole, which is reasonable

[4] All available at: http://seekingalpha.com/article/1500922-alkermes-ceo-presents-at-goldman-sachs-healthcare-conference-transcript?part=single; http://seekingalpha.com/article/1222541-alkermes-ceo-presents-at-citi-global-helathcare-conference-transcript?part=single; http://seekingalpha.com/article/1467941-alkermes-management-presents-at-deutsche-bank-38th-annual-dbaccess-health-care-conference-transcript; http://seekingalpha.com/article/1415361-alkermes-ceo-presents-at-bank-of-america-merrill-lynch-smid-cap-conference-transcript; http://seekingalpha.com/article/1009251-alkermes-management-presents-at-credit-suisse-2012-healthcare-conference-transcript?part=single.

because the active moiety is the same.") (emphases added).

On September 28, 2015, FDA abruptly changed its mind. *Id.* 1133 (Sept. 28, 2015 addendum to pharmacology/toxicology review) ("The Review (e.g., Section 1.2) refers to aripiprazole as the active moiety. However, ***the active moiety is N-hydroxymethyl aripiprazole, not aripiprazole***. Although the Review included some background information on aripiprazole lauroxil and some chemistry, the active moiety determination for aripiprazole lauroxil and related chemistry will be documented in a memorandum by Dr. Norman Schmuff."). FDA then attempted to sweep away its past analyses that the active moiety of aripiprazole lauroxil was aripiprazole in a cryptic footnote to the Division Director's Summary Review of Aristada. *Id.* 1189 ("I note that some disciplinary reviews included background information on aripiprazole lauroxil and incorrectly referred to the active moiety as ariprazole [sic] and also included various inaccurate statements regarding the related chemistry. These incorrect characterizations were not essential to their reviews. Further, the primary review for the active moiety (or NCE) determination is set forth in Dr. Schmuff's memo and I agree with it.").

On October 5, 2015, hard on the heels of FDA's change of mind (*i.e.*, seven days after), FDA approved Alkermes's 505(b)(2) NDA for Aristada. A.R. 1217-20. FDA evaluated the efficacy of aripiprazole lauroxil extended release intramuscular injection in one phase 3 safety and efficacy study that demonstrated efficacy in only two of the approved doses (441mg and 882mg) both given monthly (not every six weeks). *Id.* 1177. Without dispute, however, FDA also necessarily relied on its "previous finding of safety and efficacy from oral aripiprazole tablets . . . as evidence, along with pharmacokinetic evidence from [Alkermes's] studies that demonstrate similar serum concentrations for oral aripiprazole given daily at approved doses and aripiprazole lauroxil given monthly at the studied doses." *Id.*

FDA's review of the Aristada NDA makes clear that the efficacy of aripiprazole lauroxil is due to aripiprazole and aripiprazole-related active metabolites and not Alkermes's "innovation." Alkermes's only so-called "innovation" was in creating a long-acting formulation that would deliver aripiprazole to treat schizophrenia. *Id.* 665 ("According to Alkermes, '[d]evelopment of aripiprazole lauroxil was undertaken to improve upon the clinical profile of a depot antipsychotic injection while benefiting from the clinical and safety profile of the parent compound, aripiprazole.'"). Alkermes's drug delivers aripiprazole to treat schizophrenia. Indeed, FDA's review recognizes that only aripiprazole has been proven to treat schizophrenia:

> Following intramuscular injection, aripiprazole lauroxil is converted to aripiprazole. In vitro, aripiprazole lauroxil (AL) inhibited binding of agonists or antagonists to similar dopamine and serotonin receptor subtypes as aripiprazole . . . . However, the percent inhibition of specific binding was much less for aripiprazole lauroxil compared to aripiprazole for the majority of receptor subtypes. Aripiprazole lauroxil had **no measurable functional activity** (agonistic or antagonistic) at these receptors up to the highest usable concentration (limited by solubility) compared to aripiprazole, with the exception of weak agonist activity at the 5-HT_{1A} receptor . . . . **Therefore, the efficacy of aripiprazole lauroxil is most likely due to aripiprazole and aripiprazole-related active metabolites. The sponsor did not investigate the binding potential of the intermediate, N-hydroxymethyl aripiprazole.**

Id. 1052 (emphasis added); *see also id.* 1038 ("Aripiprazole lauroxil binds to similar receptors as aripiprazole . . . although at much lower affinity **and has no functional activity**." (emphasis added)); *id.* 807 ("[E]fficacy [of aripiprazole lauroxil] is known to be driven by aripiprazole exposures . . . ."); *id.* 784 ("[E]fficacy [of aripiprazole lauroxil] is driven by the systemic exposure of aripiprazole . . . ." (emphasis added)).

The Aristada label states plainly that aripiprazole lauroxil is simply a "drug" that uses aripiprazole to treat patients with schizophrenia. In the Full Prescribing Information, Alkermes twice says, "ARISTADA is a prodrug of aripiprazole." *Id.* 1242. Significantly, the label does not

claim that aripiprazole lauroxil is a prodrug of N-hydroxymethyl aripiprazole, which is a prodrug of aripiprazole. The Aristada label also admits that aripiprazole provides the therapeutic benefit to patients taking Aristada: "[ARISTADA's] activity in the body is primarily due to aripiprazole, and to a lesser extent dehydro-aripiprazole (major metabolite of aripiprazole) . . . ." *Id.* Alkermes's copycat product is currently on the market. Press Release, *Alkermes plc Reports Third Quarter 2015 Financial Results* (Oct. 29, 2015).[5]

III. Proceedings at FDA

On July 13, 2015, Otsuka submitted a citizen petition to FDA requesting that FDA delay or withhold final approval of the Alkermes NDA pending the expiration of Otsuka's three-year exclusivity on December 5, 2017, for the conditions of approval of aripiprazole. A.R. at 25-63.[6] Alkermes submitted comments in opposition to Otsuka's petition. *Id.* 65-100 (7/24/15), 214-21 (8/4/15), 298-308 (8/14/15). Otsuka responded to these comments in supplements to its citizen petition. *Id.* 101-112 (first supplement filed on 7/29/15), 288-97 (second supplement filed on 8/5/15), 336-41 (third supplement filed on 8/19/15).

On October 5, 2015, FDA denied Otsuka's citizen petition. *Id.* 342-72. That same day, FDA approved the Alkermes NDA for Aristada, a long-acting injectable for the treatment of schizophrenia with the same conditions of use as Abilify Maintena. *Id.* 1217-80. Aristada received five-year exclusivity as a New Chemical Entity ("NCE"). *Id.* 360, 1209-16. FDA's letter decision denying Otsuka's citizen petition focuses on distinguishing the active ingredients and active moieties of Aristada and Abilify Maintena, while ignoring that FDA approved Aristada based in

[5] http://phx.corporate-ir.net/phoenix.zhtml?c=92211&p=irol-newsArticle&ID=2104023.

[6] On September 9, 2014, Otsuka submitted a different citizen petition requesting that FDA refuse to accept for substantive review the Alkermes NDA. A.R. 1-18. The petition was based on the ground that the Alkermes NDA was facially deficient because the single adequate and well-controlled clinical trial could not satisfy the substantial evidence of effectiveness requirement. *Id.* FDA found the petition premature and denied it on February 3, 2015. *Id.* 21-24. Otsuka also requested in the July 13 citizen petition that FDA refuse to approve the Alkermes NDA because it failed to satisfy the substantial evidence of effectiveness requirement. *Id.* 25-63.

significant part on FDA's prior findings that aripiprazole is safe and effective in the treatment of schizophrenia. *Id.* 354-60. Despite relying on its prior findings that aripiprazole is safe and effective in the treatment of schizophrenia, FDA avoided Otsuka's three-year exclusivity for Abilify Maintena in approving Aristada based on the contradictory and legally unsustainable basis that the two have different active moieties. *Id.* 360-67. Thus, FDA first found the drugs were the same for safety and efficacy, and then different for exclusivity purposes.

To reach this contradictory result, FDA determined that a 505(b)(2) NDA is blocked by a first-in-time 505(b)(1) application only when the first-in-time and second-in-time drugs share the identical active moiety. *Id.* 352 ("For a single entity drug to be potentially barred by 3-year exclusivity for another single entity drug, the drug must contain the same active moiety as the drug with 3-year exclusivity."). Because FDA found (despite its reviewers' prior findings stating otherwise) that Aristada's active moiety is N-hydroxymethyl aripiprazole and Abilify Maintena's active moiety is aripiprazole, FDA concluded that Aristada is not blocked by Abilify Maintena's three-year exclusivity. *Id.* 360-64. FDA rejected Otsuka's argument that a 505(b)(2) NDA cannot avoid (violate) the exclusivity of the drug on which it relies to meet the FDCA's drug approval requirements. *Id.* 365-67. This case followed.

ARGUMENT

I. Standard of Review.

Otsuka's complaint challenges final agency action under the APA. Summary judgment is "the proper mechanism for deciding, as a matter of law, whether an agency action is supported by the administrative record and consistent with the APA standard of review." *Depomed, Inc. v. Dep't of Health & Human Servs.*, 66 F. Supp. 3d 217, 227 (D.D.C. Sept. 5, 2014). When a party moves for summary judgment in an APA judicial review case, the district court "sits as an appellate

tribunal, and the entire case on review is a question of law." *Id.* (internal quotation marks and brackets omitted). "[A] court must set aside agency action it finds to be arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." *Id.* (internal quotation marks omitted).

II. Otsuka Is Entitled To Judgment On Count One Of Its Complaint Because FDA's Decisions Are Contrary To Sections 505(c)(3)(E)(iii)&(iv).

Count one of Otsuka's complaint challenges FDA's decisions on the ground that FDA arbitrarily, capriciously, and unlawfully misconstrued the FDCA's three-year exclusivity provisions, 21 U.S.C. § 355(c)(3)(E)(iii)&(iv). ECF No. 1, ¶¶ 51-59.[7] In assessing the lawfulness of FDA's interpretation of the three-year exclusivity provisions, this Court applies the two-step framework under *Chevron, USA, Inc. v. NRDC*, 467 U.S. 837 (1984). *See Depomed*, 66 F. Supp. at 228. Under *Chevron* step one, a reviewing court must use the statutory text and structure and the legislative history[8] to determine "whether Congress has directly spoken to the precise question at issue." *Id.*; *Takeda Pharms., U.S.A., Inc. v. Burwell*, 78 F. Supp. 3d 65, 97 (D.D.C. 2015) When, as here, Congress's intent is clear, the Court must give effect to that unambiguously expressed intent. *Id.* It is only where the statute is silent or ambiguous that deference to an agency interpretation "based on a permissible construction of the statute" is permissible. *Id.* An agency's

[7] Otsuka is not separately claiming that FDA erroneously determined that the active ingredient in Aristada is aripiprazole lauroxil and the active moiety is N-hydroxymethyl aripiprazole, or that FDA erred in determining that Aristada is an NCE; therefore, *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760 (D.C. Cir. 2010), does not undermine Otsuka's argument. Otsuka's position is that it is legally irrelevant whether the active ingredient and active moiety of Abilify Maintena and Aristada are different, albeit healthy skepticism on this point is warranted given FDA's "midnight conversion" on this issue—that is, FDA changed its mind and reversed its position a mere seven days before issuing its letter decision.

[8] *See Catawba Cnty., NC v. EPA*, 571 F.3d 20, 35 (D.C. Cir. 2009) ("a statute may foreclose an agency's preferred interpretation . . . if its structure, *legislative history*, or purpose makes clear what its text leaves opaque." (emphasis added)); *Sierra Club v. EPA*, 551 F.3d 1019 (D.C. Cir. 2008) ("Although *Chevron* step one analysis begins with the statute's text, . . . the court must exhaust the traditional tools of statutory construction, including examining the statute's legislative history . . . ." (internal quotation marks omitted)); *see also FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 147 (2000) (legislative history is "certainly relevant" at *Chevron* step one); *Nat'l Fed'n of Fed. Employees, FD1, IAMAW, AFL-CIO v. McDonald*, No. 14-00960, 2015 U.S. Dist. LEXIS 118849, *17 n.7 (D.D.C. Sept. 8, 2015) ("[I]n the D.C. Circuit, courts can look to legislative history at step one of *Chevron*.").

construction is permissible "unless it is arbitrary or capricious in substance, or manifestly contrary to the statute." *Id.* (internal quotation marks omitted).

A. FDA's Decisions Should Be Reversed And Vacated Under *Chevron* Step One.

1. Statutory Background

The Hatch-Waxman Amendments to the FDCA were designed to promote twin goals: "(1) encouraging the development of generic drugs to increase competition and lower prices in the pharmaceutical industry, while (2) maintaining incentives for pharmaceutical companies to invest in innovation and the creation of new drugs." *Amarin Pharms. Ir. Ltd. v. FDA*, No. 14-cv-00324, 2015 U.S. Dist. LEXIS 68723 (D.D.C. May 28, 2015). "Facing this 'classic question of the appropriate tradeoff between greater incentives for the invention of new products and greater affordability of those products,' *Abbott Labs. v. Young*, 920 F.2d 984, 985 (D.C. Cir. 1990), Congress struck a compromise. It established an expedited process for obtaining approval for generic drugs, but, at the same time, it provided increased intellectual property rights and periods of market exclusivity for those pioneer manufacturers that invent new drugs." *Id.*; *see also Takeda*, 78 F. Supp. 3d at 68.[9]

[9]*New York v. Actavis PLC*, 787 F.3d 638, 644 (2d Cir. 2015) ("Hatch-Waxman was designed to serve the dual purposes of both encouraging generic drug competition in order to lower drug prices and incentivizing brand drug manufacturers to innovate through patent extensions."); *Veloxis Pharms., Inc. v. FDA*, No. 14-2126, 2015 U.S. Dist. LEXIS 77559, *4-5 (D.D.C. June 16, 2015); *Spectrum Pharms., Inc. v. Sandoz, Inc.*, No. 15-631, 2015 WL 3535972, *2 (D.D.C. May 27, 2015) ("The HatchWaxman Amendments were intended to balance encouraging innovation in drug development with accelerating the availability of lower-cost generic alternatives to innovator drugs."); 70 Fed. Reg. 17168, 17176 (2005) (final rule) ("[O]ne of the general intentions of the Hatch-Waxman amendments is to encourage the entry of lower-priced generic drug products into the market. However, another key purpose of the Hatch-Waxman amendments is to encourage significant innovations in human drugs (*see generally* 130 Cong. Rec. H9113-14 and H9121-22 (Sept. 6, 1984) (statements of Rep. Waxman)); Colleen Kelly, *The Balance Between Innovation and Competition: The Hatch-Waxman Act, the 2003 Amendments, and Beyond*, 66 Food & Drug L.J. 417, 417 (2011) ("The Act was a compromise designed to balance the competing interests of research-based pharmaceutical companies ('innovators' or 'pioneers') and generic drug manufacturers ('generics'). On the one hand, the Act was designed to encourage innovators to continue investing in the research and development of new drugs, and on the other hand, the Act was intended to increase generic drug competition in the pharmaceutical drug market, thereby lowering drug prices and consumer costs for drugs.").

The Amendments added two pathways to get drugs to market more quickly. Those pathways allow drug manufacturers to avoid the costly and time-consuming process of submitting a full standalone NDA under Section 505(b)(1) and, instead, rely on what is already known about a particular drug to meet the FDCA's drug approval requirements. The generic pathway of Section 505(j), which is not at issue in this case, allows applicants submitting Abbreviated New Drug Applications ("ANDA") to rely entirely on FDA's finding of safety and effectiveness for a previously approved reference listed drug.[10] The "intermediate" pathway between a standalone 505(b)(1) NDA and an ANDA is the pathway that Alkermes used—a "505(b)(2) NDA."[11] That shortcut pathway to approval allows applicants to rely on one or more prior drug investigations "not conducted by or for the applicant" and "for which the applicant has not obtained a right of reference or use" to meet the drug approval requirements. 21 U.S.C. § 355(b)(2).

To incentivize drug development, Congress in the Hatch-Waxman Amendments created corresponding tradeoffs to the benefits of these less burdensome approval pathways in the form of periods of exclusivity. H.R. Rep. No. 98-857. Five-year exclusivity was meant to incentivize the investment of time and money necessary to develop NCEs. 21 U.S.C. § 355(c)(3)(E)(ii); 130 Cong. Rec. 24425 (Sept. 6, 1984) (statement of Rep. Waxman); 130 Cong. Rec. 23765 (Aug. 10, 1984) (statement of Sen. Hatch). Three-year exclusivity was meant to incentivize drug manufacturers to invest in new clinical trials to demonstrate the safety and effectiveness for new uses of already approved drugs. 21 U.S.C. § 355(c)(3)(E)(iii)&(iv); 130 Cong. Rec. 24425 (Sept. 6, 1984) (statement of Rep. Waxman) ("[A] 3-year period of exclusive market life is afforded to

[10] The issue presented in this case is unique and very narrow and does not affect the operation of exclusivity to drugs seeking approval under 505(j) because the FDCA requires that products seeking approval under 505(j) must contain the same active moiety as the drug relied upon.

[11] For convenience, Otsuka refers to these NDAs as "505(b)(2) NDAs"; however, Section 505(b)(2) is not any more central to the identity of 505(b)(2) NDAs than the exclusivity provisions in Section 505(c)(3)(E). These provisions operate together as part of a unified scheme to establish the process by which drug manufacturers may rely on safety and/or effectiveness data. *See Takeda*, 78 F. Supp. 3d at 71-74.

nonnew chemical entities approved after enactment of the bill which have undergone new clinical studies essential to FDA approval. This provision will encourage drugmakers to obtain FDA approval for significant therapeutic uses of previously approved drugs."); 130 Cong. Rec. 24433 (Sept. 6, 1984) (statement of Rep. Waxman) ("The 3-year protection in effect, provides that a product that is not a new chemical entity would be protected for 3 years after the FDA approval because there were essential clinical trials submitted to FDA, and only when clinical trials were submitted."); *see also* 130 Cong. Rec. 24433 (Sept. 6, 1984) (statement of Rep. Waxman) ("This [three-year] protection is fair, because the manufacturer had to spend a substantial amount of money to conduct those tests. The manufacturer deserves the same period to recoup that investment."); 130 Cong. Rec. 24436 (Sept. 6, 1984) (statement by Rep. Waxman) ("The principle is that we are going to protect their investment for 3 years, and I think that is reasonable."); 130 Cong. Rec. 24436 (Sept. 6, 1984) (statement by Rep. Waxman) ("We have narrowed [the three-year exclusivity provision] to make sure that it is a significant enough change so that the 3-year rule will apply only when new clinical tests are essential to getting FDA approval and when there is an investment of some magnitude."); 130 Cong Rec. 23765 (Aug. 10, 1984) (statement of Sen. Hatch) ("For all other NDA's involving new clinical tests, there will be a 3-year period during which no ANDA approval may be made effective."); 130 Cong. Rec. 23766 (Aug. 10, 1984) (statement of Sen. Hatch) ("[T]he amendment clarifies . . . the 3-year moratorium for ANDA's. It would protect only those new drug applications which involve new clinical investigations.").

Where, unlike the present case, the manufacturer has taken no benefit, it is not subject to a corresponding tradeoff. A drug manufacturer that submits a full standalone NDA—and not an ANDA or a 505(b)(2) NDA is not subject to another drug's market exclusivity under 505(c)(3)(E) or 505(j)(5)(F). *Veloxis*, 2015 U.S. Dist. 77559, *29-30 ("[T]he FDA is prohibited only from

approving a second-in-time NDA that is a 505(b)(2) NDA, as this provision does not speak to a second-in-time 505(b)(1) NDA."); 54 Fed. Reg. 28872, 28896 (1989) (proposed rule).

2. The Three-Year Exclusivity Provisions

Where a manufacturer, like Alkermes, takes the benefit of the 505(b)(2) shortcut, the text, structure, and legislative history make clear that it is subject to the exclusivity of the drug on which it relies.[12] The provisions set forth the familiar "If x and y, then z" structure. If certain conditions are met in the exclusivity clause ("if x and y"), then the bar clause dictates that the first-in-time drug receives exclusivity for certain conditions of approval ("then z"). FDA has no discretion to ignore these limits on its approval authority. *See Depomed*, 66 F. Supp. 3d at 230.

Section 505(c)(3)(E)(iii) provides,

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

21 U.S.C. § 355(c)(3)(E)(iii).

[12] Otsuka's challenge to the scope of the bar clauses in Sections 505(c)(3)(E) can, and should, be decided under *Chevron* step one. *Contra Veloxis*, 2015 U.S. Dist. LEXIS 77559, at *40 (determining meaning of "conditions of approval" under step two); *AstraZeneca Pharms. LP v. FDA*, 872 F. Supp. 2d 60, 81 (D.D.C. 2012) (determining that Section 505(j)(5)(F)(iv) was ambiguous "because key phrases in the statutory provision are undefined and their meaning disputed").

Section 505(c)(3)(E)(iv) provides,

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

21 U.S.C. § 355(c)(3)(E)(iv).

Exclusivity under these provisions applies to "conditions of approval" and "a change," not to particular active moieties. Indeed, while 505(c)(3)(E)(iii) links the "conditions of approval" to a "drug," 505(c)(3)(E)(iv) links a change to a "supplement." FDA's reading of the statute requires the agency to impermissibly limit the entitlement of exclusivity to active moieties. FDA does this by inverting the inquiry into the scope of the first-in-time drug's exclusivity and placing the focus on "such drug" rather than, appropriately, on the "conditions of approval" or "change." *See* A.R. 361 ("FDA may not approve a 505(b)(2) for 'such drug' (i.e., a drug containing the active moiety aripiprazole) for those same conditions of approval for 3 years after the approval of the original Abilify Maintena NDA . . . ."). But that inquiry is backwards: the three-year exclusivity provisions prohibit FDA from approving a second-in-time 505(b)(2) for the "conditions of approval of such drug," not for "the approval of such drug for the conditions of approval of the application."

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

exclusivity provisions to award an innovator exclusivity for investing in the creation of significant innovations to already approved drugs. *See* 130 Cong. Rec. 23766 (Aug. 10, 1984) (statement of Sen. Hatch) ("[T]he amendment clarifies . . . the 3-year moratorium for ANDA's. It would protect only those new drug applications which involve new clinical investigations."); 130 Cong. Rec. 24436 (Sept. 6, 1984) (statement of Rep. Waxman) ("[I]f they put the money in to develop it, they ought to have a 3-year protection. We have narrowed it to make sure that it is a significant-enough change so that the 3-year rule will apply only when new clinical tests are essential to getting FDA approval and when there is an investment of some magnitude."); 59 Fed. Reg. 50339, 50358 (1994) (final rule) ("[T]he legislative history indicates that Congress created 3-year exclusivity to protect products whose development required a significant time commitment and 'an investment of some magnitude . . . .'"). As such, the text of the provisions limits exclusivity to the "conditions of approval" derived from "new clinical investigations," *Veloxis*, 2015 U.S. Dist. LEXIS 77559, at *39; *AstraZeneca*, 872 F. Supp. 2d at 65; *ViroPharma, Inc. v. Hamburg*, 898 F. Supp. 2d 1, 7 (D.D.C. 2012), and not to a specific "drug."

3. The Text And Statutory Structure Make Clear That A 505(b)(2) NDA Cannot Escape The Exclusivity Of The Drug On Which It Relies.

When the word "drug" is appropriately considered in the statutory structure, it is clear that a 505(b)(2) NDA is blocked by exclusivity attaching to the "conditions of approval" or "change" of the drug the 505(b)(2) relies on to meet the drug approval requirements. Besides focusing on the wrong part of the statute, FDA's reading of the exclusivity provisions ignores the statutory structure. "In determining whether Congress has specifically addressed the question at issue, the court should not confine itself to examining a particular statutory provision in isolation. . . . A court must . . . interpret the statute 'as a symmetrical and coherent regulatory scheme,' and 'fit, if possible, all parts into an harmonious whole.'" *FDA v. Brown & Williamson*, 529 U.S. 120, 121

(2000) (citations omitted). If "drug" is broad enough in section 505(b)(2) to permit an applicant such as Alkermes to rely on a different active moiety for approval, then "drug" in 505(c)(3)(E)(iii)&(iv) must also be read to include that same active moiety.

Despite FDA's assertion that they are "different statutory provisions with different language and different purposes," Sections 505(b)(2) and 505(c)(3)(E)(iii)&(iv) must be interpreted together given their identical text, *see Amarin Pharms.*, 2015 U.S. Dist. LEXIS 68723, at *36, *42-43;[13] *see, e.g.*, *Veloxis*, 2015 U.S. Dist. LEXIS 77559, at *30 (reading 505(b)(2) and 505(c)(3)(E)(iii) together),[14] and the definition of "drug" must have the same scope in both provisions.

Section 505(b)(2) refers to "drug" in the singular form. Section 505(b)(2) instructs that "[a]n application submitted under [505(b)(1)] for a drug for which the investigations described in [505(b)(1)(A)] and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use" must include certain certifications or statements. The "drug" referred to in Section 505(b)(2) includes both the "drug" in the 505(b)(2) application (*i.e.*, "an application submitted under [505(b)(1)] for a drug") and the "drug" in the first-in-time 505(b)(1) application (*i.e.*, "a drug for which the investigations described in [505(b)(1)(A)] and relied upon"). The use of singular "drug"

[13] *Amarin*, 2015 U.S. Dist. LEXIS 68723, at *42-43 ("Although the FDA did not discuss the issue in its administrative process, it argues before this Court that the exclusivity and ANDA provisions serve different purposes, because the exclusivity provision is designed to promote novelty while the ANDA provisions require the FDA to ascertain whether generic drugs are safe and effective. But, as explained above, while the provisions do, of course, play different roles, they are part of a unified statutory scheme intended to strike a balance between fostering innovation and promoting access to affordable medications." (citations omitted)).

[14] *Compare* 21 U.S.C. § 355(b)(2) (applying to an application submitted under 505(b)(1) "for a drug for which the investigations described in [505(b)(1)(A)] and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted"); *with id.* § 355(c)(3)(E)(iii) (directing bar clause to "application submitted under [505(b)] . . . if the investigations described in [505(b)(1)(A)] 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"), *and id.* § 355(c)(3)(E)(iv) (same).

means there is only one "drug," and the scope of the definition of "drug" includes any "drug." *See King v. Burwell*, 135 S. Ct. 2480, 2489 (2015) ("such Exchange" is the "*same* Exchange that the State was directed to establish"). "Drug" in Section 505(b)(2) includes aripiprazole lauroxil ("an application submitted under [505(b)(1)] for a drug") and aripiprazole ("a drug for which the investigations described in [505(b)(1)(A)] and relied upon").

"Drug" in Section 505(c)(3)(E)(iii) is referred to in its singular form, but just like the singular "drug" in 505(b)(2), it includes multiple "drugs" within its scope, including the "drug" in the 505(b)(2) application. "Drug" in 505(c)(3)(E)(iii) includes the "such drug" referred to earlier in the sentence ("a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved") and the drug in the first-in-time 505(b)(1) application ("conditions of approval of such drug in the approved subsection (b) application"). "Such" does not always refer to something already discussed. *E.g.*, *Aydt v. DeAnza Santa Crus Mobile Estates*, 708 F. Supp. 192, 195 (N.D. Ill. 1989) ("Thus even if it could be argued that the maxim of *ejusdem generic* [sic] is limited to specifics followed by the general, nevertheless the meaning of the word 'such' in the context of section 8 is to interpret the general by the characteristics of the specifics that succeed it."). "Such" can refer, as it does here, to something to be discussed—that is, something to come later in the sentence. *Merriam-Webster's Collegiate Dictionary* (10th ed. 1999) (defining "such" as, *inter alia*, "of a kind or charter to be indicated or suggested <a bag ~ as a doctor carries>" and "having a quality to a degree to be indicated <his excitement was ~ that he shouted>").[15] Thus, "drug" includes in its scope what FDA has interpreted to mean active moiety

[15] In *Takeda Pharmaceuticals USA, Inc. v. Burwell*, this Court interpreted the word "such" to "nearly always operate[] as a reference back to something previously discussed," 78 F. Supp. 3d at 99, leaving open the possibility that it could be interpreted in other ways.

and the "drug" in the 505(b)(1) application. As per 505(b)(2), "drug" in the 505(b)(1) application is the same drug as the drug in the 505(b)(2) NDA.

FDA avoids this reading of "drug" by focusing solely on the phrase "such drug" in Section 505(c)(3)(E)(iii) as it refers to the definition of drug earlier in the sentence. But using this phrase to include within its scope only the "drug" referenced earlier in the sentence avoids the intent and structure of the FDCA and the legislative history. *E.g.*, *King*, 135 S. Ct. at 2492-96 (looking to the broader structure and underlying purpose of the Patient Protection and Affordable Care Act to understand the meaning of the phrase "an Exchange established by the State"); *Brown & Williamson*, 529 U.S. at 133-43 (FDA has no authority to regulate tobacco products considering the statutory context). Interpreting "such drug" to mean only active moiety allows FDA, contrary to Congress's intent, to determine when a drug that has previously received three-year exclusivity will and will not actually be protected from the market entry of a 505(b)(2) NDA that has relied on its clinical investigations.[16] Congress gave FDA no such discretion.

Even if "such drug" means only "active moiety"—and thus aripiprazole here—given the statutory structure and legislative history, *see infra* Part II.A.4, Section 505(c)(3)(E)(iii)&(iv) cannot be read separately from Section 505(b)(2). Section 505(c)(3)(E)(iii)&(iv) can only be read

[16] FDA's decision on when a drug's exclusivity is applicable is also inconsistent with when a drug's patent protection is applicable. Under Section 505(b)(2), patent protection is triggered by the 505(b)(2) applicant's decision to rely on a particular drug, and nothing else. *Takeda*, 78 F. Supp. 3d at 87. As a result, when it comes to patent protection, an NCE 505(b)(2) will always be subject to the FDCA's patent protection provisions if it relies on a previously approved drug. Under FDA's decision here, however, reliance by an NCE triggers nothing and leads to the absurd result that an NCE 505(b)(2) is never subject to any non-patent exclusivity. If an NCE 505(b)(2) applicant is subject to the patent protection provisions, it should also be subject to applicable exclusivity protections when, in the same way, the 505(b)(2) applicant makes a particular previously approved drug relevant. Indeed, consistent with *Takeda*, Alkermes provided certification to patents listed for the specific drug product Alkermes decided to choose, Abilify tablet, an aripiprazole product. Because three-year exclusivity is not limited to a specific drug product chosen by a 505(b)(2) applicant (*see Veloxis*, 2015 U.S. Dist. LEXIS 77559, at *26-34), Alkermes must be subject to all aripiprazole exclusivity covering the same conditions of use.

so that a 505(b)(2) application cannot be approved for the conditions of approval of the drug it relies on to meet the FDCA's drug approval requirements.

4. The Legislative History Shows That Congress Set Up A Scheme Of Exclusivity To Protect The Innovator Drug.

Congress set up a scheme of benefits and tradeoffs: allowing a 505(b)(2) to use an innovator's data and then be subject to the innovator's exclusivity. The scheme works where all 505(b)(2) applicants taking advantage of the Hatch-Waxman benefit are subject to the corresponding Hatch-Waxman tradeoff of being blocked by the exclusivity of the drug on which they choose to rely. *See* 130 Cong. Rec. 24433 (Sept. 6, 1984) (statement of Rep. Waxman) ("The 3-year protection in effect, provides that a product that is not a new chemical entity **would be protected for 3 years after the FDA approval** because there were essential clinical trials submitted to FDA, and only when clinical trials were submitted." (emphasis added)); 130 Cong. Rec. 24436 (Sept. 6, 1984) (statement by Rep. Waxman) ("The principle is that we are going to **protect their investment for 3 years**, and I think that is reasonable." (emphasis added)); 130 Cong Rec. 23765 (1984) (statement of Sen. Hatch) ("For all other NDA's involving new clinical tests, there will be a 3-year period during which **no** ANDA approval may be made effective." (emphasis added)). This is the only way to allow for a shortcut of the drug approval process while also incentivizing innovation. *See* 130 Cong. Rec. 24425 (Sept. 6, 1984) (statement of Rep. Waxman) ("[A] 3-year period of exclusive market life is afforded to nonnew chemical entities approved after enactment of the bill which have undergone new clinical studies essential to FDA approval. This provision will encourage drugmakers to obtain FDA approval for significant therapeutic uses of previously approved drugs."); 130 Cong. Rec. 24433 (Sept. 6, 1984) (statement of Rep. Waxman) ("This [three-year] protection is fair, because the manufacturer had to spend a

substantial amount of money to conduct those tests. The manufacturer deserves the same period to recoup that investment.").[17]

Congress did not authorize a scheme of "exceptions" to three-year exclusivity in which FDA would have discretion to avoid Congress's scheme and cherry pick when a "drug" is and is not subject to the exclusivity of the drug on which it relies. The only way a "drug" avoids the exclusivity of another drug is by not taking advantage of the Hatch-Waxman shortcut process and submitting a full standalone NDA. *Veloxis*, 2015 U.S. Dist. LEXIS 77559, at *30. FDA's reading of the exclusivity provisions disregards the legislative purpose and, instead, produces the absurd result that a 505(b)(2) can rely on another drug to meet the drug approval requirements and, at the same time, avoid that drug's exclusivity. *Depomed*, 66 F. Supp. 3d at 234 ("[S]uch [policy] arguments may be relevant to the first *Chevron* inquiry based on 'the longstanding rule that a statute should not be construed to produce an absurd result.'"); *Coalition for Responsible Regulation, Inc. v. EPA*, No. 09-1322, 2012 U.S. App. LEXIS 25997, *76-77 (D.C. Cir. 2012) (Kavanaugh, J., dissenting from the denial of rehearing en banc) ("As the Supreme Court has said, 'interpretations of a statute which would produce absurd results are to be avoided if alternative interpretations consistent with the legislative purpose are available.'" (quoting *Griffin v. Oceanic Contractors, Inc.*, 458 U.S. 564, 575 (1982)).

Though the issue of "active moieties" was not addressed in *Veloxis Pharmaceuticals, Inc. v. FDA*, the district court's decision and FDA's underlying final agency action support Otsuka's reading of the legislative history: three-year exclusivity is not to be undermined by meaningless technical changes and game playing, for doing so thwarts congressional intent to incentivize

[17] The bar clauses of the three-year provisions in an earlier version of the bill (S. 2926 (1984)) make clear that the scope of exclusivity is not determined by identical active moieties: "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 . . . ." 130 Cong. Rec. 23770-71 (Aug. 10, 1984).

innovation. The policy point does not change simply because Abilify Maintena and Aristada have different active moieties.

In *Veloxis*, plaintiff challenged FDA's withholding of final approval of Envarsus XR for the prophylaxis of organ rejection in *de novo* kidney transplant patients under Section 505(c)(3)(E)(iii). Among other things, the plaintiff argued that Astagraf XL's exclusivity did not block the approval of Envarsus XR because the Envarsus XR 505(b)(2) NDA "did not rely upon any of the studies or data supporting approval of Astagraf XL or upon [the] FDA's prior findings that Astagraf XL is safe and effective." 2015 U.S. Dist. LEXIS 77559, at *26. Recognizing that "it would frustrate Congress's intent to incentivize new drug development through, among other means, marketing exclusivities, if a second-in-time 505(b)(2) NDA could escape the reach of the three-year exclusivity by simply relying on a 505(b) NDA different than the first-in-time 505(b) NDA," the court rejected plaintiff's argument. *Id.* at *31-39. FDA's letter decision at issue in *Veloxis* also recognized the need to incentivize drug manufacturers to make innovative changes by protecting exclusivity: "The Agency's interpretation balances the goals of the Hatch-Waxman Amendments by giving full effect to protections available for innovative changes and by preventing those protections from being undercut by a competitor's simple decision to reference a different listed drug."' A.R. 1711; Fed. Defs.' Memo. Of P. & A. In Supp. Of Their Mot. To Dismiss, Or In The Alt., For Summ. J. & Opp. To Pl.'s Summ. J. Mot., *Veloxis Pharms., Inc. v. FDA*, No. 14-cv-2126 (D.D.C.), ECF No. 61, at 25 (explaining that FDA's interpretation "is faithful to . . . the purpose of the Hatch-Waxman amendments, which were designed, in part, to incentivize drug manufacturers to engage in the 'protracted, expensive, and risk-laden' full NDA process").[18]

[18] *See also* Fed. Defs.' Reply In Supp. Of Defs.' Motion To Dismiss, Or In The Alt., For Summ. J., *Veloxis Pharms., Inc. v. FDA*, No. 14-cv-2126 (D.D.C.), ECF No. 62, at 7 ("As explained in the Federal Defendants' opening brief, the

The district court also rejected Veloxis's argument that there were "many other 'clinically meaningful'" differences between Astagraf XL and Envarsus XR, including dosage forms (capsule vs. tablet), dosing strengths, pharmacokinetic profiles, and dosing regimens, that should void Envarsus XR's exclusivity. *Veloxis*, 2015 U.S. Dist. 77559, at *44 (citing Pl.'s Summ. J. Mem. at 36). FDA had concluded that "a 505(b)(2) application can differ in certain ways from the previously approved product with exclusivity and nonetheless be blocked if it shares the conditions of approval for which exclusivity was granted." A.R. 1707 ("[S]uch a narrow interpretation would render 3-year exclusivity virtually meaningless because any change . . . would be sufficient to take a subsequent drug outside the scope of another's exclusivity.").

Veloxis instructs that it does not matter that Alkermes relied on Abilify tablets, not Abilify Maintena, or that Alkermes made technically meaningless, non-substantive changes to a long-acting drug that ultimately becomes aripiprazole and uses aripiprazole to provide therapeutic effect to patients. What matters is the undisputed fact that Alkermes took advantage of the Hatch-Waxman benefit and relied on aripiprazole safety and effectiveness data and, as in *Veloxis*, the copycat, therefore, should be subject to the corresponding tradeoff of waiting for the expiration of Otsuka's exclusivity. Instead, FDA's decision allows a drug that represents absolutely no meaningful therapeutic advance to rely on an innovator drug *and* avoid that innovator drug's exclusivity. That decision is contrary to the goals of the Hatch-Waxman Amendments to allow drugs to shortcut the drug approval process while incentivizing innovation by awarding drug manufacturers that invest in developing new uses of already approved drugs with exclusivity. Otsuka invested in developing a long-acting injectable of aripiprazole for the treatment of

Hatch-Waxman Amendments serve two purposes: (1) to provide an incentive for innovation in drug development, and (2) to accelerate through an abbreviated approval pathway the availability of lower-cost drugs to consumers. Three-year exclusivity is one way the Hatch-Waxman Amendments encourage drug manufacturers to continue seeking innovations with already-approved active ingredients." (citation omitted)).

schizophrenia and received three-year exclusivity for that investment. Then, Alkermes copied Otsuka's data under Section 505(b)(2) to show that aripiprazole is safe and effective in the treatment of schizophrenia, and FDA nevertheless allowed Alkermes to avoid Otsuka's three-year exclusivity. That is contrary to law.

FDA's decision here cannot be reconciled with its decision in Veloxis for an additional reason. In that decision, FDA explained that "[a] 505(b)(2) applicant is subject to applicable periods of marketing exclusivity *granted to the listed drug relied upon*" as well as situations where it does not rely on the exclusivity-protected drug. A.R. 1711. Under that rule, Aristada would be blocked by Abilify tablets—a different active moiety—but under FDA's present rule, Aristada would not be blocked by Abilify Maintena because they have different active moieties. That is an absurd result.

5. FDA's Purported Policy Arguments Fail To Make An Unambiguous Statute Ambiguous.

FDA's policy-based arguments fare no better than its analysis of the statutory text. FDA's specific suggestion that requiring a 505(b)(2) to be subject to the exclusivity of the drug on which it relies to meet the FDCA's approval requirements "could hinder the availability of therapeutic alternatives and discourage or delay the development of innovative new drugs," A.R. 367, is both plainly wrong and altogether inapplicable as a matter of fact here. The plain language reading of the statute set forth by Otsuka encourages innovation by rewarding drug manufacturers, like Otsuka, for engaging in research of already approved drugs (*e.g.*, Abilify tablets) to create new products (*e.g.*, Abilify Maintena). FDA's approach does the reverse; it eliminates that incentive by allowing a later manufacturer to rely on what is already known about a drug (*e.g.*, aripiprazole studies) to gain approval of a drug (*e.g.*, Aristada) whose claimed innovation makes no meaningful

therapeutic advance over the first-in-time drug for its exact conditions of approval and immediately come to market.

FDA's other complaint, that "limit[ing] the [exclusivity] inquiry for determining possible blocking exclusivities to products that share active metabolites . . . would . . . pose difficult and potentially insurmountable challenges from a regulatory and scientific standpoint," *id.*, is equally wrong, particularly at *Chevron* step one. FDA need not engage—indeed, is not authorized to engage—in this analysis. The question under the statute is not whether the first-in-time 505(b)(1) and second-in-time 505(b)(2) share the same "active metabolite." The question under the statute is whether the subsequent applicant (Alkermes) relied on an earlier drug's safety and/or effectiveness data to meet the drug approval requirements (here, undeniably "yes"). To administer the exclusivity provisions, FDA need only look to the 505(b)(2) application to see which drug the applicant relies on, and where, as here, that drug has an unexpired exclusivity for the same conditions of approval, FDA cannot grant final approval to the subsequent application pending the expiration of the exclusivity if the protected conditions of approval overlap. FDA must conduct this type of inquiry to administer the 505(b)(2) patent certification requirements.

* * *

The text, structure, legislative history, and goals of the Hatch-Waxman Amendments are clear. Congress intended drugs receiving three-year exclusivity to enjoy an uninterrupted period of exclusivity not to be violated by copycat drugs relying on their prior drug investigations. A 505(b)(2) NDA that relies on a first-in-time 505(b)(1) NDA is subject to the exclusivity of the first-in-time "drug," regardless of whether the drugs contain identical active moieties.

B. FDA's Decisions Should Be Reversed Under *Chevron* Step Two.

If the Court reaches *Chevron* step two, no deference should be given to FDA's interpretation of the statute for all the reasons stated above, *see* Part II.A, as well as those explained in this section. FDA's construction of the three-year exclusivity provisions is not entitled to deference because it is impermissible, arbitrary and capricious, and manifestly contrary to the FDCA. *Depomed*, 66 F. Supp. 3d at 228; *e.g.*, *Abbott Labs.*, 920 F.2d at 988 (rejecting FDA's interpretation as unreasonable under *Chevron* step two).

1. FDA's Decisions Frustrate The Policy Goals Of The Hatch-Waxman Amendments.

"[A]n agency's interpretation of an ambiguous statutory provision must still be reasonable 'in light of the language, legislative history, and policies of the statute.'" *Van Hollen v. FEC*, 74 F. Supp. 3d 407, 433-34 (D.D.C. 2014). Under *Chevron* step two, a court "must reject administrative constructions of a statute that frustrate the policy that Congress sought to implement." *Id.* (citing *Shays v. FEC*, 528 F.3d 914, 918 (D.C. Cir. 2008)). FDA's conclusion that the three-year exclusivity provisions only block approval of a 505(b)(2) containing the identical active moiety as the drug with exclusivity, notwithstanding the undisputed reliance of the 505(b)(2) applicant (Alkermes) on the first-in-time drug, is unreasonable in light of the statutory language, structure, legislative history, and policies described above. *See supra* Part II.A.

FDA's conclusion frustrates the policy goals of the Hatch-Waxman Amendments. *See supra* Part II.A. Congress allowed drug manufacturers to piggyback on what is already known about a drug but, correspondingly, required drug manufacturers to wait until the original drug's exclusivity expires before the second drug may go on the market. Here, FDA allowed Alkermes to piggyback on aripiprazole but then avoid the corresponding tradeoff of waiting to market Aristada until Otsuka's three-year exclusivity expires. FDA's decision allows manufacturers to

take all of the benefits of the Hatch-Waxman Amendments but avoid the tradeoffs, thereby undercutting the incentive for companies, like Otsuka, to invest in the development of new drugs and new uses for already approved drugs. FDA's interpretation of the statute is manifestly contrary to the policies of the Hatch-Waxman Amendments and cannot withstand scrutiny under *Chevron* step two. *Van Hollen*, 74 F. Supp. 3d at 434 (FEC regulation was unreasonable under *Chevron* step two as "it was contrary to the policy goal that Congress intended to implement").

2. FDA's Decisions Are Contrary To Its Existing Regulations.

As explained below, FDA's interpretation is inconsistent with its existing regulations at 21 C.F.R. § 314.108(b)(4)&(b)(5), *see infra* Part III, and for this additional reason, it fails under *Chevron* step, *e.g.*, *Van Hollen*, 74 F. Supp. 3d at 434-35 (regulation unreasonable in part because it was inconsistent with existing regulations).

3. FDA's Decisions Are Inconsistent With Past Agency Statements.

FDA's conclusion here is inconsistent with FDA's approach in what appears to be the only time FDA has addressed this issue, and FDA's explanation as to why this case is different is plainly inadequate. A.R. 365. For this reason as well, FDA's decision should be reversed under *Chevron* step two. *See King Broadcasting Co. v. FCC*, 860 F.2d 465, 470 (D.C. Cir. 1988) (reversing where agency issued a decision "inconsistent with its prior analysis in similar situations without any acknowledgement of the fact, or cogent explanation as to why"); *see also INS v. Cardoza-Fonseca*, 480 U.S. 421, 446 n.30 (1987) ("An agency interpretation of a relevant provision which conflicts with the agency's earlier interpretation is 'entitled to considerably less deference' than a consistently held agency view.").

FDA's statements in the Xalatan Citizen Petition response confirm that an NCE, like Aristada, may be blocked by another product's exclusivity, regardless of whether it has a different

active moiety or not. In that decision, FDA stated that Pfizer's three-year exclusivity for new clinical studies establishing that Pfizer's Xalatan (latanoprost) product could be used as a "first-line indication" precluded the marketing of Allergan's Lumigan (bimatoprost) and Alcon's Tratavan (travoprost) for a first-line indication. A.R. 1532. During Xalatan's period of three-year exclusivity, "only Pfizer could label its product for first-line use for reduction of elevated IOP [inter-ocular pressure] in patients with open-angle glaucoma or ocular hypertension." *Id.* FDA opined that the Lumigan and Tratavan products—both submitted under 505(b)(2), *id.* 1515, 1517—were blocked by the first-in-time drug they relied on even though Travatan and Lumigan were approved as NCEs. *Id.* 1532.

Here, FDA discarded this approach that an NCE may be blocked by another product's exclusivity despite having a different active moiety and, instead, has approved Aristada because, according to FDA, it has a different active moiety. FDA's decision gives no reasoned basis for its changed approach from Xalatan and dismisses its prior statement with sleight of hand. *See id.* 365 ("Although FDA made certain statements in the Xalatan Citizen Petition response regarding the scope of Xalatan's 3-year exclusivity in a factually different context, the exclusivity issue was not squarely before the Agency because any such exclusivity had already expired by the time the relevant 505(b)(2) supplement was submitted."). For this reason, FDA's decision should be reversed under *Chevron* step two.

Under FDA's new rule, a 505(b)(2) NCE is never subject to the exclusivity of the drug on which it relies. For example, if Abilify tablets had three-year exclusivity, that exclusivity would not bar Aristada because, under current FDA's reasoning, a 505(b)(2) is not blocked by the drug on which it relies to meet the FDCA's approval requirements unless the drugs contain identical active moieties. FDA's approach produces an absurd result and is yet a further reason why FDA's

decision should be reversed under *Chevron* step two.

* * *

FDA's decisions fail under *Chevron* step one and step two. Otsuka is entitled to judgment on Count One of its complaint and FDA's decisions should be vacated.

III. Otsuka Is Entitled To Judgment On Count Two Of Its Complaint Because FDA's Decisions Violate FDA's Regulations.

Count Two of Otsuka's complaint challenges the lawfulness of FDA's final approval of Aristada and FDA's denial of Otsuka's Citizen Petition on the ground that those final agency actions violate FDA's binding regulations, *see* 21 C.F.R. § 314.108(b)(4)&(b)(5). ECF No. 1, ¶¶ 60-64. FDA's regulations prohibit FDA, for a period of three years, from approving a subsequent 505(b)(2) applicant "for the conditions of approval of the original application" and "for a change." FDA's decision here is that a 505(b)(2) NDA is blocked by the exclusivity of a drug it relies on only if the two drugs have the identical active moiety. That decision violates the agency's own regulation, 21 C.F.R. § 314.108(b)(4)&(b)(5).

An agency "is bound by" and must comply with its own regulations, *Nat'l Envtl. Dev. Ass'ns Clean Air Project v. EPA*, 752 F.3d 999, 1008 (D.C. Cir. 2014), and "an agency's failure to follow its own regulations is fatal to the deviant action," *Union of Concerned Scientists v. Atomic Energy Comm'n*, 499 F.2d 1069, 1082 (D.C. Cir. 1974). Where an agency simply "ignore[s] or violate[s] its regulations while they remain in effect," the agency action may be set aside as arbitrary and capricious. *Nat'l Envtl. Ass'n*, 752 F.3d at 1009; *see also Nat'l Family Planning & Reproductive Health Ass'n v. Sullivan*, 979 F.2d 227, 234 (D.C. Cir. 1992) ("[A]n agency issuing a legislative rule is itself bound by the rule until that rule is amended or revoked."). An agency's interpretation of its regulations that is arbitrary, capricious, an abuse of discretion or otherwise not in accordance with law cannot stand. *Nat'l Envtl. Ass'n*, 752 F.3d at 1008. Similarly, deference

to the agency's interpretation is not required where "'an alternative reading is compelled by the regulation's plain language or by other indications of the [agency's] intent at the time of the regulation's promulgation.'" *Id.*

FDA issued its binding interpretation of Sections 505(c)(3)(E)(iii)&(iv) in 21 C.F.R. § 314.108(b)(4)&(b)(5), adopting what it viewed as an appropriate, if not compelled, broad interpretation of the statutory language. *See* 59 Fed. Reg. 50338 (Oct. 3, 1994) (final rule); 54 Fed. Reg. 28872 (July 10, 1989) (proposed rule). FDA cannot now run from its regulations, develop a new one contrary to those regulations, and fail to explain why departing from its regulations is lawful.

21 C.F.R. § 314.108(b)(4), which implements Section 505(c)(3)(E)(iii), provides:

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

21 C.F.R. § 314.108(b)(5), which implements Section 505(c)(3)(E)(iv), provides:

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

These regulations unambiguously prevent FDA from approving a 505(b)(2) application "for the conditions of approval of the original application" or "a change," irrespective of the active moieties in the 505(b)(2) and 505(b)(1) NDAs. *See Cape Hatteras Access Preservation Alliance*

v. U.S. Dep't of Interior, 344 F. Supp. 2d 108, 126 (D.D.C. 2004) ("*Auer* deference is warranted only when the language of the regulation is ambiguous.'" (*Christensen v. Harris Cnty.*, 529 U.S. 576, 588 (2000)). In setting out by regulation FDA's formal interpretation of Section 505(c)(3)(E)(iii), FDA interpreted the phrase "such drug" in the statute's bar clause broadly. FDA interpreted "such drug" as "original application" in 21 C.F.R. § 314.108(b)(4). That action confirms FDA's intent to apply the statutory language broadly without regard to chemical differences in "drugs." FDA's thinking at the time, thoroughly consistent with the Hatch-Waxman structure and policy scheme, was that exclusivity would be broad. 54 Fed. Reg. 28897 ("The agency does not believe that Congress intended the exclusivity provisions to discourage innovators from making improvements to their drug products nor from authorizing the marketing of competitive products.").[19] And, of course, under the plain text of the regulation, exclusivity does not run only to the particular application on which the second-in-time 505(b)(2) relies. *Veloxis*, 2015 U.S. Dist. LEXIS 77559, at *33-34 (Envarsus XR blocked by exclusivity attaching to Astagraf XL even though Envarsus XR relied on Prograf).

The regulatory context confirms FDA's intent to read the statute broadly to avoid disputes about "active moieties." The specific use of "active moiety" in 21 C.F.R. § 314.108(b)(2) and in the exclusivity clause of 21 C.F.R. § 314.108(b)(4) unequivocally evidences FDA's intent not to interpret "drug" in the bar clause of 21 C.F.R. § 314.108(b)(4) to mean "active moiety." "Where

[19] *See also* 54 Fed. Reg. 28897 ("[W]hen exclusivity attaches to an active moiety ***or to an innovative change in an already approved drug***, the submission or effective date of approval of ANDA's and 505(b)(2) applications for a drug with that active moiety or ***innovative change*** will be delayed until the innovator's exclusivity has expired, whether or not FDA has approved subsequent versions of the drugs entitled to exclusivity, and regardless of the specific listed drug product to which the ANDA or 505(b)(2) application refers." (emphasis added)). Though FDA in the Federal Register claimed that it "did not believe that Congress intended the [five- and three-year] 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," 54 Fed. Reg. 28897, FDA chose different language in the provisions.

an agency includes particular language in one section of a regulation but omits it in another, it is generally presumed that the agency acts intentionally and purposely in the disparate inclusion or exclusion." *Yonek v. Shinseki*, 722 F.3d 1355, 1359 (Fed. Cir. 2013); *United States v. Approx. 64,695 Pounds of Shark Fins*, 520 F.3d 976, 983 (9th Cir. 2008). When interpreting the five-year exclusivity provision in 505(c)(3)(E)(ii), FDA replaced the phrase "refers to the drug" in the statutory bar clause with "a drug product that contains the same active moiety as in the New Chemical Entity." *Compare* 21 U.S.C. § 355(c)(3)(E)(ii) (if exclusivity is awarded to an NCE, "no application which **refers to the drug** for which the subsection (b) application was submitted and for which the investigations described in [505(b)(1)(A)] and relied upon . . . for approval" may be submitted" for five years (emphasis added)), *with* 21 C.F.R. § 314.108(b)(2) (if exclusivity is awarded to an NCE, "no person may submit a 505(b)(2) application . . . **for a drug product that contains the same active moiety as in the NCE**" for five years (emphasis added)). FDA also conditioned entitlement to exclusivity in the three-year exclusivity regulation on the submission of a 505(b)(2) "for a drug product that contains an active moiety that has been previously approved in another application under [505(b)(1)]." 21 C.F.R. § 314.108(b)(4)(iii).

However, at the same time, FDA chose not to use the words "active moiety" in the bar clauses of 21 C.F.R. § 314.108(b)(4)&(b)(5). FDA cannot now retroactively and in the face of its regulations employ this alternative formulation. *See Yonek*, 722 F.3d at 1358-59 (plain meaning of diagnostic code in regulation is that "any 'limitation of motion of' a single arm at the shoulder joint constitutes a single disability, regardless of the number of planes in which the arm's motion is limited," given the "assignment of separate diagnostic codes to limitation of motion in different planes (or in different directions within a single plane) of the thigh, knee, and elbow"); *64,695 Pounds of Shark Fins*, 520 F.3d at 983 ("While the text of the landing prohibition, 50 C.F.R.

§ 600.1204(c), explicitly provides that a cargo vessel that lands shark fins after an at-sea transfer is considered a fishing vessel, § 1204(b) – the prohibition on *possessing* shark fins – includes no such provision.").

If FDA's objective is to align the scope of three-year exclusivity with that of five-year exclusivity by conforming the regulation governing three-year exclusivity to that governing five-year exclusivity, FDA cannot do so by fiat. Rather, FDA must change the three-year regulation lawfully in accordance with the APA's rulemaking procedures (assuming, for present purposes only, that such a change would not violate the three-year exclusivity statute and, assuming for present purposes, that the five-year regulation is a lawful interpretation of the five-year exclusivity statute).

FDA's challenged decisions violate FDA's regulations. Otsuka is entitled to judgment on Count Two of its complaint and FDA's decisions should be vacated.

IV. Otsuka Is Entitled To Judgment On Count Three Of Its Complaint Because FDA's Decision Announced A New Legislative Rule In Violation Of The APA's Rulemaking Procedures.

Count Three of Otsuka's complaint challenges the lawfulness of FDA's final approval of Aristada and its denial of Otsuka's Citizen Petition on the ground that FDA engaged in unlawful rulemaking. ECF No. 1, ¶¶ 65-74. FDA styles its letter decision as an informal adjudication; however, FDA's decision is much more than an adjudication of an individual case, *i.e.*, granting a drug approval. Rather, both as a matter of fact and as a matter of law, FDA's decision announced a new substantive rule, as the APA defines "rule," and FDA's action is unlawful precisely because FDA adopted this rule without complying with the APA's rulemaking requirements. FDA's new rule is invalid and FDA's decision predicated on that rule is equally invalid.

A. FDA's New Rule

The new rule promulgated in FDA's decision denying Otsuka's Citizen Petition changed significantly 21 C.F.R. § 314.108(b)(4)&(b)(5) by effectively adding language to—and amending—the regulations. Under the three-year exclusivity regulations, FDA could not approve a 505(b)(2) NDA "for the conditions of approval of the application" and for "a change." The statutory provisions and regulations prohibited a 505(b)(2) that relied on a previously approved drug from avoiding that drug's exclusivity in all instances. *See Veloxis*, 2015 U.S. Dist. LEXIS 77559, at *33-34 (a second-in-time 505(b)(2) is not only blocked by the specific application on which it relies).

FDA's new (not properly promulgated) "legislative rule"[20] amends that categorical rule by creating an exception that does not appear in the statute or regulatory text. That amendment provides that the exclusivity of a previously approved drug on which a 505(b)(2) relies is inapplicable where the 505(b)(2) does not contain the identical active moiety of a first-in-time application. A.R. 352. This rule denies exclusivity in many cases—the present case and others affecting a broad class of pharmaceutical companies—and allows a subsequent copycat drug on the market sooner than it was allowed under the statute and lawfully promulgated rule.

The new, significantly narrowed FDA rule reads as follows:

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

[20] The D.C. Circuit and many commentators have generally referred to the category of rules to which the APA's notice-and-comment requirements apply as "legislative rules" to distinguish such rules from those for which APA's procedural requirements do not apply. *U.S. Telecom Ass'n v. FCC*, 400 F.3d 29, 34 (D.C. Cir. 2005).

> the application the approval of a 505(b)(2) application . . . for the conditions of approval of the original application . . . . [***unless the 505(b)(2) does not contain the identical active moiety of the original application***].”

21 C.F.R. § 314.108(b)(4).

> “If a supplemental application: (i) Was approved after September 24, 1984; and (ii) Contained reports of new clinical investigations (other than bioavailability studies) that were conducted or sponsored by the applicant that were essential to approval of the supplemental application, the agency will not make effective for a period of 3 years after the date of approval of the application the approval of a 505(b)(2) application . . . for a change . . . . [***unless the 505(b)(2) does not contain the identical active moiety of the original application***].”

21 C.F.R. § 314.108(b)(5).

B. APA Rulemaking Process

The APA requires that an agency adopting a “rule” to follow formal rulemaking procedures. Those procedures require the agency to: (1) provide adequate advance notice and publication of the proposed rule in the Federal Register, 5 U.S.C. § 553(b); (2) afford all interested persons (including members of the public) an opportunity to participate through the submission of written data, views, or arguments, *id*. (c); and (3) publish the final rule in the Federal Register with a statement of basis and purpose not less than thirty days before its effective date, *id*. (c), (d).

The APA defines a rule as “the whole or a part of an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy or describing the organization, procedure, or practice requirements of an agency.” 5 U.S.C. § 551(4). FDA is prohibited from applying a “rule,” as defined in the APA, if that rule has not been adopted properly in accordance with the APA. *See* 5 U.S.C. § 553(b)-(d); *see also id*. § 706(2)(A). “[I]nterpretive rules, general statements of policy, or rules of agency organization, procedure, or practice” are exempt from formal notice-and-comment rulemaking procedures, 5

U.S.C. § 553(b)(A), as are *certain* agency adjudications. *See U.S. Telecom Ass'n v. FCC*, 400 F.3d 29, 34 n.9 (D.C. Cir. 2005); *Indep. U.S. Tanker Owners Comm. v. Lewis*, 690 F.2d 908, 922 (D.C. Cir. 1982) ("The APA rulemaking requirements . . . do not extend to informal adjudication."). However, none of these exemptions are applicable in this case.

C. The "Rule" Promulgated By FDA Is A "Legislative Rule" Subject To The APA's Notice-and-Comment Requirements.

FDA's letter decision was not simply an informal adjudication; the letter decision promulgated a new rule that amends the statute and properly promulgated regulation.

While an agency has discretion in choosing whether to announce "new principles" through adjudication or rulemaking, *POM Wonderful, LLC v. FTC*, 777 F.3d 478, 497 (D.C. Cir. 2015), *cert. filed*, No. 15-525 (U.S. Oct. 26, 2015), an agency is ultimately constrained by the APA. 5 U.S.C. § 706(2)(A). An agency may not escape the APA's notice-and-comment requirements by labeling a "rule" an "adjudication." *See Central Tex. Tel. Coop., Inc. v. FCC*, 402 F.3d 205, 211 (D.C. Cir. 2005) (order issued by the FCC in response to a petition for declaratory ruling "may comfortably be considered a 'rule'" under the APA).

"Agency action that creates new rights or imposes new obligations on regulated parties or narrowly limits administrative discretion constitutes a legislative rule," as does a rule that "establishes a standard of conduct which has the force of law" or "*modifies* or *adds* to a legal norm based on the agency's own authority flowing from a congressional delegation to engage in supplementary lawmaking." *Ass'n of Flight Attendants-CWA v. Huerta*, 785 F.3d 710, 716-17 (D.C. Cir. 2015); *Mountain States Health Alliance v. Burwell*, No. 13-641, 2015 U.S. Dist. LEXIS 120263, *21 (D.D.C. Sept. 10, 2015) ("Legislative rules are those that 'grant rights, impose obligations, or produce other significant effects on private interests.'"). Rulemaking "'affects the rights of broad classes of unspecified individuals,'" while "[a]djudications typically 'resolve

disputes among specific individuals in specific cases.'" *City of Arlington, Tex. v. FCC*, 668 F.3d 229, 242 (5th Cir. 2012).

"[N]ew rules that work substantive changes or major substantive legal additions to prior regulations" are likewise subject to APA procedures. *U.S. Telecom Ass'n v. FCC*, 400 F.3d 29, 34-35 (D.C. Cir. 2005) (internal quotation marks, citations, and emphases omitted)). Where an agency issues "a new position inconsistent" with an existing regulation or "effect[s] a substantive change in the regulation[]," notice and comment are required. *Shalala v. Guernsey Mem'l Hosp.*, 514 U.S. 87, 100 (1995); *Mendoza v. Perez*, 754 F.3d 1002, 1024 (D.C. Cir. 2014) (finding Training and Employment Guidance Letters issued by the Department of Labor "necessarily legislative rules because they 'effect[] a [substantive] change in law or policy,' and 'effectively amend[] a prior legislative rule" (citation omitted)).[21] "[A]n agency seeking to repeal or modify a legislative rule promulgated by means of notice and comment rulemaking is obligated to undertake similar procedures to accomplish such modification or repeal . . . ." *Am. Fed. of Gov't Employees, AFL-CIO, Local 3090 v. Fed. Labor Relations Auth.*, 777 F.2d 751, 759 (D.C. Cir. 1985); *id.* at 760 (Scalia, J., concurring) ("Indeed, the agency's abandonment of the rulemaking originally designed to conform its regulations to what it now says are the requirements of the statute makes it particularly appropriate that we insist upon orderly administration and decline to be accomplices in an obviously unnecessary rescission of a rule through adjudication rather than rulemaking.").

[21] *See also MacLean v. Dep't of Homeland Sec.*, 543 F.3d 1145, 1151 (9th Cir. 2008) ("An agency adjudication may require a notice and comment period if it constitutes de facto rulemaking that 'affects the rights of broad classes of unspecified individuals.'"); *Miguel-Miguel v. Gonzales*, 500 F.3d 941, 950 (9th Cir. 2007) ("Of course, in certain circumstances an agency may abuse its discretion by announcing new rules through adjudication rather than through rulemaking, such as when the rule operates retroactively and disturbs settled expectations."); *Conference Group, LLC v. FCC*, 720 F.3d 957, 965 (D.C. Cir. 2013) (holding that an FCC order was "simply [a statutory] interpretation given in the course of an informal adjudication" because the order had "none of the hallmarks of legislative rulemaking . . . such as amending a prior legislative rule").

FDA's decision in this matter went well beyond an "adjudication" by amending a current (and properly promulgated) rule and applying it retroactively. FDA's decision is not just an informal adjudication of Otsuka's exclusivity; FDA's decision sets forth a detailed explanation of and justification for a new rule to be applied in the future to other regulated entities. FDA's letter decision even acknowledges that it uses its citizen petitions for this purpose. A.R. 346 ("FDA has described its interpretation of section 505(b)(2) in a series of public statements and proceedings beginning in 1987, including the 1989-1994 Hatch-Waxman rulemaking process, its 1999 Draft Guidance, ***and previous citizen petition responses***." (emphasis added)). FDA's decision also explains that it is setting forth an "interpretation" of its statute, regulations, science, and policy, not just adjudicating a particular case. A.R. 365 ("Now that the issue of whether the exclusivity of a first-in-time application can block the approval of a 505(b)(2) NDA with a different active moiety is squarely before the Agency, . . . FDA has fully considered the statute, regulations, science, and policy, and the Agency's interpretation is set forth in this letter."). And the decision acknowledges that the new rule will be used in the future. A.R. 367 (stating that, "assuming that FDA were to limit the inquiry for determining possible blocking exclusivities to products that share active metabolites, this inquiry would also pose difficult and potentially insurmountable challenges from a regulatory and scientific standpoint," and proceeding to consider allegedly problematic scenarios).

FDA's decision promulgated a new rule that amends the properly promulgated rule by providing that the exclusivity of a previously approved drug on which a 505(b)(2) relies is inapplicable where the 505(b)(2) does not contain the identical active moiety of a first-in-time application. A.R. 352. The properly promulgated regulation prohibits approval for a period of three years a 505(b)(2) "for the conditions of approval of the original application." FDA's new

rule, contrary to what the regulation prohibits, allows FDA to approve a 505(b)(2) "for the conditions of approval of the original application" so long as FDA finds the 505(b)(2) has a different active moiety. FDA's new rule affects the rights, settled expectations, and obligations of Otsuka and other pharmaceutical companies subject to FDA's regulations; it creates a new exception that substantially restricts exclusivity. The exception takes away exclusivity from the innovator drug manufacturer and allows a copycat drug on the market earlier than allowed under the old rule, releasing it from a prior obligation to wait for the expiration of another's exclusivity.

American Federation of Government Employees, AFL-CIO, Local 3090 v. Federal Labor Relations Authority, 777 F.2d 751 (D.C. Cir. 1985), is instructive. There, the FLRA dismissed a complaint and ignored the plain language of its regulations related to when the filing of exceptions stayed an arbitration award. *Id.* at 752-53, 758. The court vacated the FLRA's order, reasoning that "[w]ere the [FLRA's] approach proper, administrative agencies could effectively repeal legislative rules and abandon longstanding interpretations of statutes indirectly, by adjudication, without providing affected parties any opportunity to comment on the proposed changes, and without providing any significant explanation for their departure from their established views." *Id.* at 759. FDA cannot similarly ignore the plain language of its regulations (21 C.F.R. §§ 314.108(b)(4)&(b)(5)) by administrative fiat to set forth a new "rule" in an adjudication that repeals the properly promulgated regulations and sets forth new ones; that approach can only be accomplished through formal notice-and-comment rulemaking.[22] *See also Tunik v. Merit Systems Protection Board*, 407 F.3d 1326, 1345-46 (Fed. Cir. 2005) (MSPB could only repeal a legislative rule through formal notice and comment procedures, not through an adjudication).

[22] This is not a situation in which a court may be able to look beyond an unlawful regulation to the statute. *See Am Fed. of Gov't Employees*, 777 F.2d at 760 (Scalia, J., concurring).

D. The APA Rulemaking Process Protects Valuable Public Policy Interests.

The present case illustrates the value of the APA rulemaking procedures and the reasons why the judiciary is strict in holding executive branch agencies accountable when, as here, an agency seeks to avoid proper rulemaking and, in its place, develops rules pursuant to some unauthorized APA process of the agency's creation. The APA notice-and-comment rulemaking process requires adequate advance notice and publication of the proposed rule in the Federal Register to allow "interested persons" (including members of the public) the opportunity to participate "through the submission of written data, views, or arguments," followed by publication of the final rule in the Federal Register, with a statement of basis and purpose "not less than 30 days before its effective date." 5 U.S.C. § 553(b)-(d). These requirements exist for sound reasons, including assuring public participation in the development of the rules under which interested parties will be governed and regulated and improving, through public exposure and opportunity for comment, the final governmental regulatory product. *See Nat'l Elec. Mfrs. Ass'n v. EPA*, 99 F.3d 1170, 1174 (D.C. Cir. 1996) (APA's notice-and-comment requirements serve purposes of "reintroduc[ing] public participation and fairness to affected parties after governmental authority has been delegated to unrepresentative agencies" and "assur[ing] that the agency will have before it the facts and information relevant to a particular administrative problem").

The rule FDA has announced here, effectively amending 21 C.F.R. § 314.108(b)(4)&(b)(5) to deny exclusivity protection where the 505(b)(2) NDA does not contain the identical active moiety of the original application, changes substantially the rules of the regulatory road and upsets reasonable and settled expectations of Otsuka and other similarly situated companies. These companies invest very substantial resources, both human and financial, in developing innovative products entitled to exclusivity based on an understanding that this earned exclusivity is real, and

not something that FDA can take away without prior notice and an opportunity to comment on FDA's proposed new regulatory approach. That, however, is what happened here. If FDA wants to change the rules here, it should do so properly and in the fashion that the APA directs.

FDA undeniably failed to comply with the APA's rulemaking requirements in announcing and applying a new legislative rule. Otsuka is entitled to judgment on Count Three of its complaint and FDA's decisions should be vacated.

CONCLUSION

For the reasons stated, the Court should grant Otsuka's motion for judgment on all three counts of its complaint and the Court should vacate FDA's October 5, 2015 letter decision and its approval on that date of the Aristada NDA.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on this 17th day of November, 2015, a copy of the foregoing PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT was filed and served electronically using the CM/ECF system to:

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