IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

OTSUKA PHARMACEUTICAL CO., LTD.,
2-9 KANDA TSUKASA-MACHI
CHIYODA-KU
TOKYO, 101-8535, JAPAN, and

OTSUKA PHARMACEUTICAL DEVELOPMENT & COMMERCIALIZATION, INC.
508 CARNEGIE CENTER
PRINCETON, NJ 08540, and

OTSUKA AMERICA PHARMACEUTICAL, INC.
508 CARNEGIE CENTER
PRINCETON, NJ 08540,

Plaintiffs,

v.

SYLVIA MATHEWS BURWELL, SECRETARY
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
200 INDEPENDENCE AVE., S.W.
WASHINGTON, D.C., 20201, and

DR. STEPHEN OSTROFF, ACTING COMMISSIONER
U.S. FOOD AND DRUG ADMINISTRATION
10903 NEW HAMPSHIRE AVENUE
SILVER SPRING, MD 20993, and

U.S. FOOD AND DRUG ADMINISTRATION
10903 NEW HAMPSHIRE AVENUE
SILVER SPRING, MD 20993,

Defendants.

SERVE ON:

SYLVIA MATHEWS BURWELL, SECRETARY

Case No. 15-1688

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
200 INDEPENDENCE AVE., S.W.
WASHINGTON, D.C., 20201, and

DR. STEPHEN OSTROFF, ACTING COMMISSIONER
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SILVER SPRING, MD 20993, and

U.S. FOOD AND DRUG ADMINISTRATION
10903 NEW HAMPSHIRE AVENUE
SILVER SPRING, MD 20993, and

ACTING U.S. ATTORNEY VINCENT H. COHEN, JR.
555 4TH STREET, NW
WASHINGTON, DC 20530, and

LORETTA E. LYNCH
ATTORNEY GENERAL OF THE UNITED STATES
U.S. DEPARTMENT OF JUSTICE
950 PENNSYLVANIA AVENUE, N.W.
WASHINGTON, DC 20530-0001

* * * * * * *

COMPLAINT

Plaintiffs Otsuka Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Development & Commercialization, Inc., and Otsuka America Pharmaceutical, Inc. (collectively, "Otsuka") bring this action for declaratory and injunctive relief against defendants, the Secretary of the U.S. Department of Health and Human Services, the Acting Commissioner of the U.S. Food and Drug Administration, in their respective official capacities, and the U.S. Food and Drug Administration

(all defendants are referred to collectively as "FDA"). Otsuka challenges FDA's final agency action and says as follows for its complaint against FDA:

Preliminary Statement

1. The FDA decisions challenged in this case undermine a fundamental aspect of the federal Food, Drug, and Cosmetic Act ("FDCA"). In the Hatch-Waxman Amendments to the FDCA, Congress balanced incentivizing innovation and drug development (by providing for periods of exclusivity), on the one hand, and getting copycat drugs to the market more quickly, on the other. Copycat drugs cannot come to market until certain periods of exclusivity have expired for the copied drugs. Here, FDA disregarded the text and purpose of the exclusivity provisions and, in their place, created a wholly unauthorized new scheme to deny Otsuka exclusivity rights it earned and to approve a so-called new drug that undeniably is not a medical advance; provides no new or additional therapeutic benefit; and, as its own manufacturer has boasted repeatedly, operates in the body exactly as does Otsuka's drug. Rather than incentivize innovation and new drug development to benefit public health, FDA's action punishes the innovator and unlawfully rewards a follow-on copycat company that proposes to bring to market a drug that provides no new or additional public health benefit. FDA's decision inverts the intent of the FDCA by denying Otsuka the protection to which it is legally entitled and rewarding what is, at best, an imitative competitor's facially clever, but substantively meaningless, chemical trick. Neither law nor sound policy supports this outcome. FDA's decision should not stand.

2. Otsuka here challenges FDA's arbitrary, capricious, and unlawful approval of the New Drug Application ("NDA") submitted by Alkermes plc ("Alkermes") under Section 505(b)(2) of the FDCA for aripiprazole lauroxil (marketed as Aristada®). FDA's approval of the Alkermes NDA violates the valuable statutory exclusivity rights Otsuka earned when it received

approval for its long-acting injectable formulation of aripiprazole for the treatment of schizophrenia. FDA's October 5, 2015 decision denying Otsuka's citizen petition (Ex. A) and its decision that day approving the Alkermes NDA are unlawful and should be vacated and reversed.

3. Otsuka is the NDA holder for Abilify Maintena®, a long-acting injectable formulation of aripiprazole indicated for the treatment of schizophrenia. In December 2014, FDA approved Otsuka's supplemental NDA for Abilify Maintena that resulted in three years of exclusivity for the use of aripiprazole to treat schizophrenia in acutely relapsed patients. However, by approving the Alkermes NDA for Aristada® (aripiprazole lauroxil), FDA violated that exclusivity. Aristada is a long-acting injectable formulation that is a prodrug of aripiprazole indicated for the treatment of schizophrenia, with conditions of use that are the same as Abilify Maintena. A prodrug is an inactive compound that requires metabolic conversion prior to becoming a molecule that actually acts in the body.

4. Aripiprazole lauroxil is not – by any means or by any definition – an innovative drug. It does not, for example, represent a therapeutic advance, nor does it provide any new or additional therapeutic benefit beyond that provided by Otsuka's Abilify Maintena. Rather, for all therapeutic purposes, aripiprazole lauroxil is aripiprazole. Indeed, FDA acknowledges that aripiprazole is an "active metabolite" in aripiprazole lauroxil and aripiprazole provides the therapeutic benefit to patients taking aripiprazole lauroxil. *See* Ex. A, at 21, 23 n.80, 26; *see also* Ex. B, Full Prescribing Information § 12.3. Alkermes strenuously agrees; Alkermes has said repeatedly that the active moiety of aripiprazole lauroxil is, in fact, aripiprazole. *See* Richard Pops, Chairman and CEO, Alkermes' CEO Presents at Goldman Sachs Healthcare Conference (June 11, 2013), *available at* http://seekingalpha.com/article/1500922-alkermes-ceo-presents-at-goldman-sachs-healthcare-conference-transcript?part=single ("[T]he active moiety is aripiprazole.");

Richard Pops, Chairman and CEO, Alkermes CEO Presents at Citi Global Healthcare Conference (Feb. 25, 2013), *available at* http://seekingalpha.com/article/1222541-alkermes-ceo-presents-at-citi-global-helathcare-conference-transcript?part=single ("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."); James Frates, CFO, Alkermes' Management Presents at Credit Suisse 2012 Healthcare Conference (Nov. 14, 2012), *available at* http://seekingalpha.com/article/1009251-alkermes-management-presents-at-credit-suisse-2012-healthcare-conference-transcript?part=single ("And one of the things – one of the questions we don't have to answer in the clinical program [for Aristada] is whether [Otsuka's drug] ABILIFY actually treats schizophrenia."). The FDA-approved label for Aristada mirrors this point. Ex. B, Full Prescribing Information § 12.3 ("ARISTADA is a prodrug of aripiprazole and its activity in the body is primarily due to aripiprazole, and to a lesser extent dehydro-aripiprazole (major metabolite of aripiprazole) . . . .").

5. Because aripiprazole lauroxil is, in substance, aripiprazole, Alkermes did not submit a full standalone NDA under Section 505(b)(1) that was supported by the standard two clinical trials to meet the FDCA's requirements that a drug be safe and effective for its proposed uses; instead, Alkermes used a "short-cut" under Section 505(b)(2) of the FDCA. Invoking that short-cut to demonstrate safety and effectiveness, Alkermes supported its NDA for aripiprazole lauroxil with only a single clinical trial and with FDA's prior findings of safety and effectiveness for orally administered aripiprazole in the treatment of schizophrenia. *See* Ex. B, Full Prescribing Information § 14 ("The efficacy of ARISTADA in the treatment of patients with schizophrenia was established, in part, on the basis of efficacy data from trials with the oral formulation of

aripiprazole.").

6. Despite the fact that both Abilify Maintena and Aristada are long-acting injectable formulations of aripiprazole indicated for the same conditions of use, FDA, in denying Otsuka's citizen petition (Ex.A), determined that Abilify Maintena and Aristada have different active moieties and, therefore, Aristada is not blocked by Otsuka's exclusivity covering aripiprazole. FDA then reversed field and simultaneously determined that the Aristada NDA could rely upon Otsuka-developed safety and efficacy data for aripiprazole to meet the FDCA's drug approval requirements for Aristada. So, in a regulatory sleight of hand, FDA determined that Abilify Maintena and Aristada are different for purposes of exclusivity, but because aripiprazole is the only active therapeutic agent in both (*i.e.*, the same), that Aristada could rely upon Otsuka's aripiprazole safety and effectiveness data.

7. FDA's decision is fundamentally unfair and badly misconstrues the FDCA's three-year exclusivity statute. *See* 21 U.S.C. § 355(c)(3)(E)(iii) & (iv). FDA's decision is sharply at odds with the plain meaning of the FDCA, the agency's regulations, and the goals of the 1984 Hatch-Waxman Amendments. FDA's decision allows Alkermes to obtain a Hatch-Waxman benefit (*i.e.*, reliance on aripiprazole under 505(b)(2)), but not to be subject to the corresponding Hatch-Waxman tradeoff (*i.e.*, subject to aripiprazole's exclusivity). By contrast, the carefully crafted Hatch-Waxman design is that a drug that relies on another drug to meet the FDCA's drug approval requirements is subject to the first drug's applicable exclusivity. FDA's unsound contrary reading of the statute allows for nonsubstantive, therapeutically meaningless, technical changes to already-approved drugs to undermine hard-earned statutory exclusivity for drugs that actually do make meaningful, substantive changes.

Parties

8. Plaintiff Otsuka Pharmaceutical Co., Ltd. ("OPC") owns the NDAs for Abilify and Abilify Maintena. OPC is located in Japan. Plaintiff Otsuka Pharmaceutical Development & Commercialization, Inc. ("OPDC") conducts research for OPC on Abilify and Abilify Maintena and has been designated to be OPC's agent in negotiations with FDA. Plaintiff Otsuka America Pharmaceutical, Inc. distributes and markets Abilify and Abilify Maintena.

9. Defendant Sylvia Mathews Burwell is sued in her official capacity as the Secretary of the U.S. Department of Health and Human Services ("HHS"), a cabinet-level agency of the executive branch of the United States Government. Defendant FDA is a major operating division of HHS. As Secretary of HHS, Secretary Burwell has supervisory responsibility for FDA.

10. Defendant Dr. Stephen Ostroff is sued in his official capacity as Acting Commissioner of FDA. Defendant HHS Secretary Burwell has delegated authority to Acting FDA Commissioner Ostroff to administer the provisions of the FDCA, including the FDCA provisions at issue in this case.

11. Defendant FDA is the agency of the United States government that administers the FDCA. In this action, Otsuka challenges FDA's final agency action.

Jurisdiction and Venue

12. This complaint arises under and asserts violations of federal law, specifically the FDCA, 21 U.S.C. § 301 *et seq.*, and the Administrative Procedure Act ("APA"), 5 U.S.C. § 551 *et seq.*; therefore, this Court has subject matter jurisdiction pursuant to 28 U.S.C. § 1331. Pursuant to 28 U.S.C. §§ 2201-2202, the Court is authorized to grant Otsuka's prayers for declaratory relief.

13. All defendants have offices and conduct business in this district. Venue is proper in this Court pursuant to 28 U.S.C. § 1391(b) and (e) and 5 U.S.C. § 703.

Background

A. Statutory Background

14. As described below, after much study and debate, Congress carefully constructed a balanced regulatory scheme designed to incentivize new drug development or new uses of existing drugs via the granting of certain market exclusivities while also allowing certain alternative drug approval routes subject to those prior exclusivities.

1. New Drug Applications Under Section 505(b)(1) And 505(b)(2)

15. FDA must approve a drug before it may be sold lawfully or distributed in interstate commerce. *See* 21 U.S.C. § 355(a). Sponsors seeking to market new or generic drugs can obtain FDA approval through one of three pathways: (1) a full standalone NDA under Section 505(b)(1) of the FDCA; (2) an Abbreviated New Drug Application; or (3) an intermediate pathway under 505(b)(2) of the FDCA.

16. "Full standalone NDAs" under Section 505(b)(1) must include "full reports of investigations" of safety and effectiveness. This type of application requires an applicant to conduct clinical and non-clinical studies to demonstrate that the proposed drug is safe and effective for its intended use.

17. The "intermediate pathway" under Section 505(b)(2) allows an applicant to short-cut the full standalone NDA process. The 505(b)(2) applicant may rely on determinations of safety and effectiveness for drugs previously submitted by a 505(b) applicant that were supported by investigations not conducted or licensed by the subsequent 505(b)(2) sponsor.

18. FDA may not approve either a 505(b)(1) or 505(b)(2) application if the investigations required are inadequate to support a finding of safety or if there is insufficient information of safety. 21 U.S.C. § 355(d)(1), (2), (4). Nor may FDA approve an NDA submitted under Section 505(b) where "there is a lack of substantial evidence that the drug will have the

effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling." 21 U.S.C. § 355(d)(5). Generally, "substantial evidence" requires two adequate and well-controlled trials. *See* 21 U.S.C. § 355(d); *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* 3 (May 1998), http://www.fda.gov/downloads/Drugs/.../Guidances/ucm078749.pdf.

2. Three-Year Exclusivity Under Section 505(c)(3)(E)(iii) and (iv)

19. In 1984, Congress adopted the Hatch-Waxman Amendments to the FDCA. These amendments created certain exclusivities to incentivize drug manufacturers to create new drugs and further develop already approved drugs. These exclusivities operate to protect the investment of innovators because, as Congress recognized, absent such protection, there will be less innovation, with fewer new therapies developed. Two of the Hatch-Waxman exclusivities are the five-year exclusivity provision in Section 505(c)(3)(E)(ii) and the three-year exclusivity provisions in Section 505(c)(3)(E)(iii) and (iv). These provisions instruct when an application submitted under the 505(b)(2) intermediate pathway is blocked by the exclusivity of a prior 505(b) application.

20. Congress created five-year exclusivity to incentivize the investment of time and resources into the development of New Chemical Entities, *i.e.*, "a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under [505(b)]." 21 U.S.C. § 355(c)(3)(E)(ii). Congress also created three-year exclusivity to incentivize drug manufacturers' investment in new clinical trials of already approved drugs (*i.e.*, non-New Chemical Entities, or "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 [505(b)]"). *Id.* § 355(c)(3)(E)(iii) & (iv); *e.g.*, 130 Cong. Rec. 24436 (Sept. 6, 1984)

(statement of Rep. Waxman); *Veloxis Pharms., Inc. v. FDA*, No. 14-2126, 2015 U.S. Dist. LEXIS 77559, *36 n.13 (D.D.C. June 16, 2015) ("Were the FDA to permit the entry of Envarsus XR into the marketplace for prophylaxis of organ rejection in *de novo* kidney transplant patients before the expiry of Astagraf XL's three-year exclusivity, the FDA would in fact be eviscerating an incentive for sponsors such as Astellas to research and develop new drugs.").

21. The exclusivity clause in Section 505(c)(3)(E)(iii) provides that "a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another [505(b)] application" is eligible for exclusivity if it is approved after 9/24/1984 and "contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." If these eligibility conditions are satisfied, the bar clause directs that "the Secretary may not make the approval of an application submitted under [505(b)] for the conditions of approval of such drug in the approved subsection (b) application [for three years] 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 whom the investigations were conducted."

22. Thus, where a drug has received exclusivity, FDA may not approve a 505(b)(2) application for the conditions of approval of the "drug" in the first-in-time 505(b) application for three years.

23. The exclusivity clause in Section 505(c)(3)(E)(iv) provides that a supplement to a 505(b) NDA that is approved after 9/24/84 and "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" is eligible for exclusivity. If these eligibility

conditions are satisfied, the bar clause directs that "the Secretary may not make the approval of a[505(b) application] for a change approved in the supplement effective [for three years] 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."

24. Reinforcing the breadth of 505(c)(3)(E)(iii), Section 505(c)(3)(E)(iv) provides that, where a supplement is eligible for exclusivity, FDA may not approve a 505(b)(2) application for a "change" in the supplement for three years.

25. Once the exclusivity conditions are satisfied, the "bar clauses" of 505(c)(3)(E)(iii) and (iv), which FDA reads in harmony, prevent FDA from approving a 505(b)(2) for the "drug in the approved subsection (b) application." The "drug in the approved subsection (b) application" is the same drug the applicant relied on under Section 505(b)(2), *i.e.*, the "drug for which the investigations described in [505(b)(1)(A)] were conducted."

26. A second-in-time 505(b)(2) NDA cannot be approved for changes for which new clinical investigations were essential, that is, for what FDA has called "innovative changes," for a period of three years. Where there is an overlap in the conditions of approval between the first filed 505(b) application and the second filed 505(b)(2) application, approval of the second application is blocked by the exclusivity attached to the first filed application. *See Veloxis Pharms.*, 2015 U.S. Dist. LEXIS 77559, at *30-31.

3. Three-Year Exclusivity Under 21 C.F.R. § 314.108(b)(4) and (5), FDA's Binding Interpretation Of Three-Year Exclusivity

27. In 1994, FDA promulgated a final rule setting forth its interpretation of and implementing the three-year provisions in Section 505(c)(3)(E)(iii) and (iv) of the Hatch-Waxman

Act. 59 Fed. Reg. 50338 (Oct. 3, 1994) (final rule); 54 Fed. Reg. 28872 (July 10, 1989) (proposed rule).

28. 21 C.F.R. § 314.108(b)(4), which implements 21 U.S.C. § 355(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 . . . ."

29. Under FDA's rule, a first-in-time application is eligible for exclusivity where the application was submitted under Section 505(b); was approved after 9/24/84; was for a drug product that contains an active moiety that has been previously approved in another Section 505(b) 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. Once those conditions are met, FDA is prohibited for a period of three years from approving "a 505(b)(2) application . . . <u>for the conditions of approval of the original application</u>." (emphasis added).

30. 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 . . . ."

31. Under FDA's rule, a supplemental application is eligible for exclusivity where the application was approved after 9/24/84 and 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. Once those conditions are met, FDA is prohibited for a period of three years from approving "a 505(b)(2) application . . . for a change." (emphasis added).

32. Thus, FDA's official regulatory interpretation of the statutory three-year exclusivity provisions is that three-year exclusivity attaches to the first-in-time "application" or "change." FDA is bound by its own regulations.

B. Case Specific Facts

1. Aripiprazole And Three-Year Exclusivity

33. Otsuka holds an approved NDA for Abilify®, an atypical antipsychotic indicated for treatment of schizophrenia and several other indications. Abilify is indicated as a once-daily oral formulation of aripiprazole for the treatment of schizophrenia.

34. Otsuka also holds an approved NDA for Abilify Maintena. Abilify Maintena, first approved on February 28, 2013, gave patients with schizophrenia a quite different and, for many patients, a much improved treatment option. The Abilify Maintena NDA was supported by a single new clinical investigation that demonstrated, for the first time, that a long-acting injectable formulation of aripiprazole was safe and effective for the treatment of schizophrenia in maintenance patients by delaying the time to relapse in comparison to placebo.

35. On December 5, 2014, FDA approved a supplemental NDA for Abilify Maintena for the treatment of schizophrenia based on clinical data from one short-term (12-week), randomized, double-blind, placebo-controlled trial that demonstrated the efficacy of the long-

acting injectable formulation of aripiprazole in the treatment of schizophrenia in acutely relapsing adults by demonstrating improvement of symptoms as compared to placebo.

36. Both Abilify Maintena approvals were supported by Otsuka's own proprietary oral aripiprazole data.

37. The long-acting injectable of aripiprazole for the treatment of schizophrenia was an innovation over the previously approved oral tablet form of aripiprazole. A once-monthly dosage is administered more easily than a daily tablet (a doctor need only see a patient once every thirty days to make sure he is treated for the next thirty days), and the decreased risk of missing a dosage prevents the disease from relapsing or progressing.

38. Otsuka received three-year marketing exclusivity under Section 505(c)(3)(E)(iii) and (iv) for the February 2013 and December 2014 approvals. As such, Otsuka has three-year exclusivity that covers long-acting aripiprazole for the conditions of use of treatment of schizophrenia in both maintenance and acutely relapsing patients. The last of these exclusivities does not expire until December 5, 2017.

2. The Alkermes NDA

39. On August 25, 2014, Alkermes announced that it had submitted an NDA to FDA seeking approval of aripiprazole lauroxil, a long-acting injectable for the treatment of schizophrenia. In its press release, Alkermes admitted that aripiprazole lauroxil converts to aripiprazole. Press Release, Alkermes Submits New Drug Application to FDA for Aripiprazole Lauroxil for Treatment of Schizophrenia (Aug. 25, 2014), *available at* http://phx.corporate-ir.net/phoenix.zhtml?c=92211&p=irol-newsArticle&ID=1960579&highlight ("Once in the body, aripiprazole lauroxil converts to aripiprazole, which is commercially available under the name ABILIFY®").

40. Alkermes has hyped its product repeatedly and aggressively as simply a prodrug 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), *available at* http://seekingalpha.com/article/1500922-alkermes-ceo-presents-at-goldman-sachs-healthcare-conference-transcript?part=single ("[T]he active moiety is aripiprazole."); Richard Pops, Chairman and CEO, Alkermes CEO Presents at Citi Global Healthcare Conference (Feb. 25, 2013), *available at* http://seekingalpha.com/article/1222541-alkermes-ceo-presents-at-citi-global-helathcare-conference-transcript?part=single ("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's Management Presents at Deutsche Bank 38th Annual dbAccess Health Care Conference (May 29, 2013), *available at* http://seekingalpha.com/article/1467941-alkermes-management-presents-at-deutsche-bank-38th-annual-dbaccess-health-care-conference-transcript ("[W]hat we are trying to do is deliver Aripiprazole, native Aripiprazole, over the course of a month."); Richard Pops, Chairman and CEO, Alkermes's CEO Presents at Bank of America Merrill Lynch Smid Cap Conference (May 8, 2013), *available at* http://seekingalpha.com/article/1415361-alkermes-ceo-presents-at-bank-of-america-merrill-lynch-smid-cap-conference-transcript ("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.").

41. Alkermes, exploiting that aripiprazole lauroxil is simply a prodrug delivering aripiprazole to the body to provide therapeutic effect, used the "short-cut," intermediate pathway

under Section 505(b)(2). Alkermes submitted an NDA for aripiprazole lauroxil that was supported by FDA's finding of safety and effectiveness for Otsuka's Abilify tablet and by a single adequate and well-controlled clinical trial. James Frates, CFO, Alkermes' Management Presents at Credit Suisse 2012 Healthcare Conference (Nov. 14, 2012), *available at* http://seekingalpha.com/article/1009251-alkermes-management-presents-at-credit-suisse-2012-healthcare-conference-transcript?part=single ("[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."); *see also* Ex. A, at 2.

C. Proceedings Before FDA

42. On September 9, 2014, Otsuka submitted to FDA a citizen petition requesting that FDA refuse to accept for substantive review the Alkermes NDA. 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. FDA found the petition premature and denied it on February 3, 2015.

43. On July 13, 2015, Otsuka submitted a second citizen petition. In that petition, Otsuka requested (1) that FDA delay or withhold final approval of the Alkermes NDA pending the expiration of Otsuka's three-year exclusivity for the conditions of approval of aripiprazole on December 5, 2017; and (2) that FDA refuse to approve the Alkermes NDA because it fails to satisfy the substantial evidence of effectiveness requirement. Alkermes submitted comments in opposition to Otsuka's petition to which Otsuka responded in supplements to its citizen petition.

3. FDA's Decision

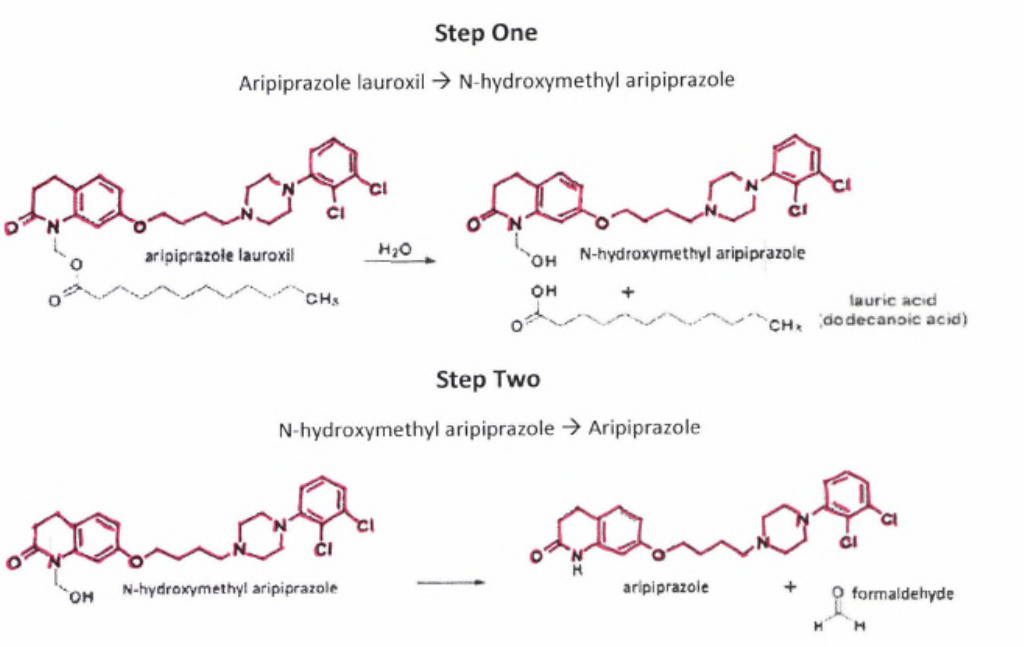
44. FDA denied Otsuka's July 2015 citizen petition on October 5, 2015. Ex. A. On that same day, FDA approved the Alkermes NDA for Aristada, a long-acting injectable for the treatment of schizophrenia with the same conditions of use as Abilify Maintena.

45. A large part of FDA's decision is devoted to attempting to distinguish the active moiety of Aristada from the active moiety of Abilify Maintena. FDA determined that Aristada's "active moiety" is N-hydroxymethyl aripiprazole, while Abilify Maintena's active moiety is aripiprazole. Ex. A, 14, 16-19. FDA's decision says aripiprazole lauroxil is a prodrug of N-hydroxymethyl aripiprazole, which is a prodrug of aripiprazole. *Id.* at 16.

46. FDA's decision is disingenuous both as a scientific and legal matter. The chemical process of Aristada is as follows: aripiprazole lauroxil is an ester that is enzymatically metabolized to N-hydroxymethyl aripiprazole; N-hydroxymethyl aripiprazole, an unstable intermediate, in turn, is simply converted to aripiprazole by spontaneous hydrolysis in plasma. Aristada's approved label says that "ARISTADA is a prodrug of aripiprazole," without claiming – as FDA does in its decision – that aripiprazole lauroxil is a prodrug of N-hydroxymethyl aripiprazole, which is a prodrug of aripiprazole. Ex. B, Full Prescribing Information § 12.1.

47. Moreover, while there are three chemical structures involved in the conversion process described above, FDA's decision acknowledges that only one (aripiprazole, indicated in red below) really matters; aripiprazole is the only molecule involved that has been shown to have therapeutic benefit in treating schizophrenia. FDA acknowledges that aripiprazole is an "active metabolite" in aripiprazole lauroxil and aripiprazole provides the therapeutic benefit to patients taking aripiprazole lauroxil. Ex. A, at 21, 23 n.80, 26. FDA's decision admits that it has no evidence that N-hydroxymethyl aripiprazole does anything. *See* Ex. A, at 23 n.80 ("The increased duration of effect of Aristada relative to Abilify Maintena *may be* attributable to the differences in

the active moieties." (emphasis added)). Even Aristada's FDA-approved label admits that Aristada's "activity in the body is primarily due to aripiprazole, and to a lesser extent dehydro-aripiprazole (major metabolite of aripiprazole)." Ex. B, Full Prescribing Information § 12.3.



48. After a so-called examination of the chemical structure of Aristada, FDA determined that Otsuka's three-year exclusivity for aripiprazole did not block approval of aripiprazole lauroxil. FDA concluded that a 505(b)(2) application, such as Alkermes's, is barred by a first-in-time approved 505(b), such as Otsuka's, only if the 505(b)(2) is an application for a drug containing the identical active moiety as the first-in-time 505(b) application. Ex. A, at 20-22. Because, by FDA's view, the Alkermes NDA has a different "active moiety" than Abilify Maintena (N-hydroxymethyl aripiprazole versus aripiprazole), FDA concluded that aripiprazole lauroxil's approval was not for the same "drug" referenced in 505(c)(3)(E)(iii) and (iv) and would not be barred by Abilify Maintena's exclusivity. *Id.* at 20-21.

49. Without citing any relevant past "precedent" and, indeed, brushing aside the only time FDA appears to have considered this issue, *id.* at 24 n.87, FDA approved aripiprazole lauroxil in the face of aripiprazole's exclusivity. FDA did so even though the aripiprazole lauroxil NDA absolutely relied on FDA's prior findings of safety and effectiveness for aripiprazole to meet the safety and effectiveness standards of the FDCA. *Id.* at 27-30.

50. FDA also determined that aripiprazole lauroxil was safe and effective for its proposed use (based in substantial measure on FDA's prior findings of safety and effectiveness for aripiprazole), notwithstanding that FDA determined that aripiprazole lauroxil was a New Chemical Entity and was only supported by one adequate and well-controlled clinical trial. *Id.* 27-30 ("It is entirely consistent with FDA's longstanding interpretation of the substantial evidence of effectiveness requirement under section 505(d) of the [FDCA] to approve Alkermes' 505(b)(2) NDA for Aristada extended-release injectable suspension on the basis of, among other things, (1) a single adequate and well-controlled clinical trial and (2) scientifically justified reliance on FDA's finding of *safety and effectiveness* for Abilify Tablets." (emphasis added)).

Count One – Violation of 21 U.S.C. § 355(c)(3)(E)(iii) and (iv) and 5 U.S.C. §§ 701 & 706

51. Otsuka here adopts and incorporates by reference Paragraphs 1-50 of this complaint as if fully set forth herein.

52. On October 5, 2015, FDA denied Otsuka's citizen petition and approved the Alkermes NDA in derogation of Otsuka exclusivity rights. FDA's denial of Otsuka's exclusivity rights and approval of the Alkermes NDA is arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law. This Court should vacate FDA's unlawful decisions.

53. FDA is an agency subject to the requirements of the APA. 5 U.S.C. § 701(b)(1). "[A]gency action, findings, and conclusions found to be arbitrary, capricious, an abuse of

discretion, or otherwise not in accordance with law" shall be held "unlawful and set aside." *Id.* § 706(2)(A).

54. Instead of submitting a full standalone NDA under Section 505(b)(1) supported by the standard two clinical trials required to meet the FDCA's drug approval requirements for safety and effectiveness, Alkermes used a short-cut under Section 505(b)(2) of the FDCA and supported its NDA for aripiprazole lauroxil with a single clinical trial plus FDA's prior findings of safety and effectiveness for Otsuka's drug aripiprazole. While relying upon Otsuka's clinical evidence, Alkermes sought to avoid (and FDA allowed it to avoid) the blocking effect of certain three-year exclusivity attaching to aripiprazole for the treatment of schizophrenia.

55. In denying Otsuka's citizen petition and approving Alkermes's NDA for aripiprazole lauroxil, FDA severely misconstrued the three-year exclusivity provisions, *see* 21 U.S.C. § 355(c)(3)(E)(iii) & (iv), to allow an NDA submitted under 505(b)(2) to rely on an already approved drug (aripiprazole) to demonstrate safety and effectiveness yet avoid that same drug's exclusivity. FDA determined that a 505(b)(2) application (here, aripiprazole lauroxil) is only barred by a first-in-time approved 505(b) (here, aripiprazole) if the 505(b)(2) application is for a drug containing the identical active moiety as the first-in-time 505(b) application. Because FDA determined that the Alkermes NDA has a different "active moiety" than Abilify Maintena (N-hydroxymethyl aripiprazole versus aripiprazole), FDA concluded that aripiprazole lauroxil's approval was not for the same "drug" referenced in 505(c)(3)(E)(iii) and (iv) and would not be barred by Abilify Maintena's exclusivity. Ex. A, at 20-22. Yet, to support that allegedly different active moiety (N-hydroxymethyl aripiprazole), the FDA allowed safety and efficacy data not of that allegedly different moiety, but of the prior drug aripiprazole, which has market exclusivity.

56. Contrary to FDA's decision and its incorrect, hyper-technical, narrowly

constrained, and therapeutically nonsensical reading of the statutory language, a 505(b)(2) NDA cannot rely on FDA's prior findings of safety or effectiveness for a particular "drug" (here, aripiprazole) to meet FDA's drug approval requirements and simultaneously avoid the exclusivity of that same "drug." Under 505(c)(3)(E)(iii) and (iv), FDA's exclusivity analysis must include the drug relied upon by the 505(b)(2) NDA to meet FDA's drug approval requirements. FDA must then determine if the 505(b)(2) NDA is seeking approval for protected conditions of approval for that drug based on the innovation demonstrated in the clinical trial that resulted in three-year exclusivity for the first applicant. Where, as here, the 505(b)(2) NDA is seeking such approval, final FDA approval must be denied pending the expiration of the first applicant's exclusivity.

57. FDA's conclusion is premised on a substantively meaningless and unsupportable determination that the active moiety of aripiprazole lauroxil is N-hydroxymethyl aripiprazole, a component of Aristada for which FDA has no proof that it provides any therapeutic benefit. *See* 21 C.F.R. § 314.108(a) (defining "active moiety" as "the molecule or ion . . . responsible for the physiological or pharmacological action of the drug substance").

58. FDA's decision is also wrong as a matter of statutory structure and public policy for it undermines the purpose of three-year exclusivity and sanctions the wholesale manipulation of the Hatch-Waxman scheme. Congress never intended that a competitor would be allowed to avoid (violate) its competitor's exclusivity rights by making meaningless (therapeutically irrelevant) chemical changes to an already approved drug, while relying on that prior drug's clinical evidence. The "bar clauses" of Section 505(c)(3)(E)(iii) and (iv) cannot be interpreted to undermine an innovator's exclusivity where a copycat makes meaningless chemical changes to the innovator's drug.

59. FDA's conclusion that it could approve the Alkermes NDA in the face of Otsuka's

still effective exclusivity is arbitrary and capricious and a decision directly contrary to law and to the undisputed fact that the Alkermes NDA is in no therapeutically meaningful sense "new" because, once injected, all of the therapeutic benefit of aripiprazole lauroxil is derived from the fact that it becomes aripiprazole.

Count Two – Violation of 21 C.F.R. § 314.108 and 5 U.S.C. §§ 701 & 706

60. Otsuka here adopts and incorporates by reference Paragraphs 1-59 of this complaint as if fully set forth herein.

61. FDA's exclusivity determination violates the agency's regulations. FDA's denial of Otsuka's exclusivity rights and approval of the Alkermes NDA is arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law. This Court should vacate FDA's unlawful decisions.

62. FDA is an agency subject to the requirements of the APA. 5 U.S.C. § 701(b)(1). "[A]gency action, findings, and conclusions found to be arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law" shall be held "unlawful and set aside." *Id.* § 706(2)(A).

63. FDA's regulations implementing Section 505(c)(3)(E)(iii) and (iv) of the FDCA represent the agency's interpretation of the statutory meaning of those provisions. When, as here, the exclusivity eligibility conditions are met, 21 C.F.R. § 314.108(b)(4) and (b)(5) prohibit FDA for a period of three years from approving a 505(b)(2) "for the conditions of approval of the original application" and "for a change." The cramped contrary interpretation set forth in FDA's October 5 decision violates FDA's broader and binding interpretation of the statute. To now interpret the statute to bar a 505(b)(2) application only where a drug contains the identical active moiety as the first-in-time 505(b) application wholly disregards and ignores FDA's regulation.

What matters under the regulation is whether the 505(b)(2) applicant is seeking approval "for the conditions of approval of the original application" or "for a change." FDA's decision and its approval of the NDA for Aristada violate FDA's regulation.

64. As a matter of law, FDA is bound by and required to comply with and follow its own regulation. Here, FDA's violation of its regulation is arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law.

Count Three – Violation of APA Rulemaking Requirements

65. Otsuka adopts and incorporates by reference the allegations contained in paragraphs 1 through 64 of this complaint as if fully set forth herein.

66. FDA is an agency subject to the requirements of the APA. 5 U.S.C. § 701(b)(1). This includes the APA's requirements for rulemaking. 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 id.* §§ 553(b)-(d); *see also id.* § 706(2)(a).

67. 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).

68. The "rule" announced in FDA's October 5 decision is a "rule" within the meaning of the APA that was not adopted in accordance with the rulemaking requirements of the APA.

69. FDA's regulations implementing the three-year exclusivity provisions in Section 505(c)(3)(E)(iii) and (iv), prohibit FDA, so long as the exclusivity eligibility conditions are met, for a period of three years from approving a 505(b)(2) "for the conditions of approval of the original application" and "for a change." 21 C.F.R. § 314.108(b)(4) and (b)(5).

70. FDA's new rule announced in this matter that Sections 505(c)(3)(E)(iii) and (iv) block approval only of a 505(b)(2) that contains an identical moiety as the original 505(b) application allows exactly what the regulation prohibits. The 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 allows FDA to approve a 505(b)(2) "for the conditions of approval of the original application."

71. FDA's new rule seeks to amend the current (and properly promulgated) rule to add the words "unless the 505(b)(2) does not contain the identical moiety of the original application" to the end of the regulation:

> "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 . . . . [***unless the 505(b)(2) does not contain the identical moiety of the original application***]"

72. Where an agency promulgates a "rule," the APA requires an agency to follow formal notice-and-comment 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).

73. FDA's process here fell far short of what the APA requires. FDA failed to provide adequate notice and publication of the proposed rule in the *Federal Register*; did not formally request comments in any proper rulemaking process; and failed to publish in the *Federal Register* a final rule.

74. Because FDA did not comply with the rulemaking requirements of the APA, the rule applied in this matter is invalid and the Alkermes approval decision based upon that rule is equally and necessarily invalid. *See* 5 U.S.C. § 706(2)(a).

Prayers for Relief

WHEREFORE, Otsuka prays as follows:

(a) that the Court expedite proceedings herein (a motion to expedite is filed herewith);

(b) that the Court declare that FDA's denial of Otsuka's exclusivity rights and approval of the Alkermes NDA were arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law;

(c) that the Court vacate FDA's approval of the Alkermes NDA and vacate any FDA decisions or actions underlying or supporting or predicated upon that approval;

(d) that the Court declare that Otsuka's exclusivity rights preclude FDA from granting approval of the Alkermes NDA pending the expiration of those rights in December 2017; and

(e) that the Court grant any and all other, further, and additional relief, including all necessary and appropriate protective preliminary, interim, or permanent relief, as the nature of the cause may require, including all necessary and appropriate declarations of rights and injunctive relief.

Dated: October 15, 2015

/s/ Ralph S. Tyler

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