IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

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	*	CIVIL ACTION NO.
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. Margaret Hamburg, Commissioner, or 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 U.S. Department of Health and Human Services	*	

200 Independence Ave., S.W.
Washington, D.C., 20201, and *

Dr. Margaret Hamburg, Commissioner, or *
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, and *

U.S. Attorney Rod J. Rosenstein *
6406 Ivy Lane, Suite 800
Greenbelt, MD 20770, and *

Eric H. Holder, Jr. *
Attorney General of the United States
U.S. Department of Justice *
950 Pennsylvania Avenue, N.W.
Washington, DC 20530-0001 *

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COMPLAINT

Plaintiffs Otsuka Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Development & Commercialization, Inc., and Otsuka America Pharmaceutical, Inc. (hereinafter referred to collectively as "Otsuka") bring this action for declaratory and injunctive relief against defendants, the Secretary of the U.S. Department of Health and Human Services, the Commissioner/Acting Commissioner of the U.S. Food and Drug Administration, all in their respective official capacities, and the U.S. Food and Drug Administration ("FDA") (defendants are referred to collectively herein as "FDA"). Otsuka says as follows for its complaint against FDA:

Preliminary Statement

1. In count one of this complaint, Otsuka challenges FDA's arbitrary, capricious, and unlawful abuse of its authority in approving a supplemental new drug application ("sNDA"). FDA unlawfully broadened the scope of Otsuka's approved "indication for use" of its prescription brand drug aripiprazole, which Otsuka markets under the name Abilify®. FDA's action of broadening the scope of Otsuka's approved indication was arbitrary, capricious, contrary to the Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 301 *et seq.*, and an unlawful abuse of discretion under the Administrative Procedure Act ("APA"), 5 U.S.C. § 706(2)(A). If allowed to stand, FDA's unlawful final agency action may jeopardize important and valuable rights and benefits to which Otsuka is entitled under the Orphan Drug Act and FDCA.

2. The second count of Otsuka's complaint seeks a declaration of Otsuka's rights under the broadened "corrected" indication that FDA approved (assuming, without conceding, the lawfulness of FDA's action of approving the broadened indication). Even under that broadened indication, the FDA-approved label includes ample pediatric information which, pursuant to Section 505A(o) of the FDCA, 21 U.S.C. § 355a(o), cannot be omitted from the label of any approved generic. Thus, even under FDA's broadened indication, FDA is precluded from approving generic versions of Abilify.

3. Otsuka submitted a sNDA to FDA for Abilify in 2014. Otsuka supported its sNDA with adequate and well-controlled clinical trial data demonstrating the safety and effectiveness of Abilify for the treatment of pediatric patients with Tourette's Disorder. Based on these data, Otsuka sought FDA approval for a new indication for Abilify for the treatment of *pediatric* patients with Tourette's Disorder. FDA initially – and properly – granted the requested approval for the treatment of *pediatric* patients with Tourette's Disorder. Two-and-a-half months later, however,

FDA, without any factual basis and without lawful justification, reversed itself and issued a "corrected" approval decision. FDA based its unlawful reversal on an alleged and altogether unexplained "error" of limiting its approval to *pediatric* patients.

4. FDA's unlawful "correction" of its belatedly discovered "error" granted Otsuka, in the absence of any supporting data in Otsuka's sNDA and in the absence of any request from Otsuka, a far broader indication. FDA approved Abilify for the treatment of *all* patients with Tourette's Disorder, without regard to the patient's age. Notably, Otsuka's clinical data demonstrated the safety and effectiveness of the drug in pediatric patients only, and *not* in non-pediatric patients.

5. FDA does not conduct its own independent clinical trials to determine the safety and effectiveness of a requested new indication; therefore, on information and belief, Otsuka alleges that FDA has no clinical trial information to substantiate the broader (age unlimited) indication the agency approved. Otsuka's sNDA contained no studies to identify the most appropriate and effective dose of Abilify in treating adult patients with Tourette's Disorder. FDA's "corrected" approval, approving Abilify for use in a far broader population group than the limited population subset in which the drug has been proven to be safe and effective, is inconsistent with FDA's obligation to act in the public interest to protect public health and safety.

6. Significantly, there was nothing innocent or unintentional in FDA's action. FDA acted deliberately, intentionally, and without justification to seek to deny Otsuka important statutory rights and economic benefits to which Otsuka is entitled. FDA's unlawful "correction" of its original approval of Abilify for treatment in pediatric patients with Tourette's Disorder was an attempt to clear a blocked path for FDA's approval of abbreviated new drug applications ("ANDA") for generic versions of Abilify.

7. With the pediatric indication, Otsuka was plainly entitled to a seven-year period of exclusivity (until December 2021) during which time FDA could not approve a generic version of Abilify for any of its FDA-approved indications. In the case of pediatric information (here, the use of Abilify for treatment in pediatric patients with Tourette's Disorder), there are very limited and expressly stated statutory exceptions to the general rule that the label of an approved generic must be the same as the label of the brand drug. None of those narrowly drawn exceptions permit the omission of a pediatric indication related to orphan drug exclusivity. Therefore, if the approved indication for Abilify for treatment of Tourette's Disorder were limited to a pediatric indication, as it initially was and should be, FDA could not approve a generic version of Abilify for any of the drug's FDA-approved indications pending the expiration of Otsuka's seven-year market exclusivity period in December 2021. FDA's unlawful broadening of the approved pediatric indication to an indication for use in the population at large was an attempt, in FDA's view, to open the closed door to approval of a generic version of Abilify (for indications other than Tourette's Disorder) on or about April 20, 2015, when Otsuka's current patent and regulatory protection expires. Any such generic approvals would immediately and greatly harm Otsuka.

8. In the alternative, assuming without conceding the lawfulness of FDA's broadened "corrected" approval, approving Abilify for treatment of Tourette's Disorder in the population at large, FDA is still and nevertheless precluded from approving generic versions of Abilify (for indications other than Tourette's Disorder) on or about April 20, 2015. The FDA approved label for the broadened indication contains substantial amounts of pediatric information that, by statute, cannot be omitted, thereby barring FDA from approving generics pending the expiration of Otsuka's seven-year market exclusivity period.

9. Pursuant to count one of Otsuka's complaint, the Court should grant final binding

declaratory and injunctive relief and order FDA (a) to rescind the unauthorized, unlawful broadened approval for treatment of all patients with Tourette's Disorder, without regard to the patient's age; (b) to approve (*i.e.*, to reinstate the approval of) Abilify for treatment in pediatric patients with Tourette's Disorder; and (c) not to grant approval of any ANDAs for generic versions of Abilify pending the expiration of Otsuka's seven-year exclusivity period. In the alternative, if the Court determines, despite Otsuka's arguments to the contrary, that FDA's "corrected" broadened approval action was lawful, the Court should, pursuant to count two of Otsuka's complaint, grant final binding declaratory and injunctive relief and order FDA not to grant approval of any ANDAs for generic versions of Abilify pending the expiration of Otsuka's seven-year exclusivity period.

Parties

10. Plaintiff Otsuka Pharmaceutical Co., Ltd. ("OPC") owns the NDAs for Abilify – N021436 (tablets), N021729 (orally disintegrating tablets), N021713 (oral solution), N021866 (injection; intramuscular) – and manufactures Abilify tablets. OPC is located in Japan and, through its sales of Abilify, conducts substantial business in the District of Maryland and throughout the United States.

11. Plaintiff Otsuka Pharmaceutical Development & Commercialization, Inc. ("OPDC") conducts research for OPC on Abilify and has been designated to be the company's agent in negotiations with FDA. OPDC received the "corrected" approval letter from FDA.

12. Plaintiff Otsuka America Pharmaceutical, Inc. distributes and markets Abilify.

13. 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.

14. Defendant Dr. Margaret Hamburg or defendant Dr. Stephen Ostroff are sued in their respective official capacities as the Commissioner of FDA (Dr. Hamburg) or Acting Commissioner of FDA (Dr. Ostroff) (Dr. Hamburg's departure from FDA is imminent and she is to be succeeded by Dr. Ostroff; Otsuka is uncertain as to the exact transition date). Defendant HHS Secretary Burwell has delegated authority to the FDA Commissioner/Acting FDA Commissioner to administer the provisions of the FDCA, including all the provisions at issue in this case.

15. 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

16. This action arises under federal law, specifically the FDCA, 21 U.S.C. § 301 *et seq.*, and the 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.

17. Venue is proper in the District of Maryland pursuant to 28 U.S.C. § 1391(e). All defendants regularly conduct business in this district and defendant FDA has its headquarters in this district in Silver Spring, Maryland.

Statement Of Facts

A. Statutory Background

1. New Drug And Supplemental Drug Applications

18. FDA must approve a prescription drug before the drug may be lawfully sold or distributed in interstate commerce. *See* 21 U.S.C. § 355(a). To gain approval, a drug manufacturer must submit either a new drug application ("NDA") or a supplemental new drug application ("sNDA") for a new indication of an already approved drug. *See* 21 C.F.R. § 314.1 *et seq.* The approval requirements are the same for NDAs and sNDAs. *Id.*; 21 C.F.R. § 314.71(b).

19. An NDA or sNDA must include evidence of the drug's safety and effectiveness for the particular indication or indications sought to be approved, with safety and effectiveness demonstrated by the applicant's submission of "full reports of [all clinical] investigations which have been made to show whether . . . such drug is safe for use and whether such drug is effective in use." 21 U.S.C. § 355(b)(1)(A); 21 C.F.R. § 314.50(d)(5).

20. FDA may not approve a new drug or a new indication for an approved drug if (1) the clinical investigations "do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe *for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof*"; (2) the results of the clinical investigations "show that such drug is unsafe *for use under such conditions* or do not show that such drug is safe *for use under such conditions*"; or (3) "evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence [*i.e.*, "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved"] 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 thereof*." 21 U.S.C. § 355(d)(1), (2), (5) (emphasis added); *see also* 21 C.F.R. § 314.126(a) ("Reports of adequate and well-controlled investigations provide the primary basis

for determining whether there is 'substantial evidence' to support the claims of effectiveness for new drugs.").

21. In short, FDA's approval of an indication for a drug is limited by the clinical data the manufacturer submits in its application in support of the use of the drug for that particular purpose. *See* FDA, Development & Approval Process (Drugs) ("[After testing its drug, t]he company then sends [FDA's Center for Drug Evaluation and Research] the evidence from these tests to prove the drug is safe and effective *for its intended use*." (emphasis added)), http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm.

22. Abbreviated New Drug Applications ("ANDAs") for a generic version of a previously approved brand drug avoid the costly and lengthy process applicable to new drugs and new indications for already approved drugs. An ANDA applicant, rather than investing the significant time and money that would be required to establish the safety and efficacy of a proposed generic drug, may rely on the safety and efficacy data contained in the predicate (brand drug) NDA. An ANDA applicant need only show that the generic has the same active ingredients and routes of administration, has the same labeling (including indications of use), and is "bioequivalent" to the innovator (brand) drug. *See* 21 U.S.C. § 355(j)(2)(A)(i)-(v).

23. To justify the exceedingly risky and uncertain investment of substantial time and sums of money involved in preparing and submitting NDAs and sNDAs, Congress's statutory scheme accommodates patent protection and provides other statutory exclusivity protections to ensure that, for a period of time, applicants will have the exclusive right to market their drugs for their respective indicated uses.

24. An important category of statutory exclusivity is granted by the Orphan Drug Act ("ODA") of 1983, Pub. L. 97-414, 96 Stat. 2049. The ODA provides drug manufacturers with

incentives to develop drugs for the treatment of rare diseases or disorders, diseases which, by definition, affect only a small patient population. Tourette's Disorder is such an "orphan disorder." Without these incentives, manufacturers would be far less likely to develop treatments for rare diseases or disorders because the small size of the potential patient population would not justify a manufacturer's risk and investment. One of the critically important incentives Congress provided in the ODA is a seven-year period of exclusivity in which FDA cannot approve another application for the orphan indication or use. 21 U.S.C. § 360cc(a) 21 C.F.R. § 316.3(b)(12) ("[N]o approval will be given to a subsequent sponsor of the same drug for the same use or indication for 7 years . . . .").

2. Labeling Requirements

a. In General

25. A prescription drug's labeling includes "all labels and other written, printed, or graphic matter upon any article or any of its containers or wrappers, or accompanying such article." 21 U.S.C. § 321(m)(1)-(2).

26. A prescription drug's labeling must "contain[a]dequate information for such use, including indications, effects, dosages, routes, methods, and frequency and duration of administration and any relevant warnings, hazards, contraindications, side effects, and precautions, under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all conditions for which it is advertised or represented." 21 C.F.R. § 201.100(d)(1).

27. A prescription drug's labeling includes the portion of the label describing "Highlights of Prescribing Information" and "Full Prescribing Information." 21 C.F.R. § 201.56(d)(1); *see also* Mary E. Kremzner, Pharm.D. & Steven F. Osborne, M.D., both of FDA,

An Introduction to the Improved FDA Prescription Drug Labeling, at 5 ("Prescription drug labeling information is also known as [p]rescribing information, [p]ackage insert, [p]rofessional labeling, [d]irection circular, [and p]ackage circular"), http://www.fda.gov/downloads/Training/ForHealthProfessionals/UCM090796.

28. The "Full Prescribing Information" portion must include an "Indications and Usage" section that "state[s] that the drug is indicated for the treatment, prevention, mitigation, cure or diagnosis of a recognized disease or condition." 21 C.F.R. § 201.57(c)(2). "If evidence is available to support the safety and effectiveness of the drug or biological product only in selected subgroups of the larger population (e.g., . . . *patients in a special age group*) . . . a succinct description of the limitations or usefulness of the drug and any uncertainty about anticipated clinical benefits" must be included. *Id.* § 201.57(c)(2)(i)(B) (emphasis added). Elsewhere the regulations explain that, "[i]f there is a specific pediatric indication different from those approved for adults that is supported by adequate and well-controlled studies in the pediatric population, it must be described under the 'Indications and Usage' section." *Id.* § 201.57(c)(9)(iv)(B).

29. The "Dosage and Administration" section that follows "must state the recommended dose and, as appropriate," among other things, "[d]osages for each indication and *subpopulation*." *Id.* 201.57(c)(3)(C) (emphasis added). This section must include appropriate pediatric dosage information "[i]f there is a specific pediatric indication different from those approved for adults that is supported by adequate and well-controlled studies in the pediatric population." *Id.* § 201.57(c)(9)(iv)(B).

30. The labeling regulations require that other specific pediatric information also be included. Where a specific pediatric indication has been demonstrated by adequate and well-controlled studies, the pediatric use section "must cite any limitations on the pediatric indication,"

among other things. 21 C.F.R. § 201.57(c)(9)(iv)(B). "If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they must be summarized in the 'Pediatric use' subsection . . . ." *Id.* § 201.57(c)(9)(iv)(C). The regulations list expressly what must be written (or a reasonable alternative) in the pediatric use subsection. *Id.* § 201.57(c)(9)(iv)(D)(1).

b. The "Same Labeling" Requirement And Specific Statutory Exceptions When It Comes To Pediatric Indications And Information.

31. Generally, generic drugs (approved through ANDAs) must contain the same information on their labels as their respective brand-name predicate (or reference listed) drug. *See* 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8)(iv).

32. By statute, pediatric label information receives special treatment. In Section 505A(o) of the FDCA, Congress delineated express exceptions to the same labeling requirement, allowing generics to omit certain specific types of pediatric indications and omissions. *See* 21 U.S.C. § 355a(o). The statute provides:

> (1) General rule. – A drug for which an application has been submitted or approved under section 355(j) of this title shall not be considered ineligible for approval under that section or misbranded under section 352 of this title on the basis that the labeling of the drug *omits a pediatric indication or any other aspect of labeling pertaining to pediatric use when the omitted indication or other aspect is protected by patent or by exclusivity under clause (iii) or (iv) of section 355(j)(5)(F) of this title*.
>
> (2) Labeling. – Notwithstanding clauses (iii) and (iv) of section 355(j)(5)(F) of this title, the Secretary may require that the labeling of a drug approved under section 355(j) of this title that *omits a pediatric indication or other aspect of labeling as described in paragraph (1)* include—
>
> (A) a statement that, because of marketing exclusivity for a manufacturer—
> (i) the drug is not labeled for pediatric use; or
> (ii) in the case of a drug for which there is an additional pediatric use not referred to in paragraph (1), the drug is not labeled for the pediatric use under paragraph (1); and

> (B) a statement of any appropriate pediatric contraindications, warnings, precautions, or other information that the Secretary considers necessary to assure safe use.

Id. (emphasis added).

33. In sum, Section 505A(o) expressly allows pediatric indications and information to be omitted from generic labeling when such information is unavailable to the generic sponsor because it is only protected by patent or three-year exclusivity under Section 505(j)(5)(F)(iii) or (iv).[1] By contrast, the statute does not allow the omission of pediatric indications or information protected by orphan drug exclusivity, which is granted pursuant to Section 527 of the FDCA (21 U.S.C. § 360cc). Therefore, pediatric information protected by orphan drug exclusivity cannot be omitted from a generic's label (because the general rule that generic drugs must contain the same information on their labels as their respective brand-name predicate drug would control, *see* 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8)(iv)).

34. Otsuka received three-year exclusivity under § 355(j)(5)(F) for its supplement. Orphan drug exclusivity is, however, a type of legal protection that is completely separate from, and operates in addition to, protection otherwise available "by patent or by exclusivity under clause (iii) or (iv) of section 355(j)(5)(F) of this title." Therefore, the fact that Otsuka received three-year

[1] Under § 355(j)(5)(F)(iii), three-year exclusivity is given to an application that includes an active ingredient that has been approved in another application, is approved after September 24, 1984, and the "application contains reports of new clinical investigations . . . essential to the approval of the application and conducted or sponsored by the applicant." Under § 355(j)(5)(F)(iv), an approved supplement approved after September 24, 1984 containing "reports of new clinical investigations . . . essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement" is entitled to three-year exclusivity for "a change approved in the supplement." *See also* 21 C.F.R. § 314.108(b)(4) & (5).

exclusivity under § 355(j)(5)(F) does not alter or diminish Otsuka's orphan drug exclusivity or the effect of that exclusivity.

B. Otsuka's Orphan Drug Exclusivity And FDA's Tourette's Disorder Approval Actions

1. Otsuka's sNDA

35. Otsuka is the owner of the highly valuable, extremely important, and medically useful prescription brand drug aripiprazole, which Otsuka markets under the name Abilify. FDA first approved Abilify on November 15, 2002, then for schizophrenia. FDA has since approved Abilify for other indications.

36. In 2005, Dr. Floyd Sallee sent an application to FDA requesting orphan drug designation for aripiprazole "for the treatment of Tourette Syndrome in children and adolescents." That application sought orphan drug designation based on an estimate that the target population of U.S. school age children with Tourette's Disorder was 120,000, and thus fewer than the ODA's statutory threshold of a disease or condition that affects fewer than 200,000 people in the U.S. *See* 21 U.S.C. § 360bb(a)(2)(A).

37. In 2006, FDA granted orphan drug designation for the use of aripiprazole for the treatment of Tourette's Disorder. Otsuka subsequently acquired that designation. Among other things, this designation meant that Otsuka would be entitled to a seven-year period of market exclusivity, running from the date of FDA's approval of an orphan drug indication. During that seven-year period, FDA is precluded from approving a drug for treatment of the same disease or condition. When the designation was granted, no sNDA had been submitted nor had safety and efficacy studies been conducted in any population group.

38. Following the conclusion of clinical trials establishing the safety and efficacy of the use of Abilify in the pediatric population, Otsuka submitted a sNDA to FDA in 2014. Otsuka's

sNDA sought approval for the new indication of the treatment of Tourette's Disorder in pediatric patients – pediatric patients being the only population group in which Otsuka had conducted safety and efficacy studies.

39. Otsuka's application was based on two trials in pediatric patients (ages 6-18) with Tourette's disorder. The safety and efficacy of Abilify for the treatment of Tourette's disorder in the pediatric population was established in one 8-week trial (patients 7 to 17 years of age) and one 10-week trial (patients 6 to 18 years of age) involving patients who met the DSM-IV criteria for Tourette's Disorder. Otsuka is also conducting 1 open-label, long-term safety trial in pediatric subjects (7-17 years old).

40. Tourette's Disorder in adults is fundamentally different than Tourette's Disorder in the pediatric population. Treatment in adults is more difficult, and adults are more commonly treatment-resistant. Effective treatment in adults often requires more intense interventions than that involved with children.

41. Based on the results of the clinical trials and in its sNDA, Otsuka only recommended dosages for its label based on weights of the pediatric population: those less than 50 kilograms (110 pounds) and those greater than or equal to 50 kilograms.

42. Dosing to treat adults with Tourette's Disorder with Abilify is very different than the dosing when the drug is used to treat pediatric patients. The dosing levels for adults are considerably higher (by a factor of two or more) than the doses for children and treatment of pediatric patients must begin at much lower doses. For these and other reasons, without specialized knowledge, a clinician could not treat an adult with Tourette's Disorder with Abilify in reliance on a label containing dosing instructions for the pediatric population.

43. Through the course of developing the clinical trials to support its sNDA (beginning in 2012 with Otsuka's submission of an Investigational New Drug Application to study the drug in the treatment of Tourette's Disorder in the pediatric population), FDA never objected to the pediatric age groups that were the subjects of Otsuka's clinical trials. Rather, FDA's recommendations were instrumental in the design of one of the two pivotal studies described above, including the selection of doses to be evaluated.

44. Nor did FDA object to Otsuka's seeking an indication limited to the pediatric population and, indeed, FDA acknowledged in comments prior to Otsuka's submission of its sNDA that Otsuka was developing Abilify for the treatment of Tourette's Disorder in children and adolescents.

45. Otsuka engaged in conversations with FDA after submitting its sNDA to substantially revise and "streamline" its label. During those discussions, Otsuka never agreed to broaden its indication beyond the pediatric population, and Otsuka never understood FDA as seeking to broaden the indication beyond the pediatric population. The "Indications and Usage" section of the label includes a reference to the supporting clinical studies, demonstrating that treatment is limited to the pediatric population.

2. FDA's Unlawful Actions

46. On December 12, 2014, FDA sent a letter to Otsuka notifying Otsuka that FDA was granting marketing approval for Abilify "based upon two adequate and well-controlled trials that demonstrate the efficacy for the new indication *in pediatric patients with Tourette's Disorder*." This approval resulted in substantial modifications to the Abilify label.

47. On January 13, 2015, FDA's Office of Orphan Products Development database was updated to reflect that Abilify had been "approved for orphan indication" of "treatment of p*ediatric patients* with Tourette's disorder." (emphasis added).

48. Counsel for Otsuka thereafter wrote to FDA's Chief Counsel setting forth Otsuka's position that FDA's approval of Otsuka's sNDA for the use of Abilify in the treatment of Tourette's Disorder *in pediatric patients*, an approval protected by orphan drug exclusivity, precluded FDA from approving an ANDA for a generic version of Abilify pending the expiration of Otsuka's statutory seven-year period of orphan drug market exclusivity for the new indication. In response to Otsuka's counsel's letter, FDA unlawfully reversed direction and issued the final agency decision which gives rise to this action.

49. FDA's unlawful about face is set forth in two letters to Otsuka. On February 24, 2015, FDA's Office of Orphan Products Development informed Otsuka that "as the first sponsor of this drug [aripiprazole] to obtain marketing approval for this indication, [Otsuka] is entitled to seven years of orphan-drug exclusive approval . . . for ***treatment of Tourette's disorder***." The agency went further, however. In its "corrected" approval letter, without explanation or elaboration, FDA advised that its earlier December 12, 2014, approval letter "contained an error in the 'indications' section," an "error" which FDA purported to change unilaterally by changing and broadening significantly the approved indication from treatment "in pediatric patients with Tourette's Disorder" to treatment of "patients with Tourette's Disorder."

50. On March 9, 2015, Otsuka emailed FDA and posed the following direct question: "[D]oes [FDA] consider the supplemental approval to be for the treatment of Tourette's disorder in the general population, or is the approval limited to the pediatric population in which Otsuka demonstrated safety and efficacy?" FDA responded unambiguously on March 11, 2015: "We

consider the supplemental approval to be for the treatment of Tourette's disorder in the general population."

51. On March 18, 2015, Otsuka emailed FDA and formally objected to FDA's reversal of decision and broadening of the indication. Otsuka requested that the broadened indication be rescinded. Otsuka noted that the initial pediatric indication was supported by clinical trial data while the broadened "in the general population" indication was not. Otsuka supported its objection with a declaration from Dr. Floyd Sallee, a Professor of Psychiatry at the University of Cincinnati School of Medicine who originally requested orphan drug designation. Dr. Sallee has many years of experience treating patients with Tourette's Disorder, both children and adults. Dr. Sallee's declaration addresses the sharp differences in Tourette's Disorder in adults as compared to children and the differences in treatment for the two groups. FDA has acknowledged receipt of Otsuka's email objecting and requesting rescission, but has not responded substantively.

52. FDA's final agency action was to grant approval for an indication for use of Abilify for the treatment of Tourette's disorder in the general population. "Treatment of Tourette's disorder in the general population" is manifestly *not* the indication for which Otsuka applied nor is it the indication for which Otsuka submitted substantiating safety and efficacy studies.

53. FDA "corrected" its approval in an attempt to skirt Otsuka's argument that FDA's approval of Otsuka's sNDA for the use of Abilify in the treatment of Tourette's Disorder *in pediatric patients* precluded FDA from approving an ANDA for a generic version of Abilify pending the expiration of Otsuka's statutory seven-year period of orphan drug market exclusivity for the new indication. Otsuka's counsel had explained that deviation from the "same labeling requirement" is not permissible where the information to be omitted is protected by orphan drug exclusivity. None of the limited and expressly stated statutory exceptions to the general rule that

the label of an approved generic must be the same as the label of the brand drug permit the omission of a pediatric indication protected by orphan drug exclusivity. *See* 21 U.S.C. § 355a(o).

54. Once FDA was advised of the direct legal consequence of its approval, FDA unlawfully reversed course and purported, without any basis in law or fact, to "strip away" the pediatric indication. In doing so, FDA acted improperly and unlawfully and attempted to open an otherwise firmly closed door to the approval of generic versions of Abilify prior to the expiration of Otsuka's seven-year period of market exclusivity in December 2021.

C. Pediatric Information In The Label Of The Approved Broadened Indication

55. The label approved by FDA, which includes the "Highlights of Prescribing Information" and "Full Prescribing Information," contains a substantial amount of pediatric information protected by orphan drug exclusivity.

56. In the "Highlights of Prescribing Information," for example, the "Indications and Usage" section includes a reference to the clinical trials supporting the new indication; the "Dosage and Administration" section lists dosages for patients less than and greater than or equal to 50 kilograms and references the dosage and administration section of the full prescribing information; and the "Adverse Reactions" section lists adverse reactions for Pediatric Patients (6 to 18 years old).

57. There are also many references in the "Full Prescribing Information." These references include the sections related to indications and usage which reference the Tourette's Disorder clinical trials (§ 1); dosage and administration for "Pediatric Patients (6 to 18 years)" (§ 2.5); warnings and precautions (§ 5.6; text following Table 7 and Table 8); adverse reactions (§ 6.1 Tables 21, 22 and related text); pediatric use (§ 8.4); clinical studies (§§ 14, 14.5 (Tourette's Disorder – Pediatric Patients)).

Count One – Unlawful, Arbitrary, And Capricious FDA Action

58. Otsuka here adopts and incorporates by reference Paragraphs 1-57 of this complaint as if fully set forth herein.

59. 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). FDA's reversal of its original approval decision in which it properly approved a new indication for Abilify for treatment of pediatric patients with Tourette's disorder was arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law. FDA acted outside its statutory and regulatory authority in reversing its original approval and approving Abilify for the treatment of Tourette's Disorder in the general population.

60. Otsuka sought approval for the use of Abilify for treatment of Tourette's Disorder in the pediatric population. The clinical trial data that Otsuka submitted in support of its sNDA related exclusively to the treatment of pediatric patients with Tourette's Disorder. *See* 21 U.S.C. § 355(b)(1)(A); 21 C.F.R. § 314.50(d)(5). FDA's approval authority is limited by the clinical data the manufacturer submits in its application in support of the use of the drug for that particular purpose. *See* 21 U.S.C. § 355(d)(1), (2), (5); *see also* 21 C.F.R. § 314.126(a) ("Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is 'substantial evidence' to support the claims of effectiveness for new drugs.").

61. Here, however, FDA approved an indication for Abilify for treatment of patients with Tourette's Disorder in the population at large in the absence of any clinical data proving the safety and effectiveness of Abilify for that broader indication. Otsuka neither requested this broader indication nor provided adequate and well-controlled studies in its sNDA proving that

Abilify is safe and effective for that particular use. FDA acted arbitrarily, capriciously, and contrary to law because, as a matter of law, FDA's authority to approve an indication for a drug is limited by the clinical data the manufacturer submits in its application in support of the use of the drug for that particular purpose.

62. FDA's reversal of its original approval decision was made without factual or evidentiary support. Because FDA does not conduct its own independent clinical trials to determine the safety and efficacy of a requested new indication, Otsuka alleges, on information and belief, that FDA has no clinical trial information to substantiate the broader age unlimited indication which the agency approved. *See* FDA, Development & Approval Process (Drugs) ("The [Center for Drug Evaluation and Research] doesn't actually test drugs itself . . . ."), http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm.

63. FDA's reversal of its original approval decision was taken for a legally impermissible reason. FDA acted to attempt to deny Otsuka important and valuable rights and benefits to which Otsuka is entitled under the FDCA. FDA attempted to impermissibly open the door to FDA's approval of generic versions of Abilify when, as a matter of law, FDA is precluded from approving generic versions of Abilify. FDA unlawfully, without justification, and for an improper reason reversed its original decision, approving a new indication for Abilify limited to the treatment of pediatric patients with Tourette's Disorder, and, in its place, impermissibly adopted its unlawful "corrected" decision.

Count Two – Violation of "Same Labeling" Requirement

64. Otsuka here adopts and incorporates by reference Paragraphs 1-63 of this complaint as if fully set forth herein.

65. Assuming, without conceding, the validity of FDA's broadened "corrected" approval decision, FDA is precluded nevertheless from approving a generic version of Abilify.

66. The general rule that generic drugs (approved through ANDAs) must contain the same information on their labels as their respective brand-name predicate (or reference listed) drug, s*ee* 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8)(iv), controls here. FDA is barred from omitting from the generic's label the ample and multiple pediatric references in the FDA-approved Abilify label for the broadened population at large indication. Those references are protected by orphan drug exclusivity, and pediatric information pertaining to orphan drug exclusivity is not a category of information that Congress permitted to be omitted. *See* 21 U.S.C. § 355a(o).

67. Section 505A(o) permits the omission of "a pediatric indication *or any other aspect of labeling pertaining to pediatric use* when the omitted indication or other aspect is protected by patent or by exclusivity under clause (iii) or (iv) of section 355(j)(5)(F) of this title." 21 U.S.C. § 355a(o) (emphasis added). The FDA approved label for Abilify is loaded with pediatric information (*i.e.*, "any other aspect of labeling pertaining to pediatric use"), all of which is protected by orphan drug exclusivity, a type of legal protection that is completely separate from, and operates in addition to, protection otherwise available "by patent or by exclusivity under clause (iii) or (iv) of section 355(j)(5)(F) of this title." Because orphan drug exclusivity is not mentioned in section 505A(o), as a matter of law, pediatric information subject to such protection cannot be omitted from a generic label under the authority of that section.

68. Absent judicial intervention, on April 20, 2015, FDA will approve generic versions of Abilify. That action will be arbitrary, capricious, and contrary to law. Accordingly, the Court should declare that even under FDA's broadened "corrected" approval decision (and without

conceding the validity of that decision) FDA is precluded as a matter of law from approving a generic version of Abilify pending the expiration of Otsuka's seven-year period of orphan drug exclusivity (in December 2021).

Prayers For Relief

WHEREFORE, Otsuka prays as follows:

(a) the Court should expedite proceedings herein;

(b) pending the determination of this matter on the merits, the Court should grant all temporary, preliminary, or interim relief as may be necessary to protect Otsuka's rights pending the final determination of this case on the merits;

(c) the Court should declare that FDA's reversal of its original approval decision, approving a new indication for Abilify for treatment of pediatric patients with Tourette's Disorder, was arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law and, accordingly, the Court should vacate FDA's unlawful "corrected" decision and reinstate or order FDA to reinstate FDA's original lawful approval decision;

(d) the Court should permanently enjoin FDA from granting approval of any ANDA for generic versions of Abilify pending the expiration of Otsuka's seven-year exclusivity period in December 2021;

(e) in the alternative, the Court should declare that even under FDA's "corrected" decision FDA is precluded from granting approval of any ANDA for generic versions of Abilify pending the expiration of Otsuka's seven-year exclusivity period in December 2021;

(f) the Court should make permanent any preliminary injunction; and

(g) the Court should grant any and all other, further, and additional relief as the nature of the cause may require, including all necessary and appropriate declarations of rights and injunctive relief.

Dated: March 24, 2015

/s/ Ralph S. Tyler

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