IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

Otsuka Pharmaceutical Co., Ltd., et al.,	*	
Plaintiffs,	*	
v.		CIVIL ACTION NO.
	*	
Sylvia Mathews Burwell, et al.,		
Defendants.		

* * * * * * * * * * * * *

PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

Pursuant to Fed. R. Civ. P. 56, plaintiffs Otsuka Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Development & Commercialization, Inc., and Otsuka America Pharmaceutical, Inc. (collectively, "Otsuka") respectfully move for summary judgment. In support of this motion, Otsuka relies upon the agency administrative record, the attached memorandum, and attached declarations which demonstrate that the material facts are not in dispute and Otsuka is entitled to judgment as a matter of law. The Court should hold that the decision of the defendant U.S. Food and Drug Administration which Otsuka challenges in this case is arbitrary, capricious, and contrary to law. A proposed Final Judgment and Order is attached.

Respectfully submitted,

Dated: March 24, 2015

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MEMORANDUM IN SUPPORT OF MOTION FOR SUMMARY JUDGMENT

Table Of Contents

Introduction 2
Statement Of Undisputed Material Facts 5
A. Otsuka's sNDA For The Use Of Abilify For The Treatment Of Tourette's Disorder In Pediatric Patients. 5
B. FDA's Original Pediatric Approval And Then FDA's Reversal And Approval Of Abilify For The Treatment of Tourette's Disorder In The Population At Large 7
C. The Difference Between Tourette's Disorder In Children As Compared To Adults. 9
D. Pediatric Information In The FDA Approved Label For The Broadened Population At Large Indication 10
Statutory And Regulatory Background 11
A. FDCA's New Drug And Supplemental Drug Approval Provisions 122
B. FDCA's Orphan Drug Provisions 144
C. FDCA's Labeling Requirements And FDA's Implementation Of Those Requirements 14
1. In General 14
2. The "Same Labeling" Requirement And Specific Exceptions When It Comes To Pediatric Indications And Information 166
Argument 177
I. Summary Judgment Standard And APA Challenges 177
II. FDA's Reversal Of Its Original Approval Decision Was Arbitrary, Capricious, And Contrary to Law. 17

1. FDA Acted Beyond Its Statutory Authority. 188
2. FDA's "Reversal" Was Without Factual Or Evidentiary Support. 233
3. FDA's "Reversal" Was Based On An Impermissible Reason.....266
III. FDA Is Precluded From Approving A Generic Version Of Abilify Under The "Corrected" Approval……..29
A. Section 505A(o) Does Not Allow Pediatric Indications Or Information Pertaining To Pediatric Use To Be Omitted From A Generic's Label When It Is Protected By Orphan Drug Exclusivity……29
B. Otsuka's "Corrected" Approval And Labeling Contains Multiple Aspects Pertaining To Pediatric Use That Cannot Be Omitted……32
C. Assuming, But Not Conceding, The Lawfulness Of FDA's "Corrected" Approval, Otsuka Is Entitled To A Declaration That FDA Is Precluded From Approving Generics……...34
Conclusion 35

Introduction

In count one of the their complaint, plaintiffs Otsuka Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Development & Commercialization, Inc., and Otsuka America Pharmaceutical, Inc. (collectively, "Otsuka") challenge a final decision of the defendant U.S. Food and Drug Administration ("FDA") that violates the most fundamental precept of FDA's statutory drug approval authority. That precept is that FDA's authority to approve a new use ("indication") for a previously approved drug is constrained by the sponsor's having first demonstrated, through adequate and well-controlled clinical trials, the safety and efficacy of the drug for the proposed new indication. FDA violated this settled and thoroughly sound principle when it approved a new indication for Otsuka's drug aripiprazole, which Otsuka markets under the name Abilify®, for an indication that has not been demonstrated to be safe and effective.

The undisputed facts are that Otsuka conducted adequate and well-controlled clinical trials demonstrating the safety and effectiveness of Abilify for the treatment of Tourette's Disorder in *pediatric* patients. Based upon this clinical trial data, Otsuka sought – and received – FDA

approval for a new indication for Abilify for the treatment of Tourette's Disorder in *pediatric* patients. And then FDA went far astray. Following receipt of a letter from Otsuka's counsel identifying a collateral legal consequence of FDA's having approved Abilify for the treatment of Tourette's Disorder in pediatric patients (*i.e.*, as a matter of law, the approved pediatric indication would preclude FDA from approving generic versions of Abilify), FDA abruptly and unlawfully reversed itself. FDA's reversal approved Abilify for the treatment of Tourette's Disorder *in the population at large*, despite the undisputed fact that Otsuka's clinical trials demonstrated the drug's safety and effectiveness for the treatment of Tourette's in *pediatric* patients only.

FDA's broadened approval action is unlawful, arbitrary, and capricious agency action. 5 U.S.C. § 706(2)(A). In approving Abilify for a broader indication than that for which Otsuka sought approval, based upon the adequate and well-controlled clinical studies in pediatric patients, FDA acted in direct contravention of the law. Further, FDA's reversal and "corrected" approval is arbitrary and capricious because it is totally lacking in factual or evidentiary support. Otsuka has not demonstrated safety and effectiveness in *non*-pediatric patients (*i.e.*, the population at large), and FDA does not conduct its own clinical trials. Thus, no clinical trial data supports FDA's approval of the use of Abilify for the treatment of Tourette's Disorder in the population at large. And finally, and most tellingly, FDA's reversal of its original decision was taken for a legally impermissible and improper reason. Rather than applying the controlling statutory and regulatory provisions governing approval of new indications for approved drugs, which plainly require a direct correlation between the drug sponsor's demonstration of safety and efficacy and FDA's approval of an indication for use, FDA acted for an improper extra-legal reason. FDA sought to prevent Otsuka from receiving the market exclusivity to which it is entitled. Honoring Otsuka's statutory market exclusivity, a result that would bar generic entry pending the expiration of that

exclusivity under Congress's statutory scheme, was apparently a result to which FDA took strong exception. In an effort to try to block that result, FDA went well outside its authority and applied improper non-statutory considerations.

In count two of the complaint, Otsuka assumes, without conceding, the validity of FDA's "corrected" approval for a broader indication than that for which Otsuka submitted supporting clinical trial data or assumes, without conceding, that the Court will uphold the validity of FDA's "corrected" approval. Notwithstanding FDA's "corrected" approval, FDA is, as a matter of law, barred from approving any generic versions of Abilify pending the expiration of Otsuka's seven-year period of orphan drug market exclusivity. While FDA acted unlawfully, without basis in fact, and for an improper reason when it reversed its original approval decision and announced its "corrected" approval (count one), FDA's attempt to deny Otsuka the market exclusivity that Congress granted and to which Otsuka is entitled failed in any event (count two).

Otsuka seeks the Court's intervention to assure that critical provisions of the drug approval statutes are enforced as Congress enacted them. The core question presented in count one of the complaint is whether FDA has the authority to approve a new indication for an approved drug when that new indication has not been shown to be safe and effective by the adequate and well-controlled studies submitted by the drug manufacturer. FDA does not. The core question in count two is whether the pediatric information included in the label FDA approved for the treatment of Tourette's Disorder in the broadened population at large indication is information Congress authorized to be omitted from the label of a generic such that FDA could approve a generic version of Abilify (for indications other than Tourette's Disorder). The information is not.

Statement Of Undisputed Material Facts[1]

A. Otsuka's sNDA For The Use Of Abilify For The Treatment Of Tourette's Disorder In Pediatric Patients

Otsuka is the New Drug Application ("NDA") holder for the drug aripiprazole, which it markets under the brand name Abilify. Ex. 1, ¶ 4. FDA first approved Abilify on November 15, 2002, then for schizophrenia, and FDA has since approved Abilify for schizophrenia in adolescents, acute treatment of manic and mixed episodes associated with Bipolar I Disorder in both adult and pediatric patients, irritability associated with autistic disorder in pediatric patients, and as an add-on treatment for depression in adults. *Id.* ¶ 7. In 2005, Dr. Floyd Sallee submitted an application to FDA requesting orphan drug designation for aripiprazole "for the treatment of Tourette Syndrome in children and adolescents." *Id.* ¶ 10, Att. B. The application sought orphan drug designation based on a conservative estimate that the target population of U.S. school age children with Tourette's Disorder was 120,000, fewer than the statutorily required 200,000. *See id.*; 21 U.S.C. § 360bb(a)(2)(A).

In 2006, FDA granted orphan drug designation for the use of aripiprazole for the treatment of Tourette's Disorder. Ex. 1, ¶ 11. Otsuka subsequently acquired that designation. *Id.* 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 the use of aripiprazole for the treatment of Tourette's Disorder. *Id.* During that seven-year period FDA would be precluded from approving a drug for the same use or indication. *Id.* When the designation was granted, no sNDA had been submitted and no safety and efficacy studies had been conducted in any population group. *Id.*

Otsuka conducted clinical trials to demonstrate the safety and efficacy of Abilify to treat

[1] For the facts set forth herein, Otsuka relies on the declaration of Robert McQuade. The administrative record, when it is filed, will confirm the facts stated herein.

Tourette's Disorder *in the pediatric population*. *Id.* ¶¶ 14-15, 24. Otsuka recognized that, although symptoms of Tourette's "can occur in patients as young as 2 years old, with patients having a mean age at onset of 7 years," the safety and efficacy of the only FDA-approved drugs for the treatment of Tourette's Disorder had not been "confirmed in patients younger than 12 years of age." *Id.* ¶ 13.[2] Otsuka thus devised trials "to investigate the safety and efficacy of aripiprazole in this indication [*i.e.*, pediatric patients (aged 6-17 years)]." *Id.* Otsuka conducted two phase 3, double-blind, placebo-controlled trials in children from 6 years of age to 18 years of age. *Id.* The first trial was an 8-week multicenter, randomized, double-blind, placebo-controlled trial that evaluated the safety and efficacy of fixed-dose once-daily aripiprazole in 133 pediatric subjects with Tourette's Disorder ranging from 7 years of age to 17 years of age. *Id.* The second trial was a 10-week multicenter, randomized, double-blind placebo-controlled, flexible-dose trial conducted in 61 pediatric subjects ranging from ages 6 years of age to 18 years of age with Tourette's Disorder or chronic tic disorders. *Id.* Otsuka is also conducting 1 open-label, long-term safety trial in pediatric subjects (7-17 years old). *Id.*

These studies demonstrated that aripiprazole is safe and effective in the treatment of Tourette's Disorder in pediatric patients as demonstrated by a reduction in the total tic[3] score of the Yale Global Tic Severity Scale. *Id.* ¶ 15. In its sNDA and based on these clinical trials, Otsuka proposed dosage recommendations based on whether the pediatric patient was less than 50

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[2] *See also* Ex. 1, ¶ 13 ("There is a clear unmet medical need in younger patients because the symptoms of TD can manifest at a very early age, and there are no well-controlled trials confirming the safety and efficacy of the currently approved medications in these younger patients. The currently approved typical antipsychotics have a poor tolerability profile and side effects that affect compliance.").

[3] A tic is a sudden, rapid, recurrent, nonrhythmic, stereotypic motor movement or vocalization. Ex. 1, ¶ 15.

kilograms (110 pounds) or greater or equal to 50 kilograms. *Id.* ¶ 16. Following the conclusion of these clinical trials on patients ranging from 6 to 18 years of age, Otsuka submitted a sNDA. *Id.* ¶¶ 12, 16. Att. C. Otsuka's sNDA sought approval for the new indication of "the treatment of Tourette's Disorder in pediatric patients," the only patient population in which Otsuka had conducted safety and efficacy studies. *Id.* ¶ 16, Att. C.

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. *Id.* ¶ 17. 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. *Id.* Nor did FDA object to Otsuka's seeking an indication limited to the pediatric population and, indeed, 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. *Id.* ¶ 18.

Otsuka engaged in conversations with FDA after submitting its sNDA to substantially revise and "streamline" its label. *Id.* ¶ 19. 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. *Id.* The "Indications and Usage" section of the label includes a reference to the supporting clinical studies, demonstrating that the indication should be limited to treatment in the pediatric population. *Id.*, Att. A ("Treatment of Tourette's disorder (14.5)").

B. FDA's Original Pediatric Approval And Then FDA's Reversal And Approval Of Abilify For The Treatment Of Tourette's Disorder In The Population At Large

On December 12, 2014, FDA sent Otsuka a letter 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*." *Id.* Att. D (emphasis added). About a month later, FDA's website was updated to reflect that Abilify had been "approved for orphan indication" of "treatment of pediatric patients with Tourette's disorder." *Id.* ¶ 21.

Counsel for Otsuka thereafter wrote to FDA's Chief Counsel setting forth the company's position that FDA's approval of Abilify of an orphan indication for treatment of pediatric patients with Tourette's Disorder meant that FDA was precluded from approving an ANDA for a generic version of Abilify for any indication pending the expiration of Otsuka's statutory seven-year period of orphan drug market exclusivity for the new indication. *Id.* ¶ 22, Att. E. As counsel's letter explained, none of the narrow exceptions to the general "same labeling rule" that requires generic drugs to contain the same information on their labels as their respective brand-name predicate (or reference listed) drug were applicable and, therefore, the general "same labeling rule" controlled. *Id*. Att. E.

Not long after receiving that letter, FDA reversed its approval. On February 24, 2015, FDA sent Otsuka a letter, informing Otsuka that "as the first sponsor of [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***." *Id.* ¶ 23, Att. F. That same day, FDA sent Otsuka a "corrected" approval letter, in which FDA went further and, without explanation or elaboration, advised that its earlier December 12, 2014, approval letter "contained an error in the 'indications' section," an "error" FDA purported to change unilaterally by changing (broadening) the approved indication from treatment "in pediatric patients with Tourette's Disorder" to treatment of "patients with Tourette's Disorder." *Id.* ¶ 23, Att. A.

On March 9, 2015, Otsuka emailed FDA: "[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?" *Id.* ¶ 25, Att. G. 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." *Id.*

C. The Difference Between Tourette's Disorder In Children As Compared To Adults

On March 18, 2015, Otsuka asked FDA to rescind its "corrected" approval decision and lodged a formal objection with FDA with respect to the agency's broadening the approved indication for Abilify for treatment of Tourette's Disorder. *Id.* In support of that objection, Otsuka submitted the declaration of Dr. Floyd Sallee, a leader in the field of treating Tourette's. *Id.* Dr. Sallee has years of experience in the use of Abilify. *Id.* ¶ 26, Att. H ¶ 3. Dr. Sallee's declaration makes clear that "Tourette's Disorder in adults presents in fundamentally different ways than the Disorder does in the pediatric population. The treatment of adults with Tourette's Disorder is more difficult than is the treatment of the pediatric population with the Disorder. . . . Effective treatment of adults often requires more intense interventions than that involved with children who have the Disorder." *Id.* ¶ 26, Att. H ¶ 6.

Dr. Sallee also addresses the differences in dosing in adults and children. The dosing in adults is twice (or more) the dose in pediatric patients must be started at much lower doses than adult patients. *Id.* ¶ 26, Att. H ¶ 7. Dr. Sallee makes the important point that "[w]ithout specialized knowledge, a clinician could not treat an adult with Tourette's Disorder with aripiprazole in reliance upon a label containing dosing instructions for the pediatric population." *Id.*

D. Pediatric Information In The FDA Approved Label For The Broadened Population At Large Indication

FDA has approved Abilify's labeling, including, as required, information about matters such as dosage and administration and adverse reactions, to accompany the drug with the "corrected" indication of treatment of Tourette's Disorder in the population at large. *Id.* ¶ 29. Given that the only safety and effectiveness data submitted related to the pediatric use of the drug, not the population at large, the label is, not surprisingly, replete with multiple and extensive references to pediatric use. *Id.*

For example, in the portion of the label titled "Highlights of Prescribing Information," the "Indications and Usage" section includes a reference to the clinical trials supporting the new indication ("Treatment of Tourette's disorder (14.5)"); the "Dosage and Administration" section for Tourette's Disorder is specifically titled for "Pediatric Patients (6 to 18 years)" and lists dosages for pediatric patients less than and greater or equal to 50 kilograms (110 pounds), quite less than the average adult; and the "Adverse Reactions" section specifically lists adverse reactions for pediatric patients (6 to 18 years old). *Id.* ¶ 30, Att. A.

The "Full Prescribing Information" section also includes substantial pediatric information. The indications for use section (§ 1) refers to the pediatric clinical studies in connection with the indication for "Treatment of Tourette's Disorder" ("Treatment of Tourette's Disorder *[see CLINICAL STUDIES (14.5)]*"). *Id.* Section 14.5, the clinical studies portion, is titled "Tourette's Disorder" and its subtitle is "Pediatric Patients." *Id.* The section contains a detailed discussion of the pediatric clinical trials conducted. *Id.*

The dosage and administration section (§ 2) is similar. Section 2.5 is titled "Tourette's Disorder" and its subtitle is "Pediatric Patients (6 to 18 years)." *Id.* The section describes the recommended dosage ranges for pediatric patients, not adult patients:

> **2.5 Tourette's Disorder**
>
> **Pediatric Patients (6 to 18 years)**
>
> The recommended dosage range for Tourette's Disorder is 5 to 20 mg/day.
>
> For patients weighing less than 50 kg, dosing should be initiated at 2 mg/day with a target dose of 5 mg/day after 2 days. The dose can be increased to 10 mg/day in patients who do not achieve optimal control of tics. Dosage adjustments should occur gradually at intervals of no less than 1 week.
>
> For patients weighing 50 kg or more, dosing should be initiated at 2 mg/day for 2 days, and then increased to 5 mg/day for 5 days, with a target dose of 10 mg/day on day 8. The dose can be increased up to 20 mg/day for patients who do not achieve optimal control of tics. Dosage adjustments should occur gradually in increments of 5 mg/day at intervals of no less than 1 week. *[see CLINICAL STUDIES (14.5)]*.

Id.

The "Use in Specific Populations" section includes a "Pediatric Use" section that includes a Tourette's Disorder section (§ 8.4). *Id.* There, the label explains that "Safety and effectiveness of aripiprazole in pediatric patients with Tourette's Disorder were established in one 8-week (aged 7 to 17) and one 10-week trial (aged 6 to 18) in 194 pediatric patients *[see DOSAGE AND ADMINISTRATION (2.5), ADVERSE REACTIONS (6.1), and CLINICAL STUDIES (14.5)]*." *Id.* The label also includes warnings related to Tourette's Disorder in the pediatric population (§ 5.6) and adverse reactions (§ 6.1). *Id.*

Statutory And Regulatory Background

Congress has enacted a complex statutory scheme under which safe and effective drugs are approved for human use. This scheme balances multiple competing interests. Among those interests are the need for clinical studies to prove drugs are safe and effective for their indicated

uses; the need to incentivize the lengthy and costly process of developing new drugs by rewarding brand drug manufacturers with periods of market exclusivity, including drugs for the pediatric population; the need to provide incentives to encourage the development of drugs for rare diseases where, by definition, the size of the commercial market is small; and the need for affordable drugs without discouraging brand companies from taking risks and innovating and developing new drugs. This case illustrates how Congress reconciled these various interests.

A. FDCA's New Drug And Supplemental Drug Approval Provisions

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") for a new drug 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*. An NDA or sNDA must include evidence of the drug's safety and effectiveness for the particular indications sought to be approved.

An applicant demonstrates safety and effectiveness for the particular indication sought by submitting to FDA "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); *see* FDA, Development & Approval Process (Drugs) ("[After testing, 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.

FDA may not approve a new drug or an new indication 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). "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 C.F.R. § 314.126(a). In short, FDA's approval of an indication is limited by the clinical data the manufacturer submits in its application in support of the use of the drug for that particular purpose.

Abbreviated new drug applications ("ANDAs") for a generic version of a previously approved brand drug short circuit this costly and lengthy process of developing new drugs and new indications for approved drugs. An ANDA applicant, rather than investing the significant time and money that would be required to establish independently the safety and efficacy of a proposed generic drug, may rely on the safety and efficacy data contained in the predicate NDA. The ANDA 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). To justify the exceedingly costly, risky, and uncertain investment of time and money in preparing and submitting NDAs and sNDAs, therefore, Congress has provided these applicants with certain periods of statutory exclusivity.

B. FDCA's Orphan Drug Provisions

One of these periods of statutory exclusivity is found in the Orphan Drug Act ("ODA") provisions of the FDCA, Pub. L. 97-414, 96 Stat. 2049. There, Congress encouraged drug manufacturers to develop drugs for the treatment of rare diseases or disorders affecting small patient populations, like Tourette's Disorder. One of the critically important incentives which Congress provided in the ODA is a seven-year period of market exclusivity for approved orphan drugs. 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 . . . ."). In other words, under the ODA, FDA cannot approve another drug for Tourette's Disorder for seven years. *See Sigma-Tau Pharms., Inc. v. Schwetz*, 288 F.3d 141, 145 (4th Cir. 2002) ("Section 360cc(a) simply provides that the FDA 'may not approve' generics for a protected indication.").

C. FDCA's Labeling Requirements And FDA's Implementation Of Those Requirements

1. In General

A 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). The 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).

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").[4] 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).

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

[4] http://www.fda.gov/downloads/Training/ForHealthProfessionals/UCM090796.

pediatric indication," among other things. *Id.* "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).

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

Generally, generic drugs (approved through ANDAs) must contain the same information on their labels as the label of their respective brand-name predicate drug. *See* 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8)(iv). In line with the special attention given to pediatric information elsewhere, Congress enacted a special provision, Section 505A(o) of the FDCA, to address the question of when pediatric information on a brand's label may be omitted, or carved out, from the generic's label. In Section 505A(o), Congress delineated express exceptions to same labeling requirement to allow pediatric information to be omitted from generic labeling when such information is only protected by protection or three-year exclusivity for conducting new clinical studies under Section 505(j)(5)(F)(iii) or (iv).[5] Section 505A(o) says that a generic is eligible for approval where the labeling "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." 21 U.S.C. § 355a(o)(1)-(2).

[5] 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 CFR 314.108(b)(4) & (5).

Argument

I. Summary Judgment Standard And APA Challenges

Under Fed. R. Civ. P. 56(a), summary judgment is appropriate when the pleadings and the evidence demonstrate that "there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Where, as here, final agency action under the APA is involved, summary judgment "serves as a mechanism for deciding, as a matter of law, whether the agency action is supported by the administrative record and otherwise consistent with the APA standard of review." *Roberts v. United States*, 883 F. Supp. 2d 56, 62-63 (D.D.C. 2012); *see also Hospira, Inc. v. Burwell*, No. GJH-14-02662, 2014 U.S. Dist. LEXIS 123972, *26 (D. Md. Sept. 5, 2014) ("'[T]he function of the district court is to determine whether or not as a matter of law the evidence in the administrative record permitted the agency to make the decision it did.'" (quoting *Kaiser Found. Hosps. v. Sebelius*, 828 F. Supp. 2d 193, 198 (D.D.C. 2011))).

II. FDA's Reversal Of Its Original Approval Decision Was Arbitrary, Capricious, And Contrary to Law.

In count one of the complaint, Otsuka's claim is that FDA abused its discretion and acted arbitrarily, capriciously, and contrary to law when it reversed its original approval decision, which approved a new indication for Abilify for treatment of Tourette's Disorder in pediatric patients. *See* 5 U.S.C. § 706(2)(A). This claim rests firmly on three closely related contentions. First, when FDA approved a broader indication that that which Otsuka requested and when this broader indication was not supported by Otsuka's adequate and well-controlled studies, FDA acted well outside its authority under the FDCA. Second, FDA's broadened approval is arbitrary and capricious because it is without factual or evidentiary support. Otsuka conducted clinical trials with pediatric patients only and FDA does not conduct its own independent clinical trials to

determine the safety and efficacy of a requested new indication. Third, FDA "corrected" and broadened its original approval for a legally impermissible reason. FDA's "corrected" its decision for reasons altogether unrelated and extraneous to the proper use of Abilify in the treatment of Tourette's Disorder. Instead of operating within the boundaries of the FDCA's approval provisions, FDA acted – and improperly so – in an effort to seek to deny Otsuka the rights and benefits to which it is entitled under the Orphan Drug Act.

1. FDA Acted Beyond Its Statutory Authority.

Agency action is unlawful where the agency acts beyond and in violation of its statutory authority. Multiple courts, including the Supreme Court, have rejected FDA's actions when, as here, FDA had no authority to take them. *See, e.g.*, *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000) (FDA has no statutory authority to regulate tobacco products); *Mylan Pharms., Inc. v. FDA*, No. 14-1522, 2014 U.S. App. LEXIS 24022, *16 (4th Cir. Dec. 16, 2014) (setting aside FDA's interpretation of the FDCA because it was contrary to its plain language); *Cook v. FDA*, 733 F.3d 1 (D.C. Cir. 2013) (FDA has no authority to exercise enforcement discretion not to review shipments of drug used in lethal injections and allow processing of them for importation because the statute required FDA to refuse admission to misbranded or unapproved drugs); *Pac. Legal Found. v. Goyan*, 664 F.2d 1221 (4th Cir. 1981) (FDA has no statutory authority to spend public funds to reimburse qualified participants in its proceedings); *Depomed, Inc. v. U.S. Dep't of Health & Human Servs.*, No. 12-cv-1592, 2014 U.S. Dist. LEXIS 126235, *50 (D.D.C. Sept. 5, 2014) (FDA violated plain language of the Orphan Drug Act).

In this case, FDA had no statutory authority to "correct" its approval decision and approve the use of Abilify for the treatment of Tourette's Disorder in the general population. The text of the FDCA is clear. *See* 21 U.S.C. § 355(b), (d). FDA may only approve a new indication for an approved drug when an applicant submits clinical data showing that the drug is safe and effective

for that particular use. *E.g.*, *Marcus v. Forest Labs., Inc.*, No. 14-1290, 2015 U.S. App. LEXIS 2631, *5 (1st Cir. Feb. 20, 2015) (FDA approved a drug for the "treat[ment of] major depressive disorder in adolescents based on a finding that substantial evidence supported the efficacy of that use"). The first step under *Chevron* is whether Congress has spoken directly to the precise question at issue. "If the statute is clear and unambiguous that is the end of the matter, for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *King v. Burwell*, 759 F.3d 358, 367 (4th Cir. 2014) (citing *Chevron U.S.A. Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 842 (1984)) (internal quotation marks omitted).

Section 355(b) & Section 355(d) are unambiguous. The applicant must submit studies showing that the drug is "safe for use" and "effective in use," and then Section(d)(1), (2), and (5) make clear that FDA's approval of an indication for a drug is limited by that clinical data. With its application, an applicant must include evidence of the drug's safety and effectiveness for the particular indication sought to be approved by submitting "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); *see also* 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.

FDA then evaluates the clinical data the applicant has submitted. FDA may not approve a new drug or a new indication 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";

- (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
- (5) "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)(1), (2), (5) (emphasis added).

Substantial evidence means "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, on the basis of which it could fairly and responsibly be concluded by such experts 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 labeling or proposed labeling thereof*." *Id.* § 355(d)(1), (2), (5) (emphasis added). "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 C.F.R. § 314.126(a).

FDA's approval authority is limited by the clinical data the applicant submits: the data must show that the "drug is safe for use *under the conditions prescribed, recommended, or suggested in the proposed labeling*," that the "drug is safe *for use under such conditions*," and 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*." In short, FDA may only approve a new indication for an approved drug when an applicant submits clinical data showing that the drug is safe and effective for that particular use suggested in the applicant's proposed

labeling. *See Forest Labs.*, 2015 U.S. App. LEXIS 2632, at *2 ("The FDA may only approve the drug if the NDA or sNDA provides 'substantial evidence that the drug will have the effect it . . . is represented to have.'"); *Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1322 (Fed. Cir. 2012) ("An NDA that seeks FDA approval for a particular use for a drug must include 'full reports of investigations' demonstrating that the drug is safe and effective *for that use*, 21 U.S.C. § 355(b)(1)(A), and it must include 'the labeling proposed to be used for such drug . . . .,' *id.* § 355(b)(1)(F)." (emphasis added)).

FDA's reliance on scientific evidence demonstrating safety and efficacy was highlighted in the recent Plan B contraception case, *Tummino v. Hamburg*, -- F. Supp. 2d --, 2013 WL 1348656, (E.D.N.Y. Apr. 5, 2013). There, Commissioner Hamburg made clear that, "It is our responsibility at FDA to approve drugs that are safe and effective for their intended use based on the scientific evidence." *Id.* at *3. In a press release explaining that the Secretary of Health and Human Services had invoked her authority to, in effect, deny a drug manufacturer's supplement for nonprescription use of Plan B in females under the age of 17 (an action the court subsequently reversed), the Commissioner noted that, "based on the information [the manufacturer] submitted to the agency," FDA determined that the product was safe and effective for its intended use. *Id.* The Commissioner's remarks highlight the importance of the science in approving drugs for public use. Unsubstantiated, if not random, judgment, as distinguished from science, is at play when, as here, "the information [the manufacturer] submitted to the agency" on safety and efficacy does not determine the scope of the approved indication.

The legislative history supports this reading of the statute. *See King*, 759 F.3d at 371 (considering legislative history under first step of *Chevron*). The Senate Report to the amendments adding the requirement that drugs be proven to be effective noted that "it is our understanding that

the manufacturer would be required to provide only substantial evidence that a drug produces the effects *claimed for it*. . . . Thus, if a number of tests by competent clinicians show that in well-conducted clinical trials a drug produced the claimed effect on their patients, the drug would not be barred simply because other tests did not produce the identical results with different patients." S. Rep. No. 87-1744 (1962) (emphasis added), *reprinted in* 1992 U.S.C.C.A.N. 2884, 2921. The Report also confirms that FDA only "*evaluate[s]* the claims of effectiveness in the light of the information submitted *to* him in the new drug application and any other information before him with respect to such drug and to decide whether there is substantial evidence . . . to support the claim." And that the question of whether or not to allow the claim is to "be determined by his evaluation of whether the claim had been supported by substantial evidence." S. Rep. No. 87-1744 pt. 2; *see also Warner-Lambert Co. v. Heckler*, 787 F.2d 147, 154 (3d Cir. 1986) (quoting legislative history for the same purpose).

Despite this, FDA did not "evaluate" the proposed indication and the supporting clinical data. FDA "corrected" its original approval and broadened Otsuka's indication without a request from Otsuka and in the absence of clinical data. Ex. 1, ¶ 24. Otsuka purposefully sought approval of a pediatric indication because of the "clear unmet need in younger patients . . . and there are no well-controlled trials confirming the safety and efficacy of the currently approved medications in these younger patients." *Id.* As a result, Otsuka devised trials "to investigate the safety and efficacy of aripiprazole in this indication [*i.e.*, pediatric patients]." *Id.* The trials tested the safety and efficacy of the drugs in children ranging in ages 6 to 18, and the proposed dosing recommendations were for individuals less than 50 kilograms (110 pounds) and those greater than 50 kilograms. *Id.* ¶¶ 14-16.

FDA's unlawful action here is that it broadened the approval in the total absence of any

statutory authority to approve Abilify for the treatment of Tourette's Disorder in the general population. *Id.* ¶ 24. The law does not permit FDA to approve an indication broader than the one requested by the sponsor (Otsuka) and for which the sponsor (Otsuka) provides adequate and well-controlled studies demonstrating safety and effectiveness. But that is what FDA did.

2. FDA's "Reversal" Was Without Factual Or Evidentiary Support.

Further, FDA's "corrected" approval is without factual or evidentiary support. FDA has no evidence to support its approval of a new indication for the use of Abilify for the treatment of Tourette's Disorder in the general population. Otsuka's clinical trials did not study the safety and effectiveness of the drug on the adult population, *id.* ¶¶ 13-14, 24; the trials proved the safety and effectiveness of the drug in the pediatric population only, *id.* ¶¶ 14-15; and FDA does not conduct its own independent clinical trials to determine the safety and effectiveness of a requested new indication.

There is no factual or evidentiary support demonstrating the safety and efficacy of Abilify for treatment of Tourette's Disorder in the general population. *See In re Zyprexa Prods. Liability Litig.*, 253 F.R.D. 69, 109 (E.D.N.Y. 2008) ("To determine whether a drug is 'safe and effective,' the FDA relies on information provided by a drug's manufacturer; it does not conduct any substantial analysis or studies itself. . . . FDA approval of prescription drugs is wholly dependent upon the accuracy of information provided by drug manufacturers."), *rev'd on other grounds by UFCW Local 1776 & Participating Emp'rs Health & Welfare Fund v. Eli Lilly & Co.*, 620 F.3d 121 (2d Cir. 2010); *State ex rel. Wilson v. Ortho-McNeil-Janssen Pharms., Inc.*, No. 27502, 2015 S.C. LEXIS 83, *7 (S.C. Feb. 25, 2015) ("As the FDA does not conduct independent scientific testing, it is incumbent upon sponsors to disclose all clinical data to ensure the safe and effective use of drugs."); *Cline v. Okla. Coalition for Reproductive Justice*, 313 P.3d 253, 257 n.9 (Okla. 2013) ("The FDA does not design or test the proposed protocol and does not conduct its own

clinical trials; rather, FDA experts scrutinize submissions by the drug's sponsor and other interested parties, concerning the safety and efficacy of the drug.").

The clinical data demonstrating the safety and effectiveness of Abilify to treat Tourette's Disorder in the pediatric population cannot simply, let alone lawfully, be extrapolated to demonstrate the same in the general population. The pediatric population is fundamentally different from the adult population. FDA itself has recognized this scientific fact. 62 Fed. Reg. 43900, 43901 (Aug. 15, 1997) ("Potentially significant differences in pharmacokinetics may alter a drug's effect in pediatric patients. The effects of growth and maturation of various organs, maturation of the immune system, alterations in metabolism throughout infancy and childhood, changes in body proportions, and other developmental changes may result in significant differences in the doses needed by pediatric patients and adults."). Indeed, Congress has recognized this fact and limited extrapolation; the FDCA allows extrapolation of pediatric effectiveness from the adult population to the pediatric population, *see* 21 U.S.C. § 355c(a)(2)(B)(i) (limiting extrapolation of pediatric effectiveness "from adequate and well-controlled studies in adults usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies"); *see also id.* § 355(c)(2)(B)(ii) ("A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group."), and of course, FDA has followed suit in its regulations. *See* 21 C.F.R. § 314.55(a) (same); 21 C.F.R. § 201.80(f)(9)(iv) ("FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults . . . ."). Extrapolation of safety data is not allowed. *See* 63 Fed. Reg. 66632, 66641 (Dec. 2, 1998) (final rule) ("FDA agrees, however, that extrapolation from adult effectiveness data would not always be appropriate and that it may not be appropriate to extrapolate pediatric safety from adult safety data."); FDA, *Guidance for Industry and Review*

Staff – Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling, at 5 (Feb. 2013) ("Extrapolation of data from adults to the pediatric population under PREA generally refers only to efficacy and not to safety or dosing."); *see also* Dianne Murphy, MD, FAAP, Dir., Office of Pediatric Therapeutics, Office of the Comm'r, FDA, "Pediatric Extrapolation: FDA Approach," at 8 ("Extrapolation is, by regulation for Drugs, restricted to Efficacy."); Dianne Murphy, MD, FAAP, Dir., Office of Pediatric Therapeutics, Office of the Comm'r, FDA, "Extrapolation of Efficacy in the Pediatric Population," at 10 (Sept. 2012) ("1998 Pediatric Rule Regulation . . . makes it clear that safety is not to be 'extrapolated.'").[6]

In the specific case of Tourette's Disorder, disallowing extrapolation from pediatrics to adults is scientifically sound. The disorder presents itself in adults "in fundamentally different ways than the Disorder does in the pediatric population," and adult treatment "is more difficult than is the treatment of the pediatric population with the Disorder." Ex. 1, Att. H ¶ 6. "Effective treatment of adults often requires more intense interventions than that involved with children who have the Disorder." *Id.* Dosing is also "very different" among the two populations: "The dose for adults is typically 20 mg. or more, a factor of two or more times than that administered to pediatric patients. In addition, pediatric patients must be started at much lower doses than adults with the dose gradually increased." *Id.*, Att. H ¶ 7; *see also* Ex. 2, Jennifer Cheng-Shannon, M.D., et al., *Second Generation Antipsychotic Medications in Children & Adolescents*, Journal of Child and Adolescent Psychopharmacology, at 385, Vol. 14, No. 3 (2004) (study submitted in support of

[6] FDA's guidance is available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm341394.pdf. Both presentations are available at http://www.fda.gov/downloads/NewsEvents/MeetingsConferencesWorkshops/UCM415210.pdf; http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM340587.pdf.

sNDA explaining that "[o]ptimal dosing [of aripiprazole in conduct disorder] appears to be lower in children than in adults"); Ex. 3, Claudia Wenzel, M.D., et al., *Aripiprazole for the Treatment of Tourette Syndrome: A Case Series of 100 Patients*, Journal of Clinical Psychopharmacology, Vol. 32, No. 4 (Aug. 2012) (study suggesting that dosing of aripiprazole for the treatment of tics "seems to be individually different and may range from 5-45mg").

FDA was wrong to approve a broader indication in the absence of any clinical trials demonstrating the effectiveness of the drug for the treatment of Tourette's Disorder in the general population. *See* Ex. 1, ¶ 24. Abilify's FDA approved label demonstrates (in its omission) that nothing is known about warnings and precautions that should be given to the adult population or adverse reactions that might occur in the adult population when treated with Abilify for Tourette's Disorder. *Id.* ¶ Att. A. Abilify's approved label lists none of these things for *adults* because the drug was not studied in that population for the treatment of Tourette's. FDA's "reversal" is unlawful because it is without factual or evidentiary support. *E.g.*, *Almay, Inc. v. Califano*, 569 F.2d 674, 682-83 (D.D.C. 1977) (FDA's definition was arbitrary and capricious for lack of sufficient evidence).

3. FDA's "Reversal" Was Based On An Impermissible Reason.

a. Agency Action Taken For An Impermissible Reason Is Invalid.

FDA's action is unlawful for the separate and further reason that it was based on an impermissible reason. "[A]n agency action can be arbitrary and capricious, even if it is ultimately correct, if the action is taken for the wrong reasons." *Russo Dev. Corp. v. Reilly*, No. 87-3916, 1991 U.S. Dist. LEXIS 20965, *8-9 (D.N.J. May 17, 1991) (citing *SEC v. Chenery Corp.*, 318 U.S. 80, 95 (1943)); *Latecoere Int'l, Inc. v. U.S. Dep't of Navy*, 19 F.3d 1342, 1356 (11th Cir. 1994) ("[P]roof of subjective bad faith by [agency decision-makers], depriving a [petitioner] of

fair and honest consideration of its proposal, generally constitutes arbitrary and capricious action.").

In *Tummino v. Torti*, 603 F. Supp. 519 (E.D.N.Y. 2009), FDA's denial of a citizen petition involving Plan B was reversed as arbitrary and capricious because FDA's "lack of good faith." Among other things, the lack of good faith was evidenced by delays, political pressure, and significant departures from FDA's normal procedures and policies. *Id.* at 544; *see also Tummino v. Hamburg*, 936 F. Supp. 2d 162, 192 (E.D.N.Y. 2013) ("Because the Secretary's action was politically motivated, scientifically unjustified, and contrary to agency precedent, it cannot provide a basis to sustain the denial of the Citizen Petition.").

b. FDA Acted For An Impermissible Reason To Attempt To Avoid Section 505A(o).

Here, as in *Tummino*, FDA acted without factual or evidentiary support, as demonstrated above, and, instead, for an impermissible, unlawful reason. Shortly after Otsuka's counsel wrote to FDA, informing the agency of the legal significance of the original approval for orphan indication of treatment of pediatric patients with Tourette's Disorder (*i.e.*, Otsuka was entitled to a seven-year period of statutory market exclusivity), FDA suddenly "corrected" its approval in a transparent effort intended to eliminate Otsuka's statutory exclusivity rights. Ex. 1, ¶ 23.

Counsel informed FDA that the approval for the orphan indication of treatment of Tourette's Disorder in pediatric patients precluded FDA from approving an ANDA for a generic version of Abilify for any indication pending the expiration of Otsuka's statutory seven-year period of orphan drug market exclusivity. *Id.* ¶ 22, Att. E. Generally, generic drugs must contain the same information on their labels as their respective brand-name predicate drug. *See* 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8)(iv). With respect to pediatric indications and information on a brand-name label, Congress delineated specific exceptions to this so-called

"same-labeling" requirement. In Section 505A(o) of the FDCA, Congress expressly allows pediatric indications and information to be omitted from ANDA labeling when such information is protected only by patent or three-year exclusivity under Section 505(j)(5)(F)(iii) or (iv) for receiving approval based on new clinical studies. *See* 21 U.S.C. § 355a(o). The statute undeniably does not allow the omission of pediatric information protected by orphan drug exclusivity, which is granted pursuant to Section 527 of the FDCA (21 U.S.C. § 360cc).

In other words, although a generic label must be identical to its brand-name counterpart, Congress has said that certain pediatric information protected only by a patent or three-year new clinical studies exclusivity can be omitted, thus allowing generics to carve out that pediatric information from their labels and be approved. However, Congress specifically did not allow generics to carve out a pediatric indication protected by orphan drug exclusivity. Therefore, when FDA approved Abilify for Tourette's Disorder in pediatric patients, that precluded FDA from approving generic versions of Abilify for any of the drug's FDA-approved indications. Congress does not permit generics to omit that type of pediatric indication from their labels, and they cannot include that type of pediatric indication on their labels until Otsuka's seven years of orphan drug exclusivity for the Tourette's pediatric indication expires.

Faced with this position, FDA's response was to issue a "corrected" approval, informing Otsuka that its earlier December 12, 2014, approval letter "contained an error in the 'indications' section," and that the new indication was for treatment of patients with Tourette's Disorder. Ex. 1, ¶ 23, Att. A & F. FDA later clarified, at Otsuka's request, that the supplemental approval was for the treatment of Tourette's disorder in the general population. *Id.*, Att. A. There is no explanation for this about face other than FDA's unlawful reason to change the approval to eliminate Otsuka's entitlement to seven years of exclusivity and allow generic entry on April 20,

2015. And certainly FDA has offered no alternative explanation. FDA's action is unlawful because it was taken for an impermissible, bad faith reason. *See Torti*, 603 F. Supp. 2d. at 544; *Latecoere Int'l*, 19 F.3d at 1356 (reversing summary judgment in favor of government and officials where there was evidence they arbitrarily increased ratings of appellant's rival to make it eligible for award when it otherwise would not have been and award was motivated by bias against appellant).

For the reasons stated, the Court should grant Otsuka's motion for summary judgment on count one of its complaint. The Court should reverse and vacate FDA's broadened "corrected" approval decision and reinstate FDA's original "pediatric patients only" approval decision.

III. FDA Is Precluded From Approving A Generic Version Of Abilify Under The "Corrected" Approval.

Assuming, without conceding, the validity of FDA's broadened "corrected" approval, FDA is nevertheless precluded from approving a generic version of Abilify. FDA's attempt to avoid the consequence of Otsuka's orphan approval fails. While FDA (unlawfully) sought to eliminate the pediatric indication, there still remains "any other aspect[s] of labeling pertaining to pediatric use" that is protected by for orphan drug exclusivity and cannot, under Section 505A(o), be omitted from a generic's label. On count two of its complaint (as on count one), Otsuka prevails under *Chevron* step one because "the statute is clear and unambiguous . . . [and] the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *King*, 759 F.3d at 367.

A. Section 505A(o) Does Not Allow Pediatric Indications Or Information Pertaining To Pediatric Use To Be Omitted From A Generic's Label When It Is Protected By Orphan Drug Exclusivity.

As explained above, Section 505A(o) addresses the precise subject of when and what pediatric information may be omitted from generic labeling. The statute, by its plain terms, allows

FDA to approve a generic despite the difference in the generic and brand label where the generic "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 three-year exclusivity under [Section 505(j)(5)(F)(iii) or (iv)]." 21 U.S.C. § 355a(o)(1)-(2).

Congress expressly allows pediatric indications and information to be omitted from ANDA labeling when such information is only protected by patent or three-year new clinical studies exclusivity (under Section 505(j)(5)(F)(iii) or (iv)). *See* 21 U.S.C. § 355a(o). The statute does not allow the omission of pediatric information protected by orphan drug exclusivity, which is granted pursuant to Section 527 of the FDCA (21 U.S.C. § 360cc).[7] The pediatric information with respect to Abilify cannot be omitted as it is protected by orphan drug exclusivity.

The familiar principle of statutory construction *expressio unius est exclusio alterius* (the expression of one thing is the exclusion of another) controls here. *See Leatherman v. Tarrant County Narcotics Intelligence & Coordination Unit*, 507 U.S. 163, 168 (1993). When, as here, Congress expressly identifies specific statutory exceptions (*i.e.*, pediatric labeling protected by patent or three-year exclusivity), the exceptions so identified are an exclusive list and all other

[7] The fact that Otsuka received three-year new clinical studies exclusivity makes no meaningful difference here. Assuming FDA's "corrected" approval is lawful, Otsuka's pediatric information is protected by orphan drug exclusivity and Congress did not include that exclusivity in the statute. FDA itself has recognized the difference in the two exclusivities: "The scope of orphan drug exclusivity differs from that of 3-year exclusivity for a supplement under section 505(c)(3)(E)(iv) or 505G)(5)(F)(iv) of the FD&C Act. Specifically, orphan exclusivity prevents approval of the same drug for the same indication whereas 3-year exclusivity under section 505(c)(3)(E)(iv) or 505G)(5)(F)(iv) of the FD&C Act prevents approval for 'a change approved in the supplement.' Given the difference in the scope of these exclusivities, a decision in one context does not dictate the same determination in a different context." Letter from FDA to Gary L. Veron, Esq. (Feb. 15, 2013), http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-1018-0003; *see also AstraZeneca Pharms. LP v. FDA*, 872 F. Supp. 2d 60 (D.D.C. 2012) (setting forth scope of three-year exclusivity).

exceptions are excluded (*e.g.*, pediatric labeling protected by orphan drug exclusivity). *See Andrus v. Glover Constr. Co.*, 446 U.S. 608, 616-17 (1980) ("Where Congress explicitly enumerates certain exceptions to a general prohibition, additional exceptions are not to be implied, in the absence of evidence of a contrary legislative intent."); *TRW Inc. v. Andrews*, 534 U.S. 19, 28-29 (2001); *Shays v. FEC*, 528 F.3d 914, 933-34 (D.C. Cir. 2008) (holding that regulation failed at *Chevron* step one because Congress had spoken directly to the issue; "most important," the statute contained three express exceptions and there was no basis for creating an implied fourth exception); *NRDC v. EPA*, 489 F.3d 1250, 1259-60 (D.C. Cir. 2007) (EPA may not, consistent with *Chevron*, create an additional exception to a statutory prohibition on its own despite the agency's belief that it is necessary to avoid results inconsistent with the statutory purpose).

The Orphan Drug Act was enacted in 1983 and Section 505A(o), the pediatric exceptions to the same labeling requirement, was enacted almost 20 years later in 2002. Section 505A(o) was thus enacted against the background of the Orphan Drug Act. Congress could have included the omission of pediatric labeling covered by orphan exclusivity as a permissible exclusion from the otherwise applicable same labeling requirement. The dispositive point is that Congress chose not to do so and that choice must be respected. *United States v. Langley*, 62 F.3d 602, 605 (4th Cir. 1995) ("Congress acts with knowledge of existing law, and . . . 'absent a clear manifestation of contrary intent, a newly-enacted or revised statute is presumed to be harmonious with existing law and its judicial construction.'" (quoting *Estate of Wood v. C.I.R.*, 909 F.2d 1155, 1160 (8th Cir. 1990))).

A recent decision of the U.S. District Court for the District of Columbia, upholding the plain language of the Orphan Drug Act, is directly relevant:

> Congress not only unambiguously described the conditions necessary for exclusivity to attach [in the Orphan Drug Act], it also specifically enumerated the

> circumstances in which exclusivity would not result despite the fact that a drug had been designated and approved. 21 U.S.C. § 360cc(b). The express statutory exceptions are significant because it is well-established that "[w]here Congress explicitly enumerates certain exceptions to a general prohibition, additional exceptions are not to be implied, in the absence of evidence of a contrary legislative intent." *Andrus v. Glover Const. Co.*, 446 U.S. 608, 616-617 (1980). Here, the statute generally prohibits the FDA from approving orphan drugs for the same indication as one that has previously been approved and designated, and also provides two specifically enumerated exceptions, neither of which includes the fact that a prior (non-designated) drug for the same disease or condition and with the same active ingredients might already be on the market. This Court will not impute to Congress an intention to authorize an exception that Congress itself did not think worth enacting. *See, e.g.*, *NRDC v. EPA*, 489 F.3d 1250, 1259-1260 (D.C. Cir. 2007) (holding that where Congress provides certain enumerated exceptions in a statute, an agency "may not, consistent with Chevron, create an additional exception on its own").

Depomed, Inc., 2014 U.S. Dist. LEXIS 126235, at *38-39.

The statute thus defines and thereby limits the universe of permissible categories of exclusion. Orphan drug exclusivity is granted through Section 527, and not under 505(j)(5)(F)(iii) or (iv); therefore, where pediatric information is protected by orphan drug exclusivity, it may not be omitted and the general rule that the ANDA's label must be the same as that of its respective listed drug applies.

B. Otsuka's "Corrected" Approval And Labeling Contains Multiple Aspects Pertaining To Pediatric Use That Cannot Be Omitted.

Despite FDA's about face removal of Otsuka's pediatric indication, there are multiple aspects of the labeling pertaining to pediatric use that cannot be omitted. The type of information that Congress allowed generics to omit if it was only protected by patent or three-year exclusivity but not orphan drug exclusivity, as explained above, is broad: it expressly reaches "any other aspect of labeling pertaining to pediatric use." "Any" and "pertaining to" are broad terms.

"Any" is defined as "unmeasured or unlimited in amount, number, or extent" and "ALL – used to indicate a maximum or whole." Merriam-Webster's Collegiate Dictionary (10th ed. 1999); *see also Bakery & Confectionary Union & Indus. Int'l Pension Fund v. New World Pasta Co.*, 309

F. Supp. 2d 716, 727 (D. Md. 2004) ("'Any' is defined as: 'One, some, every, or all without specification' and 'exceeding normal limits, as in size or duration.'" (citing The American Heritage Dictionary of the English Language, 4th ed., 2000)); *Hammaker v. Brown & Brown, Inc.*, 214 F. Supp. 2d 575, 580 (E.D. Va. 2002) ("The term 'any' is defined as 'one or more.' Thus, the term 'any' is subject to a broad interpretation . . . ." (citing Webster's Third New Int'l Dictionary (1993); citation omitted); *United States ex rel. Barajas v. United States*, 258 F.3d 1004, 1011 (9th Cir. 2001) ("The term 'any' is generally used to indicate lack of restrictions or limitations on the term modified."). Courts interpreting the meaning of the word "any" in the FDCA have interpreted the term broadly. *E.g.*, *Medical Ctr. Pharm. v. Mukasey*, 536 F.3d 383, 394-96 (5th Cir. 2008) (interpreting "any" in the definition FDCA definition of "new drug" broadly to include drugs created by compounding); *United States v. Gen. Nutrition, Inc.*, 638 F. Supp. 556, 563-64 (W.D.N.Y. 1986) (concluding that "'[a]ny' means any" and dismissing defendants' claim that their "relatively low position in the corporate hierarchy" "excuse[d]" their conduct in violation of the FDCA).

"Pertaining to" is likewise broad. *See James Madison Project v. CIA*, No. 1:08-cv-1323, 2009 U.S. Dist. LEXIS 78671, *11 (E.D. Va. Aug. 31, 2009) (concluding that "pertaining to" is "as broad as" "relating to" and therefore "overbroad"). "Pertain" means "to belong as a part, member, accessory, or product" or "as an attribute, feature, or function," Merriam-Webster's Collegiate Dictionary (10th ed. 1999), or "relating to" or "concerning," *James Madison Project*, 2009 U.S. Dist. LEXIS 78671, at *11 (defining the term from Black's Law Dictionary 381 (8th ed. 2004); The Random House Dictionary of English Language 1447 (2d ed. 1987); American Heritage Dictionary of English Language (4th ed. 2006); Webster's Revised Unabridged Dictionary (1996)).

The Otsuka label is full of "any other aspect of labeling pertaining to pediatric use." Ex 1, ¶ 29. In the portion of the label titled "Highlights of Prescribing Information," for example, the "Indications and Usage" section includes a reference to the clinical trials supporting the new indication ("Treatment of Tourette's disorder (14.5)"); 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). *Id.* ¶ 30, Att. A.

The "Full Prescribing Information" section also includes substantial pediatric information. The indications for use section (§ 1) refers to the pediatric clinical studies in connection with the indication for "Treatment of Tourette's Disorder": "Treatment of Tourette's Disorder *[see CLINICAL STUDIES (14.5)]*." *Id.* ¶ 31, Att. A. Section 14.5 is titled "Tourette's Disorder" and its subtitle is "Pediatric Patients." *Id.* The section contains a detailed discussion of the pediatric clinical trials conducted. *Id.*

The dosage and administration section (§ 2) is similar. Section 2.5 is titled "Tourette's Disorder" and its subtitle is "Pediatric Patients (6 to 18 years)." *Id.* The section describes the recommended dosage ranges for pediatric patients, not adult patients. *Id.* The "Use in Specific Populations" section also includes a "Pediatric Use" section with a portion focused on Tourette's Disorder (§ 8.4). *Id.* There, the label explains that "Safety and effectiveness of aripiprazole in pediatric patients with Tourette's Disorder were established in one 8-week (aged 7 to 17) and one 10-week trial (aged 6 to 18) in 194 pediatric patients *[see DOSAGE AND ADMINISTRATION (2.5), ADVERSE REACTIONS (6.1), and CLINICAL STUDIES (14.5)]*." *Id.* The label includes warnings related to Tourette's Disorder in the pediatric population (§ 5.6) and adverse reactions in the pediatric population (§ 6.1). *Id.*

C. Assuming, But Not Conceding, The Lawfulness of FDA's "Corrected" Approval, Otsuka Is Entitled To A Declaration That FDA Is Precluded From Approving Generics.

The text of Section 505A(o) is clear, and the consequence of FDA's approval and designation of orphan drug status of a pediatric indication or inclusion of information pertaining to pediatric use is overriding. Assuming FDA's broadened indication is lawful, FDA still cannot approve a generic version of Abilify for any of its FDA-approved indications because Abilify's label contains information pertaining to pediatric use that Congress has decided cannot be omitted from a generic's label. When Congress enacted Section 505A(o) it did not allow a generic to omit information protected by orphan drug exclusivity. That is the end of the matter.

Absent this Court's intervention, on April 20, 2015, FDA will approve generic versions of Abilify. Accordingly, the Court should grant Otsuka's motion for summary judgment on count two of its complaint and 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).

Conclusion

For the reasons stated above, Otsuka's motion for summary judgment should be granted. A proposed final judgment is attached.

Respectfully submitted,

Dated: March 24, 2015

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CERTIFICATE OF SERVICE

I HEREBY CERTIFY that the above motion for summary judgment and memorandum in support was served electronically on counsel for FDA this 24th day of March, 2015 as follows:

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

Otsuka Pharmaceutical Co., Ltd., et al.,	*	
Plaintiff,	*	
v.		CIVIL ACTION NO.
	*	
Sylvia Mathews Burwell, et al.,	*	
Defendants.		

* * * * * * * * * * * * *

[Proposed] FINAL JUDGMENT AND ORDER

Pending before the Court is Otsuka's motion for summary judgment. Having reviewed the motion and the oppositions thereto and having heard the oral arguments of counsel at a hearing on _____, and finding that the material facts are not in dispute and that for the reasons stated on the record [and in the Court's Memorandum Opinion, ECF No. __] Otsuka Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Development & Commercialization, Inc., and Otsuka America Pharmaceutical, Inc. (collectively "Otsuka") are entitled to judgment as a matter of law, Otsuka's motion for summary judgment is hereby GRANTED.

FINAL JUDGMENT is, therefore, entered FOR Otsuka and AGAINST all defendants on Count I of Otsuka's complaint, and it is further ORDERED and DECLARED that:

1. FDA is ORDERED to approve (*i.e.*, to reinstate the approval of) Abilify for treatment in pediatric patients with Tourette's Disorder; and

2. FDA is ORDERED to rescind and vacate the unauthorized, unlawful broader approval for treatment of all patients with Tourette's Disorder without regard to the patient's age; and

3. FDA is ORDERED not to grant approval of any ANDAs for generic versions of Abilify pending the expiration of Otsuka's seven-year exclusivity period.

4. [Other equitable relief which the Court deems just and proper.]

Dated: _____, 2015 _____