IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

OTSUKA PHARMACEUTICAL CO., LTD., OTSUKA PHARMACEUTICAL DEVELOPMENT & COMMERCIALIZATION, INC. and OTSUKA AMERICA PHARMACEUTICAL, INC.

Plaintiffs,

v.

SYLVIA MATHEWS BURWELL
Secretary of Health and Human Services

MARGARET HAMBURG, M.D.,
STEPHEN OSTROFF, M.D.,
Commissioner/Acting Commissioner of U.S. Food and Drug Administration

and

UNITED STATES FOOD AND DRUG ADMINISTRATION

Defendants,

APOTEX, INC., APOTEX CORPORATION, TEVA PHARMACEUTICALS USA, INC., and ALEMBIC PHARMACEUTICALS LTD.

Intervenor-Defendants.

Civil Action No. 15-cv-00852-GJH

INTERVENOR-DEFENDANTS APOTEX, INC., APOTEX CORPORATION, AND TEVA PHARMACEUTICALS USA, INC.'S MEMORANDUM IN SUPPORT OF THEIR MOTION TO DISMISS AND IN OPPOSITION TO PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Federal Cases

Federal Statutes

Federal Regulations

Other Authorities

Intervenor-Defendants Apotex Inc. and Apotex Corporation (collectively, "Apotex") and Teva Pharmaceuticals USA, Inc. ("Teva") respectfully submit this memorandum in support of their Motion to Dismiss and in opposition to the Motion for Summary Judgment filed by Otsuka Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Development & Commercialization, Inc., and Otsuka America Pharmaceutical, Inc. (collectively, "Otsuka").

I. INTRODUCTION

This case represents Otsuka's latest attempt to forestall generic competition to preserve billions of dollars in annual profits on aripiprazole, which it sells under the trade name Abilify®. Over the last 12 years Otsuka has grossed over $40 billion in revenues as the sole marketer of Abilify®. With the clock winding down towards April 20, 2015—the date upon which lower-priced generic competition should lawfully begin—Otsuka advances arguments that have no basis in fact or law, in an attempt to gain another seven years free from generic competition.

The U.S. Food and Drug Administration ("FDA") recently gave Otsuka a substantial additional benefit known as orphan drug exclusivity—seven years with the exclusive right to market aripiprazole *for the treatment of Tourette's disorder*. But aripiprazole is approved for the treatment of four other conditions as well, and in this lawsuit Otsuka seeks to leverage its exclusivity for Tourette's disorder into seven more years without generic competition. Otsuka claims in Count I of its Complaint that FDA impermissibly "broadened" its approved indication for Tourette's disorder from pediatric patients to all patients. In Count II, Otsuka argues that regardless of the scope of FDA's approval, FDA's award of marketing exclusivity limited to the Tourette's indication means that FDA has no authority to approve Abbreviated New Drug Applications ("ANDAs") that seek to market generic versions of Abilify® for

any use, even if the ANDAs exclude the Tourette's disorder indication as they are permitted to do. Otsuka's challenges fail.

As a threshold matter, Otsuka's Complaint must be dismissed because the agency action that it contends will cause it injury has not occurred. Otsuka is still marketing its Abilify® products without generic competition, unaffected by any action FDA may have taken on February 24, 2015. Otsuka's asserted injury—generic competition that it alleges should not materialize until 2021—has not materialized, and depends on whether, when, and how FDA approves an ANDA to market aripiprazole. The agency has not, to date, approved any generic aripiprazole products that would compete with Abilify®; it cannot do so until April 20, 2015. Because Otsuka's claim of injury remains wholly speculative, there is no live controversy and Otsuka's claims are not ripe.

Otsuka's arguments fare no better on the merits. Otsuka challenges FDA's alleged "broadened approval action" solely so that it can then argue that, because its orphan indication is directed to pediatric patients, generics cannot carve this indication out of their labeling. Otsuka then expands upon that argument and challenges FDA's authority to allow generic Abilify® applicants to carve-out *any* pediatric information relating to Otsuka's Tourette's indication during its seven-year orphan exclusivity period. Thus, under Otsuka's tortured logic, a particular exclusivity that is expressly limited in application to one specific indication nonetheless has the effect of preventing the approval of ANDAs that *exclude* that indication and would be labeled only for *other* indications. Neither argument can survive. This is simply not how the relevant prescription drug labeling laws work, and for good reason. Under FDA's long-standing "carve-out" authority under the federal Food, Drug, and Cosmetic Act ("FDCA"), as well as the unambiguous language of the Orphan Drug Act itself, the agency's own implementing regulations, and judicial and administrative precedent, FDA is allowed to approve generic

applicants that seek approval for uses not protected by Otsuka's exclusivity. Section 505A(*o*) of the FDCA, the provision on which Otsuka bases its entire argument, relates to the agency's award of *six months* of pediatric exclusivity, has no relevance here, and certainly provides no basis for Otsuka to extend its monopoly for another *seven years*. Otsuka cannot use as a sword a statutory provision that Congress intended as a shield to protect ANDA applicants from precisely the type of anti-competitive gamesmanship Otsuka engages in here.

This Court should reject Otsuka's legally flawed efforts to delay generic competition and grant Intervenor-Defendants' motion to dismiss and deny Otsuka's motion for summary judgment.

II. STATUTORY AND REGULATORY BACKGROUND

A. Approval of New Drugs and Labeling Requirements

1. NDA Requirements

Under the FDCA, a company seeking to sell a new (previously unapproved) drug must file a New Drug Application ("NDA") containing technical data on the composition of the drug, the means for manufacturing it, clinical trial results to establish the safety and efficacy of the drug, and labeling for the use of the drug for which approval is requested. *See* 21 U.S.C. § 355(b)(1). FDA publishes and makes available a list of these drugs and the associated patent information and exclusivities related to each drug product to put other applicants on notice regarding the scope and expiration dates of potential barriers to approval. 21 U.S.C. § 355(j)(7); *see* APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (35th ed., 2015) (commonly referred to as the "Orange Book").

Among other things, FDA will approve an NDA only if the drug is shown to be both safe and effective for its intended use under the conditions set forth in the drug's labeling. *See* 21 U.S.C. § 355(c). The approved indications for a drug are listed as such in FDA-approved labeling. FDA's

"comprehensive review is embodied in the labeling for the product which reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively." 73 Fed. Reg. 2484, 2851 (Jan. 16, 2008); *see also* 71 Fed. Reg. 3922, 3961 (Jan. 24, 2006) ("The purpose of prescription drug labeling is to provide health care practitioners information necessary for safe and effective use.")

2. ANDA Requirements

In 1984, Congress passed the Hatch-Waxman Amendments to the FDCA, which created an abbreviated and expedited pathway for companies seeking to market a generic version of a previously approved drug. One of the main purposes of Hatch-Waxman was "to make available more low cost generic drugs by establishing a generic drug approval procedure . . . ." H.R. REP. NO. 98-857, pt. 1, at 14 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647; *see also FTC v. Actavis, Inc.*, 133 S. Ct. 2223, 2228 (2013) (noting that the Hatch-Waxman Amendments' streamlined approval process "speed[s] the introduction of low-cost generic drugs to market, thereby furthering drug competition" (internal citation and quotation marks omitted)). Under the ANDA process, the FDCA permits an ANDA applicant to rely upon the agency's prior finding of safety and efficacy for the approved drug, provided that the applicant demonstrates that its proposed generic version meets certain statutorily mandated showings of sameness and bioequivalence. More specifically, with certain exceptions, an ANDA applicant needs only to establish that its proposed generic has the same active ingredient(s), dosage form, route of administration, strength, labeling (with certain permissible differences), and conditions of use as the previously approved drug (referred to as the reference listed drug ("RLD")), and that it is bioequivalent to that drug. 21 U.S.C. § 355(j)(2)(A)(i)-(v); 21 C.F.R. § 314.94(a)(8)(iv). FDA will approve an ANDA

when the application has met all requirements for approval and any applicable patents, stays, and exclusivity periods have expired.

The statute, importantly, does not require that a generic drug's labeling be identical to the RLD in every instance, and allows differences when the generic product is produced or distributed by a different manufacturer:

> An abbreviated application for a new drug shall contain . . . information to show that ***the labeling proposed for the new drug is the same as the labeling approved for the listed drug*** referred to in clause (i) ***except for changes*** required because of differences approved under a petition filed under subparagraph (C) or ***because the new drug and the listed drug are produced or distributed by different manufacturers*** . . . .

21 U.S.C. § 355(j)(2)(A)(v) (emphasis added); *see also, e.g., id.* § 355(j)(2)(A)(viii) (providing that an ANDA may omit a "use" approved for the RLD). Crucially for purposes of this dispute, in enacting Hatch-Waxman, Congress explicitly acknowledged that "the bill permits an ANDA to be approved for less than all of the indications for which the listed drug has been approved." H.R. REP. NO. 98-857, pt. 1, at 21 (1984) ("[T]he applicant need not seek approval for all of the indications for which the listed drug has been approved."); *see also id.* at 22 ("The committee recognizes that the proposed labeling for the generic drug may not be exactly the same [as the listed drug]."). This means that, among other things, the "indications" section of a generic drug label may list fewer indications than those contained in the label for the corresponding brand drug.

By regulation, FDA allows ANDA labeling to include "differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, ***or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity*** under [the FDCA]." 21 C.F.R. § 314.94(a)(8)(iv) (emphasis added); *see also* 21 C.F.R. § 314.92(a)(l) (a generic drug product must have the same conditions of use as the

listed drug except for "conditions of use for which approval cannot be granted because of exclusivity or an existing patent may be omitted"). FDA will approve an ANDA despite such differences in labeling so long as "***such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use***." 21 C.F.R. § 314.127(a)(7) (emphasis added).

FDA has a long practice of allowing ANDA applicants to exclude information from their labeling that is protected by patents or other periods of exclusivity—a practice that is known in the industry as a "carve-out." (*See, e.g.*, Ltr. from J. Woodcock to R. Church, at 7, Dkt. No. FDA-2014-P-1649 (Feb. 24, 2015) (allowing ANDA applicants to omit orphan-protected indication even though brand-name manufacturer contended that generic products inevitably would be used to treat the omitted orphan indication as well) ("Fusilev CP Ruling"); Ltr. from J. Woodcock to G. Veron, at 13, Dkt. No. FDA-2012-P-1018 (Feb. 15, 2003) (concluding ANDA applicants could omit clinical data related to orphan indication because it would not render generic products less safe for remaining indications) ("Colcrys CP Ruling"); Ltr. from S. Galson to D. Fox, at 8 n.21, Dkt. No. 2003P-0321/CP1 (Apr. 6, 2004) (noting that pediatric information protected by orphan drug exclusivity would not prevent ANDA applicants from seeking approval for unprotected adult use) ("Rebetol CP Ruling"); *see also infra* at n.7 (collecting additional examples)).[1]

The Fourth Circuit, this Court, and other courts have upheld FDA's broad carve-out authority, including with respect to information protected by orphan drug exclusivity. *See, e.g.*, *Sigma-Tau Pharms., Inc. v. Schwetz*, 288 F.3d 141, 145, 148 n.3 (4th Cir. 2002) (upholding FDA's decision to allow ANDA applicant to omit an indication protected by orphan drug exclusivity and noting that the brand's

[1] All FDA administrative rulings cited herein are publically available at Regulations.gov at the listed docket numbers.

"argument constitutes nothing more than another attempt to obtain market exclusivity for any and all uses of its drug, thereby preventing generic competitors from entering the market for any indication"); *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996) (ruling that "the statute expresses the legislature's concern that the new generic be safe and effective for each indication that will appear on its label; whether the label for the new generic lists every indication approved for the use of the pioneer is a matter of indifference"); *AstraZeneca Pharms. LP v. Apotex Corp.*, 669 F.3d 1370, 1379 (Fed. Cir. 2012) ("And while generic applicants cannot obtain approval for uses beyond those already approved by the FDA, nothing in the Act requires that an ANDA must encompass *every* approved indication.") (internal citations omitted); *Hospira, Inc. v. Burwell*, No. GJH-14-02662, 2014 WL 4406901 (D. Md. Sept. 5, 2014) (upholding labeling carve-out of patent-protected use of dexmedetomidine hydrochloride).

B. Orphan Drug Exclusivity

Congress enacted the Orphan Drug Act (Public Law No. 97-414) in 1983, amending the FDCA to provide incentives to develop drugs to treat rare diseases and conditions (defined as any disease or condition that affects fewer than 200,000 persons in the United States). *See* 21 U.S.C. § 360aa *et seq*. Among other incentives, the statute generally grants seven years of orphan drug exclusivity to the first drug approved to treat a protected disease or condition:

> (a) Exclusive approval, certification, or license
>
> Except as provided in subsection (b) of this section, if the Secretary—
>
> (1) approves an application filed pursuant to section 355 of this title, or
>
> (2) issues a license under section 262 of Title 42
>
> for a drug designated under section 360bb of this title for a rare disease or condition, ***the Secretary may not approve another application under section 355 of this title*** or issue another license under section 262 of Title 42 ***for such drug for such disease or condition*** for a person who is not the

> holder of such approved application or of such license ***until the expiration of seven years from the date of the approval of the approved application or the issuance of the license.***

21 U.S.C. § 360cc(a)(2) (emphasis added); *see also* 21 C.F.R. § 316.31(a).

Orphan drug exclusivity applies *only* to the orphan *indication* for which the drug has been approved and begins on the date that the marketing application is approved for that indication. 21 U.S.C. § 360cc(a)(2); 21 C.F.R. § 316.31(b) ("Orphan-drug exclusive approval protects only the approved indication or use of a designated drug.").

C. Pediatric Exclusivity

To encourage pediatric drug development and provide healthcare professionals with adequate information about the use of prescription drugs in pediatric patients, Congress enacted the Food and Drug Administration Modernization Act of 1997, which added Section 505A to the FDCA (21 U.S.C. § 355a). *See, e.g.*, 147 CONG. REC. H10204-05 (daily ed. Dec. 18, 2001) (statement of Rep. Tauzin). Under Section 505A, if FDA determines that information relating to use of an approved drug in the pediatric population would benefit the public, FDA may issue a written request to the NDA sponsor to conduct studies in a particular population; if the sponsor completes the studies to FDA's satisfaction, the statute directs FDA to extend by six months any exclusivity or patent protection covering that drug. 21 U.S.C. §§ 355a(b)(1), (c)(1).

Unlike other types of statutory and regulatory exclusivities, pediatric exclusivity does not stand alone; it can only attach to the end of another exclusivity period (granted pursuant to another statutory provision) or a patent existing at the time the sponsor fulfills the written request to conduct pediatric studies. 63 Fed. Reg. 66632, 66633 (Dec. 2, 1998) (recognizing that qualifying pediatric studies under 505A will "extend[] by 6 months any *existing* exclusivity or patent protection on a drug whose

manufacturer submits pediatric studies in compliance with [FDA's regulations], if the studies meet the completeness, timeliness, and other requirements of Section 505A." (emphasis added)). "Previously earned pediatric exclusivity ***will not apply*** to new patents or ***exclusivity covering later-filed*** . . . ***supplements*** containing the same active moiety for which a sponsor previously earned pediatric exclusivity." (FDA Guidance for Industry, *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*, at 15 (Sept. 1999) (emphasis added)).[2]

III. FACTUAL BACKGROUND

Otsuka holds five approved NDAs for Abilify® (aripiprazole) products, four of which are relevant here: (1) NDA No. 21-436 for Abilify® Tablets, 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg, which was first approved for the treatment of schizophrenia on November 15, 2002; (2) NDA No. 21-729 for Abilify® orally disintegrating tablets, 10 mg and 15 mg, first approved on June 7, 2006; (3) NDA No. 21-713 for Abilify® oral solution, 1 mg/mL, first approved on December 10, 2004; and (4) NDA No. 21-866 for Abilify® intramuscular injection, 9.75 mg/1.3 mL (7.5 mg/mL), first approved on September 20, 2006.

On or about November 14, 2007, FDA awarded Otsuka pediatric exclusivity for Abilify® under Section 505A in connection with studies Otsuka had conducted "in pediatric patients with (1) schizophrenia, and with (2) acute mania, as part of bipolar I disorder," pursuant to a written request which explicitly stated "that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request." (*See* Ltr. from R. Temple, M.D., to Otsuka Pharmaceutical Company, Ltd., at 1, 11

[2] *Available at* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049924.pdf (last visited Apr. 7, 2015).

(Feb. 11, 2003)[3] ("PED Written Request"); *see also* List of Determinations Including Written Requests, at Aripiprazole.[4] This pediatric exclusivity will expire April 20, 2015 as it relates to U.S. Patent No. 5,006,528, which is listed in the Orange Book for Abilify® products.

Abilify® is currently marketed for the following five indications:

1 INDICATIONS AND USAGE

ABILIFY Oral Tablets, Orally-Disintegrating Tablets, and Oral Solution are indicated for the treatment of:

- Schizophrenia *[see CLINICAL STUDIES (14.1)]*
- Acute Treatment of Manic and Mixed Episodes associated with Bipolar I Disorder *[see CLINICAL STUDIES (14.2)]*
- Adjunctive Treatment of Major Depressive Disorder *[see CLINICAL STUDIES (14.3)]*
- Irritability Associated with Autistic Disorder *[see CLINICAL STUDIES (14.4)]*
- Treatment of Tourette's Disorder *[see CLINICAL STUDIES (14.5)]*

(FDA 000190).

The last indication, for Tourette's disorder, is new. FDA added the Tourette's disorder indication and related information to the Abilify® labeling in connection with the agency's December 12, 2014 approval of Otsuka's supplemental NDAs for its Abilify® tablets, oral solution, orally disintegrating tablets, and injectable formulations. (FDA 000001-96). The December 12, 2014 approval letter states:

> These "Prior Approval" supplemental new drug applications provide for labeling revisions based upon two adequate and well-controlled trials that demonstrate the efficacy for the new indication in pediatric patients with Tourette's Disorder.

[3] *Available at* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm073289.pdf (last visited Apr. 7, 2015).
[4] *Available at* http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049997 (last visited Apr. 7, 2015).

(FDA 000001). The letter also states that the sNDAs were "approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text." (*Id*.). The enclosed labeling shows the approved indication as "Treatment of Tourette's Disorder." (FDA 000005).

On February 24, 2015, FDA issued a supplemental approval letter which contains the following "Corrected Statement":

> These "Prior Approval" supplemental new drug applications provide for labeling revisions based upon two adequate and well-controlled trials that demonstrate the efficacy for the new indication in patients with Tourette's Disorder.

(FDA 000184). This supplemental approval letter also notes that "[t]he corrected labeling is unchanged." (*Id*.).

The same day, FDA issued a separate letter to Otsuka referencing the agency's January 25, 2006 designation of aripiprazole as an "orphan drug" for "treatment of Tourette's syndrome," and 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***." (Otsuka Mem. Ex. 1, at Ex. F). According to the letter, Otsuka's seven-year exclusivity began with approval of its supplemental NDAs on December 12, 2014. (*Id*.). FDA has updated its Orange Book listings for the four relevant Abilify® products to reflect this "ODE" (orphan drug exclusivity) period, which will expire on December 12, 2021.[5] This "ODE" period is <u>not</u> subject to a six-month pediatric exclusivity extension, however, presumably because FDA awarded Otsuka orphan drug exclusivity *years* after the date FDA awarded Otsuka pediatric exclusivity under Section 505A (*i.e.*, November 14, 2007).

[5] *See* Orange Book for NDA Nos. 21-436, 21-729, 21-713, 21-866, *available at* http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm (searchable by NDA number or proprietary name) (last visited Apr. 7, 2015) ("Orange Book Searchable Database").

On March 27, 2015, FDA issued a General Advice letter to Otsuka providing "comments" on, among other things, the agency's December 12, 2014 and February 24, 2015 approval letters. In that letter, FDA states that "the corrected approval letter did not broaden the indication or the scope of the underlying approval. The corrected letter simply harmonized the letter with the [Indications and Usage] statement in the [Full Prescribing Information]." (FDA 000284). FDA also notes that the Indications and Usage statement in Otsuka's labeling "has always listed 'Treatment of Tourette's Disorder' as the indication," and that the indication was "unchanged when the approval letter was corrected." (FDA 000283-84). FDA goes on to explain that "the correction was a housekeeping matter and not a change intended to alter the conditions of approval." (FDA 000284).

IV. ARGUMENT

A. Otsuka's APA Claims Are Not Fit For Judicial Review Because They Claim Injury From a Decision FDA Has Not Yet Made

Otsuka's claims are not justiciable and should be dismissed on that basis. While Otsuka's Complaint presents two different counts, both turn on an assertion that Otsuka will be injured by what FDA might do in the future, not on any final agency action FDA has already completed. Otsuka's sole concern in this litigation is that FDA might approve one or more ANDAs for aripiprazole, which Otsuka contends FDA cannot do for seven years because it would involve improperly carving out pediatric information from the generic labels. But FDA has not yet approved an ANDA for aripiprazole, and the agency evaluates proposed generic labels—which often differ among ANDA applicants—on a case-by-case basis. The Court should not get out in front of the agency and decide an abstract legal question that is premised on "contingent future events that may not occur as anticipated, or indeed may not occur at all." *Texas v. United States*, 523 U.S. 296, 300 (1998) (internal quotation marks omitted).

1. Legal Standards

Rule 12(b)(1) mandates dismissal of an Administrative Procedure Act ("APA") case where there has been no final administrative or agency action. *See, e.g., Golden & Zimmerman, LLC v. Domenech*, 599 F.3d 426, 433 (4th Cir. 2010) ("[W]e hold that the [agency's] publication . . . did not constitute final agency action reviewable in court, and, accordingly, we affirm the district court's order dismissing this case for lack of subject matter jurisdiction."); *Flue-Cured Tobacco Coop. Stabilization Corp. v. EPA*, 313 F.3d 852, 857 (4th Cir. 2002) ("[W]e conclude that the Report was not final agency action, and therefore, that the district court lacked subject matter jurisdiction to hear plaintiffs' claims[.]"); *Long Term Care Partners, LLC v. United States*, 516 F.3d 225 (4th Cir. 2008). To be reviewable under the APA, the challenged agency conduct must both (1) constitute "agency action" and (2) be "final." 5 U.S.C. § 704; *Domenech*, 599 F.3d at 431; *Flue-Cured Tobacco*, 313 F.3d at 857.

Moreover, "[e]ven when an agency has taken final action, a court may refrain from reviewing a challenge to the action if the case is unripe for review"—a doctrine that "springs from the Article III case or controversy requirement that prohibits courts from issuing advisory opinions on speculative claims." *Marcum v. Salazar*, 694 F.3d 123, 129 (D.C. Cir. 2012) (quoting EDWARDS & ELLIOTT, FEDERAL STANDARDS OF REVIEW 119-20 (2007)). Ripeness turns upon two primary considerations: (1) "the fitness of the issues for judicial decision"; and (2) "the hardship to the parties of withholding court consideration." *Lansdowne on the Potomac Homeowners Ass'n, Inc. v. OpenBand at Lansdowne, LLC*, 713 F.3d 187, 198 (4th Cir. 2013) (quoting *Miller v. Brown*, 462 F.3d 312, 319 (4th Cir. 2006)). A case is "fit" for adjudication when the issues are "purely legal" *and* when the agency action is "final and not dependent on future uncertainties." *Id.* Conversely, a claim is not ripe when "it rests on contingent future events that may not occur as anticipated." *AstraZeneca v. Apotex*, 669 F.3d at 1380 (quoting

Texas, 523 U.S. at 300); *accord Scoggins v. Lee's Crossing Homeowners Ass'n*, 718 F.3d 262, 270 (4th Cir. 2013). To evaluate the hardship element, the court considers the immediacy of the threatened injury and the burden imposed on parties. *Lansdowne*, 713 F.3d at 199.

Neither claim presented in Otsuka's Complaint is justiciable.

2. Counts I and II Are Not Justiciable

In Count I, Otsuka challenges as arbitrary, capricious, and unlawful FDA's February 24, 2015 supplemental approval letter that states that it corrects an error in its earlier (December 12, 2014) approval letter for Otsuka's supplemental NDAs. (FDA 000184-272). In Count II, Otsuka challenges FDA's authority to approve generic versions of Abilify® and argues that such approval would unlawfully deny Otsuka the rights to which it is entitled under its seven-year orphan drug exclusivity for Tourette's disorder. Even if the February 24, 2015 letter at issue in Count I constitutes final agency action, that action on its own did not produce the injury of which Otsuka complains (or any injury at all). Otsuka's alleged injury—approval of generic versions of Abilify®—has not yet occurred. That makes both of Otsuka's claims unripe.

On December 12, 2014, when FDA approved Otsuka's supplemental NDAs for Abilify®, it also approved the "agreed-upon labeling text" reflecting a new indication for Tourette's disorder. (FDA 000001-94). FDA's December 12, 2014 approval letter refers to the newly approved indication as treatment of "pediatric patients with Tourette's Disorder," (FDA 000001), instead of the language in the approved and agreed-upon labeling that was attached to the December 12, 2014 letter. On February 24, 2015, FDA sent Otsuka a supplemental approval letter, correcting what it considered inconsistencies between its original approval letter and the approved labeling. (FDA 000184-272). Otsuka asserts that the correction FDA made in its February 24, 2015 letter, which clarifies that Abilify® is indicated for

treatment of "Tourette's disorder," (FDA 000184), unlawfully expands the Tourette's Disorder indication sought by Otsuka.

Even assuming that FDA's February 24, 2015 letter qualifies as a final agency action with respect to Otsuka's supplemental NDAs, Otsuka's claim is not ripe because Otsuka has not demonstrated any injury that it has suffered as a result of that particular agency decision. *See also* Federal Defendants' Opposition to Motion to Compel the Administrative Record, at 10 n.7 (Apr. 6, 2015), ECF 47 ("Fed. Def.'s Admin. Record Opp.") ("Plaintiffs do not and cannot show in any concrete fashion how any of these 'actions,' including the original 'lawful' approval, injure them and, instead, offer only pure speculation that these actions may affect FDA's future decisions regarding generic approvals."). Nor could it. After all, FDA *approved* Otsuka's supplemental NDAs and granted its new orphan indication for Abilify® to treat patients with Tourette's disorder. In light of that approval, Otsuka is free to market Abilify® for the treatment of Tourette's disorder, and it is also entitled to seven years of orphan drug exclusivity with respect to that particular indication. While Otsuka asserts that FDA's approval should have been more limited, FDA's determination on that issue has not imposed any present legal burdens on Otsuka. The scope of the approval has not impacted Otsuka's labeling or its marketing rights.

Rather, Otsuka filed this suit because it asserts (based on a tortured reading of the FDCA) that FDA's approval (whether limited to pediatric patients or not) should have the collateral consequence of preventing FDA from approving *any* aripiprazole ANDA for seven years for *any indication*. For the reasons discussed below, Otsuka's statutory claim is meritless. But leaving the merits aside, the claim is not ripe, because FDA has not decided whether to grant final approval to any ANDA for aripiprazole. *See* Fed. Def.'s Admin. Record Opp., at 12 n.10 ("[A]s FDA has not approved any generics, it is entirely

speculative whether those documents will actually be part of any final administrative record . . . ."). Unless and until FDA grants final approval, FDA's February 24, 2015 letter decision clarifying the scope of Otsuka's new indication will have had no effect on Otsuka.

This Court should not disrupt the statutory scheme by adjudicating the lawfulness of an action the agency has not taken. Congress has mandated that FDA—not the courts—determine in the first instance whether ANDAs have met the requirements for approval and whether any blocking impediments exist. FDA must make its decisions and complete this quintessential agency function before judicial review is possible. *See, e.g.*, *AstraZeneca v. Apotex*, 669 F.3d at 1381 ("AstraZeneca's claims based on presumed future labeling amendments are unripe"); *AstraZeneca Pharms. LP v. FDA*, 850 F. Supp. 2d 230, 250 (D.D.C. 2012) ("This Court simply is not in a position to prophesy whether the FDA will ultimately decide to give final approval to a competing generic, when that hypothetical decision might happen, or what relationship the agency's proffered rationale for that hypothetical decision would have to the specific claim raised by AstraZeneca in this action.").

Indeed, until the "factual components" of Otsuka's claim are "fleshed out" and FDA takes a "concrete action" on a particular ANDA application, judicial review of FDA's authority would be hopelessly abstract. *Ohio Forestry Ass'n Inc. v. Sierra Club*, 523 U.S. 726, 737 (1998) (internal quotation marks omitted). The decision FDA must make is not based on an application of law (however clear) devoid of case-specific facts. When FDA approves ANDAs that carve out one or more indications that appear in the RLD, it analyzes the precise labeling that a generic applicant proposes (labeling that may differ between ANDAs), and it determines whether that proposed labeling remains as safe and effective for the remaining uses as the RLD's labeling. *See* 21 C.F.R. § 314.127(a)(7) (providing that an ANDA will be denied where differences in labeling make it "less safe or effective

than the listed drug for all remaining, non-protected conditions of use"). To be sure, the Intervenor-Defendants fully believe they have met all the requirements for approval, and they are actively working to secure that approval by April 20, 2015. FDA submits, however, that it has not yet reached a judgment whether to approve any ANDAs for aripiprazole. And the administrative record contains no evidence of any such decision that could provide a basis for this Court's review of whether particular labeling proposals are lawful. In short, the claim is not ripe.

For essentially the same reasons, Count II of Otsuka's Complaint is also nonjusticiable. As with Count I, Otsuka's asserted injury is premised on the notion that FDA *might* grant final approval to generic applicants for aripiprazole, which Otsuka asserts would be unlawful in light of the FDCA's labeling requirements and the aspects of Otsuka's Abilify® label that Otsuka says pertain to pediatric use. But according to FDA, the agency has not yet made any decision with respect to any ANDA or its proposed labeling. Final agency action "mark[s] the consummation of the agency's decision-making process" and is the action "by which rights or obligations have been determined, or from which legal consequences will flow." *Bennett v. Spear*, 520 U.S. 154, 178 (1997) (internal quotations omitted). Until FDA has made an actual decision, there is no agency action for this Court to review.

In addition, the claim is not ripe. Judicial review with respect to the abstract question Otsuka presents would unduly interfere with the administrative process where FDA has not yet decided whether to grant approval of any of the aripiprazole ANDAs, much less explained a decision in the context of specific label proposals. *See Ohio Forestry Ass'n Inc.*, 523 U.S. at 736 ("This type of review threatens the kind of abstract disagreements over administrative policies that the ripeness doctrine seeks to avoid." (internal quotation marks and citation omitted)). And Otsuka has not suffered any hardship based on a decision FDA has not made that could justify immediate review. *See AstraZeneca v. FDA*, 850 F. Supp.

2d at 243 (brand manufacturer's claims were not ripe when they sought judicial review before ANDA approval despite several tentative approvals).

B. In the Alternative, The Court Must Deny Otsuka's Motion for Summary Judgment Because FDA Has Clear Authority To Permit ANDAs To Carve Out Abilify®'s Indication For Tourette's Disorder

Counts I and II ultimately collapse on each other because, regardless of any conclusion this Court makes on the validity or import of FDA's corrected February 24, 2015 approval letter for Abilify®, the ultimate relief Otsuka seeks is not merely a pronouncement on the lawfulness of that FDA decision. As discussed below, the relief Otsuka seeks still depends on its argument (in Count II) that FDA has no authority to approve ANDAs for *seven years* absent consent from Otsuka, even ANDAs with a carve-out. Thus, the ultimate question Otsuka's motion poses is whether FDA has authority to approve ANDAs that carve out the orphan indication for Tourette's disorder (whether or not the indication includes any reference to a pediatric population). FDA's authority to do so is clear. Otsuka's motion rests on a myopic view of FDA's authority to approve ANDAs that carve out portions of brand-name drug labeling—a view that is belied by the FDCA as a whole, the Orphan Drug Act, agency regulations entitled to deference, and clear Fourth Circuit authority. Otsuka's claims must fail because FDA has authority to approve ANDAs carving out a Tourette's disorder indication, and that authority is not abrogated or constrained by Section 505A(*o*). While these textual bases are themselves clear and unambiguous, it also merits noting that Otsuka's proposal would lead to absurd results that could lead to significant and unwarranted delays in generic drug entry that are antithetical to the pro-consumer, pro-competition goals of the laws at issue.

1. The APA Standard

Under the APA, FDA's administrative decisions may be disturbed only if "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). The scope of review in an APA action is very limited: "[t]he Court's role is only to assess whether the agency's decision is 'within the bounds of reasoned decision-making.'" *Audubon Naturalist Soc'y of the Cent. Atl. States Inc. v. United States*, 524 F. Supp. 2d 642, 659 (D. Md. 2007) (internal citations omitted). The review of FDA's administrative decisions begins with a presumption of validity. *See Clement v. LaHood*, No. 09-01056-CMH, 2010 WL 1779701, at *4 (E.D. Va. Apr. 30, 2010) (citing *Fla. Power & Light Co. v. Lorion*, 470 U.S. 729, 743 (1985)). "[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." *Kaiser Found. Hosps. v. Sebelius*, 828 F. Supp. 2d 193, 198 (D.D.C. 2011) (internal quotations and citations omitted); *accord Hospira*, 2014 WL 4406901, at *9-*10. The court must determine whether the agency considered the relevant factors, and whether it made a clear error of judgment. *See Citizens to Pres. Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971). In so doing, the court may not "substitute its judgment for that of the agency," *id.*, and must uphold any agency action that is "rational, based on consideration of the relevant factors and within the scope of the authority delegated to the agency by the statute." *Motor Vehicle Mfrs. Ass'n, Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 42 (1983).

2. FDA Has Broad Authority To Approve ANDAs That Carve Out Portions of RLD Labeling, Including Labeling Protected By Orphan Drug Exclusivity

Otsuka's motion puts a laser focus on one provision of the FDCA that it asserts precludes FDA from approving ANDAs that carve out labeling protected by orphan drug exclusivity when that labeling

includes pediatric information. Otsuka's interpretation is so focused on a specific phrase in section 505A(*o*) that it fails to account for (or even quote) the entire provision, much less the FDCA as a whole. Reading section 505A(*o*) in its entirety shows that it merely constrains FDA's authority to *disapprove* an ANDA—not its authority to *approve* an ANDA (the reading Otsuka seeks). And pulling back from Otsuka's tunneled view shows how contrary to law its preferred reading is. FDA has broad authority under the FDCA generally, and under the Orphan Drug Act specifically, to approve ANDAs that carve out many aspects of RLD labeling, including orphan drug information and pediatric information. That authority has been upheld as clear and unambiguous by the courts, including the Fourth Circuit; FDA has promulgated rules clarifying that authority that are entitled to deference; and FDA has consistently exercised that authority to approve ANDAs that carve out orphan drug exclusivities—*including those with pediatric indications*. These types of "carve outs" implement the legislative judgment that a drug sponsor will not be permitted to use an exclusivity covering just one use of its product to delay the entry of lower-priced generics when there are other approved uses not covered by any exclusivity.

Otsuka seeks to turn all that on its head, and to use a new exclusivity covering just one of several approved uses for its product to block generic entry for *all* uses—even those indisputably not covered by any patent or regulatory exclusivity—for seven more years. Otsuka ignores *all* the controlling statutory, regulatory, and judicial authority, not to mention direct agency precedent, and fundamentally misconceives the relevant issue and authority. FDA cannot delay approval of aripiprazole ANDAs under any of Otsuka's unfounded theories. The Court should reject Otsuka's anti-competitive efforts to impermissibly extend its monopoly and block lawful generic competition, and enter judgment for the Federal and Intervenor-Defendants.

a. The FDCA Gives FDA Clear Authority To Approve Labeling Carve-Outs That Are Safe and Effective

The FDCA provides FDA with broad, clear, and unambiguous authority to approve ANDAs that carve out labeling approved for a listed drug. FDA has promulgated rules setting forth how it exercises that authority, and it has consistently exercised that authority to allow carve-outs. FDA's authority to permit such carve-outs has been challenged in court and has been upheld by the Fourth Circuit, this Court, and the District of Columbia Circuit.

Although, in general, the labeling of a generic drug must be the same as the labeling for the brand-name drug, there are exceptions. Congress anticipated that generic and brand-name drug labeling would not be identical under all circumstances. One key exception to the general rule of "sameness" has always been that ANDA applicants are permitted to seek approval for less than all of the FDA-approved indications and uses for the RLD, and that in such situations the labeling for the ANDA product must differ correspondingly from the RLD's labeling. The House Report on the Hatch-Waxman Amendments made this point explicitly: it recognized that there would be instances where "the proposed labeling for the generic drug may not be exactly the same," including, for example, situations where "an ANDA [is] approved for less than all of the indications for which the listed drug has been approved." H.R. REP. NO. 98-857, pt. 1, at 2654-55 (1984)). It went on to explain that "***[t]he [ANDA] applicant need not seek approval for all of the indications for which the listed drug has been approved.*** For example, if the listed drug has been approved for hypertension and angina pectoris, and if the indication for hypertension is protected by patent, then the applicant could seek approval for only the angina pectoris indication." *Id*. at 2654 (emphasis added). In accordance with its drafters' clear intent, the Hatch-Waxman Amendments as enacted expressly authorize different labeling for brand and generic

drugs under these circumstances. An ANDA must contain "information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug . . . ***except for changes required . . . because the new drug and the listed drug are produced or distributed by different manufacturers.***" 21 U.S.C. § 355(j)(2)(A)(v) (emphasis added). The rest of the FDCA is in accord with this general rule of sameness *for a given use*, but there is no requirement that an ANDA applicant seek approval for *all* uses approved for the brand. For example, the FDCA lists certain situations in which FDA may not approve an ANDA. One of those situations is where "information submitted with the [ANDA] is insufficient to show that each of the proposed conditions of use have been previously approved for the listed drug." 21 U.S.C. § 355(j)(4)(B).[6] The FDCA thus does not require that an ANDA include every "condition of use" for which the RLD was approved, only that where an ANDA includes such a use, that use has been approved for the RLD.

FDA's regulations, promulgated pursuant to formal notice-and-comment rulemaking and entitled to judicial deference, make clear the agency's understanding that section 355(j)(2)(A)(v) permits labeling changes based on the "***omission of an indication or other aspect of labeling protected by patent or accorded exclusivity*** under [the FDCA]." 21 C.F.R. § 314.94(a)(8)(iv) (emphasis added); *accord* 21 C.F.R. § 314.127(a)(7). FDA will approve an ANDA that omits "aspects of the listed drug's labeling [that] are protected by patent, or by exclusivity [if] such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use." 21 C.F.R. § 314.127(a)(7).

[6] In addition, the FDCA requires applicants to notify FDA if their labeling does not contain certain "use[s]" approved for the RLD where those uses are protected by a method of use patent. *See* 21 U.S.C. § 355(j)(2)(A)(viii). This provision also makes clear that carve-outs are anticipated and permitted by the FDCA.

FDA has consistently applied its clear statutory and regulatory authority to approve generic drug products with labeling that omits indications protected by an RLD's statutory exclusivity (including orphan drug exclusivity). *See, e.g.*, Fusilev CP Ruling at 5 n.15 (allowing ANDAs to carve out an orphan drug protected indication and acknowledging FDA's authority to approve generic drug products with labeling that omits protected information); Ltr. from J. Woodcock to D. Bunce, at 6, Dkt. No. FDA-2013-P-1293 ("FDA has affirmed its authority to approve generic drug products with labeling that omits protected information on many occasions."); Ltr. from J. Woodcock to G. Trout, at 6, Dkt. No. FDA-2013-P-0247 (Aug. 1, 2013) (same); Ltr. from J. Woodcock to R. Trainor, at 9 n.14 (Dkt. No. FDA-2010-P-0545 (Feb. 24, 2011) ("On a number of occasions, we have affirmed our authority to approve ANDAs with carved out labeling.") (citing ribavirin, pregabalin, amifostine, dronabinol, and ramipril).[7]

The Fourth Circuit and other courts repeatedly have upheld FDA's broad carve-out authority under the FDCA. *See, e.g.*, *Sigma-Tau*, 288 F.3d at 148 n.3 (recognizing that FDA's authority to approve ANDAs that carved out an indication protected by orphan drug exclusivity did not violate the FDCA's "sameness" requirement); *AstraZeneca v. Apotex*, 669 F.3d at 1379 (noting that, "while generic applicants cannot obtain approval for uses beyond those already approved by the FDA, nothing in the Act requires that an ANDA must encompass *every* approved indication") (internal citations omitted); *Bristol-Myers Squibb Co.*, 91 F.3d 1493 (upholding FDA's authority to approve generic captopril

[7] *See also* Ltr. from J. Woodcock to S. Auten, at 8 n.11, Dkt. No. FDA-2010-P-0087 (Jul. 30, 2010) ("On a number of occasions, we have affirmed our authority to approve ANDAs with carved-out labeling.") (collecting decisions); Ltr. from J. Woodcock to R. R. Wilk-Orescan, at 9, Dkt. Nos. FDA-2008-P-0343 and FDA-2008-P-0411 (Dec. 4, 2008) (collecting decisions); Ltr. from J. Woodcock to E. Lengle, at 8-9, Dkt. No. FDA-2008-P-0069 (Jul. 28, 2008) ("[W]e again reaffirm our authority to approve generic drug products with carved-out labeling.") (collecting decisions); Ltr. from G. Buehler to ANDA for Metaxalone Tablets Applicant, at 1 (Mar. 1, 2004) ("The regulatory principles governing FDA's decision on this matter are well established. FDA has authority to approve ANDAs that omit labeling carried by the listed drug, when such labeling is protected by patent or exclusivity."); Ltr. from J. Woodcock to M. Macdonald, D. Jaskot, and J. Hurst, at 6, Dkt. Nos. 01P-0495/CP1, 02P-0191/CP1, & 02P-0252/CP1 (Jun. 11, 2002) ("FDA has the authority to approve ANDAs with labeling that is not identical to that of the listed drug.").

ANDAs for use in the treatment of hypertension during the brand's three-year exclusivity for the treatment of diabetic nephropathy). In *Bristol-Myers*, for example, the brand-name drug manufacturer argued that a three-year marketing exclusivity awarded to it under 21 U.S.C. § 355(j)(5)(D)(iv) for a new indication that was based on new studies should preclude generic competition for three years for *any* indication. The D.C. Circuit disagreed, reasoning that it would turn an exclusivity awarded for a "change approved in the supplement," *id.* § 355(j)(5)(D)(iv) (there, a new "indication"), into "three more years of protection against the approval of any ANDA based upon that pioneer drug, including one that lists only the original indication(s) of the pioneer"—"much broader protection from competition than [the statute] would otherwise confer." *Bristol-Myers Squibb Co.*, 91 F.3d at 1500. As the D.C. Circuit aptly observed, the FDCA:

> expresses the legislature's concern that the new generic be safe and effective for each indication that will appear on its label; ***whether the label for the new generic lists every indication approved for use of the pioneer is a matter of indifference***.

Bristol-Myers Squibb Co., 91 F.3d at 1500 (emphasis added). The court closely reviewed the text of the FDCA and held that under the only permissible reading of the statute, Congress has provided FDA with the authority to approve ANDAs that carve out aspects of labeling protected by marketing exclusivity. *Id.* at 1499.

That same reasoning applies here, particularly in view of FDA's unquestionable authority under the Orphan Drug Act to approve ANDAs for uses not covered by Otsuka's orphan drug exclusivity, as explained more fully below. FDA thus has broad authority under the FDCA, its own implementing regulations, and judicial precedent to approve aripiprazole ANDAs that are not labeled for this protected use—provided they are no less safe or effective than Abilify® for the conditions of use that remain in their labeling.

Tellingly, at no point does Otsuka argue that, by omitting labeling information relating to the Tourette's indication, generic aripiprazole products would be any less safe or effective than Abilify® for the treatment of *any* of the four remaining approved indications. Nor could it. Until December 12, 2014, Otsuka marketed Abilify® with labeling that did not contain any information related to this indication. Thus, the omission of the Tourette's indication (and related labeling information) will not, and could not, render generic aripiprazole products any less safe or effective than Abilify® for the treatment of the remaining indications.

b. The Orphan Drug Act Provides FDA Authority To Permit Labeling Carve-Outs

Otsuka claims that 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." (Compl. ¶ 68). Yet, in addition to the FDCA provisions cited above, the Orphan Drug Act itself provides FDA with the authority to approve ANDAs carving out that indication. Otsuka entirely ignores this authority, which alone is fatal to their argument.

Section 527 of the FDCA (21 U.S.C. § 360cc) provides that "for a drug designated under section 360bb of this title for a rare disease or condition, *the Secretary may not approve another application under section 355 of this title . . .* ***for such drug for such disease or condition*** *. . . until the expiration of seven years from the date of the approval of the approved application*[.]" 21 U.S.C. § 360cc(a)(2) (emphasis added). As the Fourth Circuit has held, "the plain language of the [Orphan Drug Act] is unambiguous." *Sigma-Tau Pharms.*, 288 F.3d at 144-45; *see also id.* at 148 ("The statute governing the outcome of this case is clear on its face."). "[Section 527(a)] simply provides that FDA 'may not approve' generics for a protected indication," and does not preclude ANDA approvals for other approved uses unprotected by an orphan drug exclusivity:

> By using the words "such drug for such disease or condition," Congress made clear its intention that [Section 527 of the FDCA] was to be disease-specific, not drug-specific. In other words, the statute as written protects uses, not drugs for any and all uses. Congress could have written [Section 527(a)] more broadly by prescribing that the FDA "may not approve another application ... for such drug," but it chose not to draft the statute in that way. Because Congress has spoken directly to the dispositive question before us, our inquiry is at an end.

Id. at 145. Likewise, FDA's implementing regulations similarly provide that "[o]rphan drug exclusive approval *protects only the approved indication or use of a designated drug*," in recognition of the statute's unambiguous limitations. 21 C.F.R. § 316.31(b) (emphasis added).

Otsuka does not even cite this authority, much less explain how the Orphan Drug Act can be read to permit carve-outs only if the orphan indication is directed to adults. That is because the Orphan Drug Act includes no such limitation; it does not differentiate between orphan drug information directed to pediatric patients and information directed to adults. As such, the statute applies with full force here, permitting FDA to approve ANDAs that carve out Abilify®'s orphan-protected indication.

Notably, the interpretation Otsuka seeks here would disturb the agency's consistent and considered decision making, effecting an about-face of FDA's prior decisions on orphan drug exclusivity carve-outs where that exclusivity incorporated pediatric information. FDA has on numerous occasions approved ANDA drug products during the NDA-holder's seven-year period of orphan drug exclusivity, *despite the fact that the orphan indication covered a pediatric use*. For example:

- **Viread® (tenofovir disoproxil fumarate) (NDA No. 21-356)**

    - Gilead Sciences obtained orphan drug exclusivity for Viread® for the treatment of HIV-1 infection in pediatric patients that expires on March 24, 2017. The six-month pediatric exclusivity extension for this orphan indication expires on September 24, 2017.[8]
    - FDA approved Teva's ANDA on March 18, 2015—nearly 2.5 years before Gilead's orphan drug exclusivity (as extended by pediatric exclusivity) expired.[9]

- **Colazal® (balsalazide disodium) (NDA No. 20-610)**

    - Salix Pharmaceuticals obtained orphan drug exclusivity for Colazal® for the treatment of mildly to moderately active ulcerative colitis in pediatric patients, which expired on December 20, 2013. The six-month pediatric exclusivity extension for this orphan indication expired on June 20, 2014.[10]
    - FDA approved ANDAs submitted by Roxane, Mylan, and Apotex on December 28, 2007—nearly 6.5 years before Salix's orphan drug exclusivity (as extended by pediatric exclusivity) expired.[11]

- **Rebetol® (ribavirin) (NDA No. 21-546)**

    - Schering Corporation received orphan drug exclusivity for Rebetol® for the treatment of chronic hepatitis C in pediatric patients, which expired on July 29, 2010. The six-month pediatric exclusivity extension for this orphan indication expired on Jan. 29, 2011.[12]
    - On April 6, 2004, FDA acknowledged that generic applicants were permitted to seek approval of the adult use of ribavirin even though the pediatric use was protected by orphan drug exclusivity. (Rebetol CP Ruling at 8 n.21 ("[C]ertain pediatric information is currently protected by orphan exclusivity but ANDA applicants for generic ribavirin capsule drug products may still receive approval for the adult use of ribavirin capsules in combination with Intron A.")).

This agency practice, which is grounded in the plain language of the statute and binding judicial precedent, is equally applicable here. FDA's interpretation of its authority under the Orphan Drug Act

[8] *See* Orange Book Searchable Database, at Patent and Exclusivity Search Results for NDA No. 21356.
[9] *See* Approval Letter for Teva Pharmaceuticals USA, ANDA No. 91-612 *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/091612Orig1s000ltr.pdf (last visited Apr. 7, 2015).
[10] *See* Orphan Drug Designations and Approval Database, at Orphan Drug Approval for Colazal, *available at* http://www.accessdata.fda.gov/scripts/opdlisting/oopd/ (last visited Apr. 7, 2015) (searchable by proprietary name) ("Orphan Drug Database").
[11] *See* Drugs@FDA, Approval Histories related to ANDA Nos. 77-806 (Roxane); 77-807 (Mylan) and 77-883 (Apotex Inc.), *available at* http://www.accessdata.fda.gov/scripts/cder/drugsatfda/ (last visited Apr. 7, 2015).
[12] *See* Orphan Drug Database, at Orphan Drug Approval for Rebetol.

and its implementing regulations is entitled to "'substantial deference.'" *See Sigma Tau*, 288 F.3d at 146 (citing *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994)). Otsuka fails even to acknowledge this consistent body of FDA decision-making, much less explain why FDA should treat its orphan drug exclusivity for Tourette's disorder any differently than the rest of the orphan drug exclusivities FDA has allowed ANDA applicants to carve out of their labeling.

Further, the end Otsuka seeks would destroy the balance Congress struck when it enacted the Orphan Drug Act and the Hatch-Waxman Amendments to the FDCA, a balance the Fourth Circuit weighed in *Sigma-Tau* and found to reinforce FDA's carve-out authority under the Orphan Drug Act. As the Fourth Circuit has explained:

> FDA . . . must balance the [Orphan Drug Act]'s incentive structure for the development of orphan drugs against the goals of the [Hatch-Waxman Amendments]. ***This statute seeks "to make available more low cost generic drugs"*** by establishing an abbreviated generic drug approval procedure[.]

Sigma-Tau, 288 F.3d at 148 (quoting H.R. REP. NO. 98-857, pt. 1, at 14 (1984) (emphasis added)). Here, much like in *Sigma-Tau*, "[r]ather than balancing the [Orphan Drug Act] and the Hatch–Waxman Amendments, [Otsuka] quite unapologetically puts all weight on the orphan drug development end of the scale, as if no tension exists between the two statutes that the FDA must negotiate." *Sigma-Tau*, 288 F.3d at 148.

Otsuka has already enjoyed well over 12 years of market exclusivity for its products. Abilify® accounted for over *$4.7 billion* of Otsuka's U.S. revenues in its fiscal year for 2013, and *$3.9 billion* in Otsuka's U.S. revenues during the nine months that contributed to its fiscal year for 2014.[13] While those revenues may represent the legitimate results Otsuka earned for the patent covering the

[13] Otsuka Holdings Co., Ltd., *Fact Book: Supplementary Materials, Financial Results FY 2014*, 6 (2014), *available at* http://www.otsuka.com/en/financial/pdf.php?financial=338.

aripiprazole compound and the associated pediatric exclusivity that expire this month, those exclusivity periods are now ending. A patent has a limited life. Any regulatory exclusivities Otsuka may have for this product do not cover all uses, and Otsuka should not be permitted to leverage the single exclusivity for Tourette's disorder into something it is not. Any further delay in generic entry will harm consumers who would otherwise be saving hundreds of millions of dollars each year that generics were on the market.[14] The statute simply will not bear such an anticompetitive and anti-consumer result. Otsuka's arguments "constitute[] nothing more than another attempt to obtain market exclusivity for any and all uses of its drug, thereby preventing generic competitors from entering the market for any indication." *Sigma-Tau*, 288 F.3d at 148 n.3.

In the end, the plain language of the Orphan Drug Act and FDCA control. FDA is entitled, indeed compelled, to approve generic aripiprazole ANDAs that do not seek approval for the protected Tourette's indication (regardless of how it is characterized) and that have otherwise met the statutory requirements for approval. Otsuka's Count II fails for this reason alone.

c. Section 505A(*o*) Enhances, Rather Than Diminishes, FDA's Authority To Permit Carve-Outs

Otsuka asks this Court to ignore the controlling statutory, regulatory, and administrative authority, and read a restriction into Section 505A(*o*) that would prohibit FDA from approving ANDAs that carve out labeling protected by orphan drug exclusivity when that exclusivity purportedly covers pediatric labeling. Otsuka's interpretation of Section 505A(*o*) is wrong. For its bold claim that it deserves seven more years without generic competition, Otsuka does not rely on the complete text of the statute, much less any FDA interpretation, regulation, or precedent, all of which reinforce, rather than

[14] Declaration of Philip B. Nelson, Ph.D. in support of Defendants' Opposition to Otsuka's Motion for a Temporary Restraining Order and Preliminary Injunction, at ¶ 93b (submitted in *Otsuka Pharm. Co., Ltd. v. Apotex Corp*., No. 14-08074-JBS (D.N.J. Mar. 27, 2015) (ECF 66-6)).

detract from FDA's authority to approve ANDAs that carve out information from the listed drug's labeling. Instead, Otsuka relies on an incomplete quotation from the statute and the canon of *expressio unius est exclusio alterius* (the expression of one thing is the exclusion of another). *Expressio unius* does not apply here and, in any event, would create absurd results. It would ascribe a meaning to this law that is directly contrary to the reason the law was passed, which was to ensure marketing exclusivities did not unnecessarily preclude generic drug approvals. It also would abrogate portions of the Orphan Drug Act, the FDCA, FDA's notice-and-comment rulemaking, and more than a decade of agency precedent broadly permitting carve-outs, including of pediatric information. Tellingly, Otsuka does not even cite, *much less grapple with*, this overwhelming authority against its stingy view of Section 505A(*o*). That law and administrative precedent controls and is fatal to their argument.

But even before this Court reaches the question of Section 505A(*o*)'s proper interpretation, it can, and should, reject Otsuka's argument for the simple reason that Section 505A does not apply here. As noted above, while FDA did award Otsuka pediatric exclusivity in 2007 in connection with Otsuka's pediatric studies in patients *with schizophrenia and bipolar I disorder*, that pediatric exclusivity has not attached to Otsuka's orphan drug exclusivity *for Tourette's disorder* according to FDA's Orange Book. This is consistent with the agency's position that pediatric exclusivity will not apply to later-filed supplements. For this reason, Section 505A has no relevance here, and Otsuka has provided no reason to conclude otherwise.

Nevertheless, even if the Court chooses to consider the proper interpretation of Section 505A(*o*) and how it might be applied to these facts, Otsuka's interpretation of Section 505A(*o*) is, quite simply, wrong. Section 505A(*o*) states an ANDA "shall not be considered ineligible for approval" when it carves-out pediatric information that "is protected by patent or by exclusivity under clause (iii) or (iv) of

section 355(j)(5)(F)." 21 U.S.C. § 355a(*o*). Otsuka does not explain (or even quote) the operative language—"shall not be considered ineligible for approval"—in its motion for summary judgment. But that language is fatal to Otsuka's position. Instead of restricting FDA's ability to *approve* an ANDA (the interpretation Otsuka urges), Section 505A(*o*) restricts when FDA may *disapprove* an ANDA. And Congress left no room for negative inferences, because elsewhere in the FDCA it provided explicitly that FDA "**shall** approve an [ANDA] **unless** . . ." approval is expressly barred by one of a limited set of grounds for disapproval. 21 U.S.C. § 355(j)(4) (emphases added). A basis for disapproving an ANDA must be listed in the statute, or it is not valid. In light of that baseline command to FDA, Otsuka cannot turn a provision limiting FDA's *disapproval* authority into a provision limiting its *approval* authority, particularly where that provision left untouched the FDCA's express grant of authority to make exceptions to the rule of sameness and allow carve-outs when approving ANDAs.

Likewise, at no point does Section 505A(*o*) say that ANDAs that omit pediatric information protected by orphan drug exclusivity "*shall*" be ineligible for approval—leaving the door open for FDA to approve generics by virtue of its authority under both the Orphan Drug Act and the FDCA, as discussed more fully above. *See Clinchfield Coal Co. v. Fed. Mine Safety & Health Review Comm'n*, 895 F.2d 773, 779 (D.C. Cir. 1990) ("The drafter (here Congress) may simply not have been focusing on the point in the second context; and, where an agency is empowered to administer the statute, Congress may have meant that in the second context the choice should be up to the agency.").

The statutory canon of interpretation of *expressio unius est exclusio alterius* does not save Otsuka's claim. At the same time Otsuka ignores important provisions of the statute, it urges this Court to write a significant limitation into it, relying on a canon of interpretation counseling that an item on a list impliedly excludes other items from belonging on that list. This canon, however, is "***only a guide***,

whose fallibility can be shown by contrary indications that adopting a particular rule or statute was probably not meant to signal any exclusion of its common relatives." *United States v. Vonn*, 535 U.S. 55, 65 (2002).

The Supreme Court has "long held that the *expressio unius* canon does not apply 'unless it is fair to suppose that Congress considered the unnamed possibility and meant to say no to it,' and that the canon can be overcome by 'contrary indications that adopting a particular rule or statute was probably not meant to signal any exclusion.'" *Marx v. Gen. Revenue Corp.*, 133 S. Ct. 1166, 1175 (2013) (internal citations omitted); *see also Barnhart v. Peabody Coal Co.*, 537 U.S. 149, 168 (2003) ("We do not read the enumeration of one case to exclude another unless it is fair to suppose that Congress considered the unnamed possibility and meant to say no to it."); *Chevron USA, Inc. v. Echazabal*, 536 U.S. 73, 81 (2002) (*expressio unius* is not absolutely applied, there must be a "sensible inference that the term left out must have been meant to be excluded"). Otsuka cites no evidence—*none*—that Congress even contemplated orphan drug exclusivity at the time Section 505A(*o*) was proposed and enacted, let alone that Congress expressly considered orphan drug exclusivity and meant to exclude it. Without this, Otsuka's argument fails. *Barnhart*, 537 U.S. at 170 ("The enunciation of two exceptions does not imply an exclusion of a third unless there is reason to think the third was at least considered.").

In fact, the interpretation Otsuka urges would produce a result that could not be further from Congress's intent. Congress added Section 505A(*o*) as part of the Best Pharmaceuticals for Children Act ("BPCA") in January 2002, and intended it to constrain FDA's authority to delay final approval of an ANDA on the basis that the RLD included pediatric information that the ANDA had carved out. Under the regulations existing at that time, FDA deemed any drug product that did not include pediatric labeling information (when available) as misbranded, thereby preventing the distribution of these

products in interstate commerce. 147 CONG. REC. H10209 (referencing 21 C.F.R. § 201.57(f)(9)(ii)). By 2002, certain companies, such as Bristol-Myers Squibb ("BMS"), had exploited this "loophole" as a means to block generic competition. Indeed, citing BMS as an example, Congress noted that:

> [BMS] . . . succeeded in convincing FDA that it was entitled to [an] additional 3½ years of exclusivity for the same pediatric study of its drug, Glucophage, that . . . they had submitted to acquire the initial six months of monopoly marketing. Three of those years of alleged exclusivity were based on the company's claim that a study of some 68 pediatric patients was sufficient to merit a new indication of use under Section 505(j) of the Act. ***Normally such claims only result in differential labeling between a product that was the subject of a new trial and other therapeutically equivalent products on the market.*** However, [BMS] . . . apparently succeeded in convincing at least some decision makers in FDA that the differential labeling regarding pediatric use may constitute a safety risk if not found on equivalent generic products. Because FDA has granted three-year exclusivity to the pediatric label of Glucophage, [BMS] has argued that no generic may be marketed during the pendency of its labeling exclusivity.

147 CONG. REC. H8105 (daily ed. Nov. 13, 2001) (emphasis added); *accord* 147 CONG. REC. H10210.

Frustrated at the prospect that such tactics would result in profound and adverse consequences to consumers, Congress added Section 505A(*o*) "to revise the Hatch-Waxman Act to override the [existing] requirement that generic versions of pioneer drugs bear labeling for pediatric indications." 147 CONG. REC. H10210 (referring to the proposal as the "Anti-Glucophage Bill"). Congress expressly noted that the misuse of pediatric information to garner three-year exclusivity for a certain indication and wholly block generic competition for *all* approved indications is "a fundamental abuse of the system and were the FDA . . . to accept the claim, consumers would be harmed." 147 CONG. REC. H8105. Congress also noted that the provision that eventually became Section 505A(*o*) "closes this potential loophole by instructing the FDA to approve generic drugs without proprietary pediatric labeling awarded to products sponsors under the Hatch-Waxman Act." *Id.*; 147 CONG. REC. H10212 (same); *see*

also id. at H10210 ("Importantly the bill we will vote on today . . . closes the 'Glucophage loophole' which allowed one company to get an additional 3 years of marketing exclusivity. This bill ensures that no company will be able to take advantage of the exclusivity granted by this very important legislation.").

Given this clear and unambiguous evidence of Congressional intent, it defies logic and common sense to suggest, as Otsuka does here, that Section 505A(*o*) can be interpreted to block generic competition for all uses for an additional **seven** years, when Congress enacted the provision to prevent exactly this type of unwarranted extension of exclusivity. Indeed, Congress thought that an additional **three** years was too long—Otsuka unabashedly wants **seven**. This Court should not countenance such an absurd result.

This Court should reject Otsuka's interpretation, especially when (1) neither the plain language of the statute nor its legislative history provides any evidence that Congress intended Section 505A(*o*) to prohibit generics from carving out orphan-protected pediatric information from their labeling, and (2) such an interpretation leads to such absurd and profoundly anticompetitive results.

V. CONCLUSION

For the foregoing reasons, Intervenor-Defendants Apotex and Teva respectfully request that the Court grant their motion to dismiss and deny Otsuka's motion for summary judgment.

Dated: April 7, 2015

Respectfully submitted,

APOTEX INC. and
APOTEX CORPORATION

By: /s/

Jerrold A. Thrope (Bar No. 01376)
GORDON FEINBLATT LLC
233 East Redwood Street
Baltimore, Maryland 21202
Telephone: (410) 576-4295
Facsimile: (410) 576-4269
jthrope@gfrlaw.com

William A. Rakoczy (*pro hac vice*)
Lara E. FitzSimmons (*pro hac vice*)
Joseph T. Jaros (*pro hac vice*)
Trang D. Hoang (*pro hac vice*)
RAKOCZY MOLINO MAZZOCHI SIWIK LLP
6 West Hubbard Street, Suite 500
Chicago, IL 60654
Telephone: (312) 222-6301
Facsimile: (312) 222-6321
wrakoczy@rmmslegal.com

Attorneys for Intervenor-Defendants Apotex Inc. and Apotex Corporation

TEVA PHARMACEUTICALS USA, INC.

By: /s/

Brian T. Burgess (D. Md. Bar No. 19251)
William M. Jay (*pro hac vice*)
GOODWIN PROCTER LLP
901 New York Avenue NW
Washington, DC 20001
Tel.: (202) 346-4000
Fax.: (202) 346-4444

Christopher T. Holding (*pro hac vice*)
Sarah K. Frederick (*pro hac vice*)
GOODWIN PROCTER LLP
Exchange Place
53 State Street
Boston, MA 02109
Tel.: (617) 570-1000
Fax.: (617) 523-1232

Attorneys for Intervenor-Defendant Teva Pharmaceuticals USA, Inc.