IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

Otsuka Pharmaceutical Co., Ltd., et al.	*	
Plaintiff,	*	
v.		Case No. 15-cv-0852-GJH
	*	
Sylvia Mathews Burwell, et al.	*	
Defendants.		

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

PLAINTIFFS' MOTION FOR TEMPORARY RESTRAINING ORDER AND/OR PRELIMINARY INJUNCTION AND REQUEST FOR HEARING

Pursuant to Fed. R. Civ. P. 65, Plaintiffs Otsuka Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Development & Commercialization, Inc., and Otsuka America Pharmaceutical, Inc. (collectively, "Otsuka") hereby move for a temporary restraining order and/or preliminary injunction. Otsuka seeks a temporary restraining order and/or preliminary injunction prohibiting the defendant U.S. Food and Drug Administration ("FDA") from granting approvals for any generic versions of Otsuka's prescription brand drug aripiprazole, which Otsuka markets under the name Abilify®, absent a license from Otsuka, and ordering intervenor-defendant generic pharmaceutical companies not to distribute and/or to cease distribution of their generic versions of Abilify pending the Court's final decision. Absent temporary and/or preliminary injunctive relief, Otsuka will suffer irreparable injury starting immediately upon FDA's approval of one or more generic versions of Abilify. FDA's approval action is anticipated on or shortly after April 20, 2015. In support of Otsuka's motion for a temporary restraining order and/or preliminary injunction, Otsuka relies upon its amended complaint, the memorandum and declarations filed with and in support of the motion, and the administrative record. A proposed Order is filed herewith.

Respectfully submitted,

Dated: April 15, 2015

/s/ Ralph S. Tyler

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MEMORANDUM IN SUPPORT OF PLAINTIFFS' MOTION FOR A TEMPORARY RESTRAINING ORDER AND/OR A PRELIMINARY INJUNCTION

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Introduction

Plaintiffs Otsuka Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Development & Commercialization, Inc., and Otsuka America Pharmaceutical, Inc. (collectively, "Otsuka") seek a temporary restraining order and/or preliminary injunction to enjoin the defendant U.S. Food and Drug Administration ("FDA") from granting approvals of generic versions of Otsuka's prescription brand drug aripiprazole, which Otsuka markets under the name Abilify®, except where the generic holds a license from Otsuka, and ordering intervenor-defendant generic pharmaceuticals not to distribute and/or to cease distribution of generic versions of Abilify pending the hearing and determination of this case on the merits. For the reasons set forth in this memorandum, Otsuka's motion should be granted because (1) Otsuka is "likely to succeed on the merits" of the claim set forth in its complaint; (2) Otsuka will suffer irreparable harm in the absence of injunctive relief; (3) "the balance of hardships tips in [Otsuka's] favor"; and (4) granting the requested injunctive relief is in the public interest. *See Pashby v. Delia*, 709 F.3d 307, 320-21 (4th Cir. 2013).

The undisputed record of this case confirms that FDA has engaged in an extraordinary series of twists and turns involving a highly irregular drug approval, all in furtherance of the agency's agenda to approve generic versions of Abilify while denying Otsuka its exclusivity rights. FDA first approved Abilify for the treatment of Tourette's Disorder in pediatric patients; however, after Otsuka brought to FDA's attention the exclusivity implications of that approval, FDA "corrected" and broadened its approval, approving Abilify for use in the general population (notwithstanding the absence of supporting clinical trial data). After Otsuka filed its original complaint and moved for summary judgment, FDA was ordered to file the administrative record. FDA resisted and filed a scant, incomplete record. Otsuka moved for an Order compelling FDA to supplement FDA's grossly truncated so-called "administrative record to date." The Court

ordered FDA to do so. Then, with the Court-compelled record filing deadline fast approaching and the hearing on Otsuka's motion for summary judgment days away, FDA thought better of its "corrected" broadened approval and abruptly reverted back to its original and properly limited approval to pediatric patients only. The FDA action challenged here of denying Otsuka's exclusivity rights and approving generic versions of Abilify in the face of Otsuka's exclusivity rights is no more credible or correct than was FDA's broadened (and then retracted) approval.

This case involves the interplay between statutory exclusivities, particularly orphan drug exclusivity awarded to companies that invest time and money in developing drugs for rare diseases and disorders, and statutory and regulatory requirements that require labels of generic drugs to contain the same information as their brand counterpart (the "same labeling" requirement) and requirements mandating that pediatric information be included on drug labels. In Section 505A(o) of the federal Food, Drug and Cosmetic Act ("FDCA"), Congress directly answered the question of when generics can omit from their labels pediatric labeling included in the brand's label, in contravention of the otherwise generally controlling same labeling rule. Balancing the interests at stake, Congress decided that generics could omit pediatric labeling protected by a patent or three-year new clinical study exclusivity. Congress, the body charged with making the policy choices, did not allow, however, for the omission of pediatric orphan drug exclusivity. Congress's choices are not to be undone because one party (FDA) or another (a generic) is dissatisfied with the outcome that Congress determined.

At the moment of generic launch, on or about April 20, 2015, Otsuka will be irreparably harmed. This harm can be avoided only if the Court grants Otsuka's request for temporary or preliminary injunctive relief pending the final resolution of this case on the merits. This case cries out for emergency injunctive relief. Without it, Otsuka will be without a full and adequate remedy

even if it prevails on the merits of this action. Abilify is Otsuka's only blockbuster drug, and the impact on Otsuka of the loss of exclusivity would be enormous and damaging. *See* Ex. A (Declaration of Aaron Deves). Those injuries would be irreparable because Otsuka will have no monetary recovery remedy against either FDA or any generic drug manufacturer and they are exceedingly difficult, if not impossible, to quantify with any accuracy and inadequate.

Factual Background

A. Otsuka Has Been Approved For A Pediatric Tourette's Disorder Indication That Is Protected By Orphan Drug Exclusivity.

Otsuka is the New Drug Application ("NDA") holder for the drug aripiprazole, which it markets under the brand name Abilify. Ex. B ¶ 4.[1] FDA first approved Abilify on November 15, 2002, then for schizophrenia, and FDA has since approved Abilify for other indications. *Id.* ¶ 7. After acquiring orphan drug designation in 2006, Otsuka conducted clinical trials to demonstrate the safety and efficacy of Abilify to treat Tourette's Disorder in the pediatric population. *Id.* ¶¶ 11, 14-15, 24. The 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[2] score of the Yale Global Tic Severity Scale. *Id.* ¶ 15. Following the conclusion of these trials, Otsuka submitted a sNDA to FDA that sought approval for the new indication of the treatment of Tourette's Disorder in pediatric patients. *Id.* ¶ 16.

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."

[1] Exhibit B is a declaration submitted from Robert McQuade. Otsuka relies on the declaration, as well as the existing administrative record in support of this motion.
[2] A tic is a sudden, rapid, recurrent, nonrhythmic, stereotypic motor movement or vocalization. Ex. B ¶ 15.

AR 1. 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." Ex. B ¶ 21.

The narrow pediatric indication is made clear by Otsuka's label. The "Indications and Usage" section of the Highlights of Prescribing Information in the proposed, and agreed-upon, labeling includes a reference to the supporting clinical studies (14.5), demonstrating that the indication is limited to treatment in the pediatric population:

----------INDICATIONS AND USAGE----------

ABILIFY is an atypical antipsychotic. The oral formulations are indicated for:

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

AR 5 (highlight added).

Likewise, the "Indications and Usage" section of the Full Prescribing Information indicates that the indication should be limited to treatment in the pediatric population, as it includes a reference to the clinical trials:

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)]*

Id. at 7 (highlight added).

The approved label is replete with extensive references to pediatric use. In the Highlights of Prescribing Information portion of the label, the "Dosage and Administration" section for Tourette's Disorder lists dosages for 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.* at 5. The Full Prescribing Information portion also includes substantial pediatric information. Section 14.5, the clinical studies portion, is titled "Tourette's Disorder" and its subtitle is "Pediatric Patients." *Id.* at 79-81. 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.* at 10. The section describes the recommended dosage ranges for pediatric patients, not adult patients. *Id.*

The "Use in Specific Populations" section includes a "Pediatric Use" section that includes a Tourette's Disorder section (§ 8.4). *Id.* at 55. There, the label explains, "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.* at 21-22, 25, 27, 46-47.

B. FDA's Flip Flops On The Scope Of Abilify's Tourette's Disorder Indication.

FDA has flip flopped on the scope of the approved indication for the use of Abilify in the treatment in Tourette's Disorder, finally coming to rest where it began.

1. **December 12, 2014: Pediatric Indication**

FDA's original position on the scope of Abilify's Tourette's indication was stated in its

December 12, 2014 letter to Otsuka. There, FDA notified 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." AR 1. 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." Ex. B ¶ 21.

In January 2014, counsel for Otsuka wrote to FDA's Chief Counsel to request a meeting "to discuss an issue which arises from FDA's recent approval of Otsuka's supplemental New Drug Application for use of Abilify in the treatment of Tourette's disorder in pediatric patients." AR 286. Counsel set forth the company's position that FDA's approval precluded FDA from approving an ANDA for a generic version of Abilify for any of its FDA-approved indications pending the expiration of Otsuka's seven-year period of orphan drug market exclusivity for the new indication under Section 505A(o) of the FDCA. *Id.* at 286-88.

2. **February 24, 2015 And March 11: General Population Indication**

Not long after receiving that letter, FDA adopted a dramatically different position on the scope of Abilify's Tourette's indication. On February 24, 2015, FDA sent Otsuka a "corrected" approval letter, and without explanation or elaboration, FDA advised that its earlier December 12, 2014, approval letter "contained an error in the 'indications' section," an "error" FDA purported to correct unilaterally by broadening the approved indication from treatment "in pediatric patients with Tourette's Disorder" to treatment of "patients with Tourette's Disorder." AR 184-272. FDA's February 24 elimination of the "pediatric qualifier" in the approval was not preceded by any new clinical trial data (the only data was still from trials in pediatric patients), nor was it accompanied by any changes to the FDA-approved label. FDA also 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***." Ex. B ¶ 23, Att. F.

On March 9, 2015, Otsuka emailed FDA posing a direct question: "[D]oes [FDA] consider the supplemental approval to be for the treatment of Tourette's disorder in the general population, or is the approval limited to the pediatric population in which Otsuka demonstrated safety and efficacy?" AR 275. 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.* at 274.

On March 18, 2015, Otsuka asked FDA to rescind the February 24 letter containing the broadened elucidation of the approval. *Id.* Otsuka pointed out, "As the agency is well aware, the clinical trial data submitted in support of the request for a new indication for Abilify for the treatment of Tourette's Disorder was data demonstrating the safety and effectiveness of Abilify for the treatment of Tourette's Disorder in pediatric patients only; no data was submitted demonstrating safety and effectiveness in the non-pediatric adult population of patients with Tourette's Disorder." *Id.* Otsuka also submitted the declaration of Dr. Floyd Sallee, a leader in treating Tourette's, which makes clear that the disorder "presents in fundamentally different ways" in adults and pediatric patients and there is different dosing for the two populations. *Id.* FDA did not respond.

Otsuka had no choice but to file this lawsuit and did so on March 24. Otsuka's original complaint challenged the lawfulness of FDA's drug approval decision, a final agency action which, as Otsuka asserted, unlawfully approved Abilify for the treatment of Tourette's Disorder in the general population when the drug had only been shown to be safe and effective in pediatric patients. Count two of that complaint sought a declaratory judgment, requesting that the Court

declare that, under the broadened approval, assuming without conceding its validity, FDA was nevertheless precluded as a matter of law from approving generic versions of Abilify.

3. **March 27: General Population Indication**

After Otsuka filed this litigation, FDA sought to embroider the record. On March 27, FDA sent a letter to Otsuka that, according to FDA's Court filing, was intended "to clear up apparent confusion." ECF No. 54, at 10. There was, however, no "confusion." Prior to February 24, FDA had not communicated (what turned out to be its short-lived view) that FDA had ever considered its approval for the new indication for Tourette's to be for the general population. Rather, the December 12 letter informed Otsuka, consistent with its clinical trial data and its FDA approved labeling (with, for example, the indications section referencing the pediatric clinical trials), that Otsuka's approval was for a pediatric indication for Tourette's. FDA's March 27 letter claimed that, supposedly, "the corrected approval did not broaden the indication or the scope of the underlying approval," AR 284, a claim plainly impossible to square with the text of the agency's December 12 letter, or its February 24 letter, or the FDA-approved label. Nevertheless, FDA's March 27 letter stated definitively, albeit falsely, that there is no limitation of use based on age and that "[t]he indication was . . . unchanged when the approval letter was corrected." *Id.* at 283-84.

4. **April 10: Pediatric Indication**

FDA rather quickly abandoned the definitive position it took in its March 27 letter. As this Court observed, in seeking to avoid filing the complete administrative record, FDA "misconstru[ed] the obvious thrust of Otsuka's complaint" and "excluded documents, either purposely or inadvertently, that were plainly relevant to its December 12, 2014 approval of Otsuka's sNDA." ECF No. 57, at 6. The Court compelled FDA to file the complete record by 9:00 AM on April 13. *Id.* at 7. Late in the day on Friday, April 10, as the supplemental record

filing deadline loomed and as the hearing on Otsuka's motion for summary judgment approached, FDA flip-flopped (again). On April 10, FDA concluded that "the approval of Abilify for Tourette's Disorder is only for the pediatric population." Ex. C. FDA's approval decision had come full circle.

Following FDA's latest and presumably final flip-flop, Otsuka, with leave of the Court, filed an amended complaint and its present motion. Otsuka's amended complaint challenges FDA's denial of Otsuka's exclusivity rights and FDA's approval of generic versions of Abilify in violation of those exclusivity rights.

Statutory And Regulatory Background

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

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 through adequate and well-controlled clinical trials. 21 U.S.C. § 355(b)(1)(A); 21 C.F.R. § 314.50(d)(5); *see also* 21 U.S.C. § 355(d)(1), (2), (5); 21 C.F.R. § 314.126(a).

Abbreviated new drug applications ("ANDAs") for a generic version of a previously approved brand drug short circuit this costly and lengthy process for 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), 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, Congress has provided these brand applicants with certain periods of statutory exclusivity.

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 that Congress provided in the ODA is a seven-year period of market exclusivity for approved orphan drugs. 21 U.S.C. § 360cc(a). FDA's regulations provide that, when a drug receives orphan exclusivity, "no approval will be given to a subsequent sponsor of the same drug for the same use or indication for 7 years." 21 C.F.R. § 316.3(b)(12). Because Otsuka has received orphan drug exclusivity for its Tourette's Disorder indication, FDA cannot approve another drug for that pediatric indication for seven years. *See Sigma-Tau Pharms., Inc. v. Schwetz*, 288 F.3d 141, 145 (4th Cir. 2002).

B. Labeling Requirements

1. Pediatric Labeling Requirements

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).

FDA has promulgated regulations requiring certain pediatric information to be included on a prescription drug's label. In the "Indications and Usage" section of the Full Prescribing Information portion, for example, "[i]f 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. 21 C.F.R. § 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).

Likewise, the "Dosage and Administration" section "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 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 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), (j)(4)(G); 21 C.F.R. § 314.94(a)(8)(iv). However, 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. Section 505A(o) delineates express exceptions to the same labeling requirement to allow pediatric labeling to be omitted from generic labeling when such information is protected by patent or three-year exclusivity for conducting new clinical studies under Section 505(j)(5)(F)(iii) or (iv).[3] Section 505A(o) provides 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).

[3] 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. Standard For Preliminary Injunctive Relief

Parties seeking preliminary injunctions must demonstrate that (1) "they are likely to succeed on the merits"; (2) "they are likely to suffer irreparable harm"; (3) "the balance of hardships tips in their favor"; and (4) "the injunction is in the public interest." *Pashby*, 709 F.3d at 320. Otsuka satisfies all four factors.

II. Otsuka Is Entitled To Temporary And/Or Preliminary Injunctive Relief.

A. Otsuka Is Likely To Succeed On The Merits.

Otsuka is likely to prevail on the merits of its claim that FDA's approval of generic versions of Abilify is unlawful. Congress has spoken to the precise issue of when FDA can approve a generic that omits pediatric labeling, and pediatric labeling protected by orphan exclusivity (here, treatment of Tourette's Disorder in pediatric patients) is not among the categories of permissibly omitted pediatric labeling. That is why FDA's generic approval actions are unlawful.

The general rule is that a generic drug must contain the same information in its label as the label of the respective brand-name predicate drug. *See* 21 U.S.C. § 355(j)(2)(A)(v), (j)(4)(G); 21 C.F.R. § 314.94(a)(8)(iv). FDA's regulations require pediatric indications and other information to be included in prescription drug labeling. *See* 21 C.F.R. § 201.57(c)(2)(i)(B); (c)(3)(C); (c)(9)(iv)(B)-(C). As an exception to these general rules, Section 505A(o) addresses when and what pediatric indications and information may be omitted from generic labeling.

The "plain meaning" of Section 505A(o), as clarified by the statute's language, the context, and the legislative history, makes clear that FDA cannot approve a generic drug that omits a pediatric indication or any aspect of labeling pertaining to pediatric use that is protected by orphan drug exclusivity. *See King v. Burwell*, 759 F.3d 358, 367-72 (4th Cir. 2014) (considering these factors under *Chevron* step one), *cert.granted* 135 S. Ct. 475 (2014). But even if the plain meaning

were ambiguous, which it is not, FDA's interpretation is not a permissible construction of the statute. *Id.* 367, 372-73.

1. **The Text of Section 505A(o)**

Section 505A(o) provides, "A drug for which an application has been submitted or approved under section 355(j) of this title shall not be considered ineligible for approval under that section or misbranded under section 352 of this title on the basis that the labeling of the drug omits a pediatric indication or any other aspect of labeling pertaining to pediatric use when the omitted indication or other aspect is protected by patent or by three-year exclusivity under [Section 505(j)(5)(F)(iii) or (iv)]." 21 U.S.C. § 355a(o)(1). The statute, by its plain terms, directs FDA's approval authority by limiting the agency's ability to disapprove a generic drug based on specific pediatric labeling omissions. The only labeling omissions the statute allows are those expressly delineated: pediatric indications or information pertaining to pediatric use protected by patent or by three-year exclusivity under § 355(j)(5)(F).

By its terms, the statute does not allow the omission of pediatric labeling protected by orphan drug exclusivity, which is granted pursuant to Section 527 of the FDCA (*see* 21 U.S.C. § 360cc). Reading the statute to allow the omission of pediatric labeling protected by orphan exclusivity requires adding text to the statute that Congress adopted, an impermissible approach to statutory construction. *See 62 Cases, More or Less, Each Containing Six Jars of Jam v. United States*, 340 U.S. 593, 596 (1951) ("[O]ur problem is to construe what Congress has written. After all, Congress expresses its purpose by words. It is for us to ascertain – neither to add nor to subtract, neither to delete nor to distort."); *Ayes v. U.S. Dep't of Veterans Affairs*, 473 F.3d 104, 108-11 (4th Cir. 2006) ("We must presume that 'Congress says in a statute what it means and means in a statute what it says . . . ." (internal quotation marks omitted)).

The familiar principle of statutory construction *expressio unius est exclusio alterius* (the expression of one thing is the exclusion of another) is helpful here, as well. *See Leatherman v. Tarrant County Narcotics Intelligence & Coordination Unit*, 507 U.S. 163, 168 (1993). When 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 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) (quoting *Andrus*, 446 U.S. at 616-17); *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; "[m]ost 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"); *Depomed, Inc. v. U.S. Dep't of Health & Human Servs.*, No. 12-cv-1592, 2014 U.S. Dist. LEXIS 126235, *38-39 (D.D.C. Sept. 5, 2014) (quoting *Andrus*, 446 U.S. at 616-17).

2. **Section 505A(o)'s Legislative History And Context**

The legislative history and context make clear that Section 505A(o) directs FDA's authority to approve an ANDA that omits pediatric labeling information protected by patent or three-year exclusivity *but not to omit pediatric labeling information protected by orphan drug exclusivity*.

Section 505A(o) was a legislative fix to a specific problem. After Bristol Myers Squibb ("BMS") conducted pediatric studies for an oral type 2 diabetes treatment, the company submitted a sNDA seeking approval to add pediatric use information to its label. 147 Cong. Rec. H10210 (daily ed. Dec. 18, 2001). FDA approved the sNDA and granted BMS three-year Hatch Waxman exclusivity under 21 U.S.C. § 355(j)(5)(D)(iv). *Id.* Under then-existing law, the grant of three-year exclusivity resulted in "total marketing exclusivity" because, under FDA's pediatric labeling requirements, generics could not omit the pediatric use from their labels. *Id.* ("Under existing law, that grant resulted in total marketing exclusivity with respect to Glucophage for the applicable period because BMS has acquired exclusive rights to the only pediatric use indication that applied under the pediatric labeling requirements.").

In seeking to close the BMS "loophole," 147 Cong. Rec. H8105 (daily ed. Nov. 13, 2001), the legislative history explains how the problem arose, making clear that the provision was meant to direct FDA's approval authority. Congress recognized the problem posed by the statutory "same labeling" requirement and FDA's 1994 regulations that require pediatric information to be included in every prescription drug's labeling. 147 Cong. Rec. H10209 (citing 21 C.F.R. § 201.57(f)(9)(ii)). The legislative history recounts that FDA promulgated a regulation in 1992 that allowed, as an exception to the "same labeling" requirement, generic manufacturers to omit certain information protected by patent or exclusivity, but explains that later 1994 regulations "requir[ed] that pediatric information be included in the labeling of every prescription drug." *Id.* (citing 21 C.F.R. §§ 201.57(f)(9)(ii), 314.94(a)(8)(iv), 314.127(a)(7)). The legislative history notes that FDA's 1994 regulation was meant to "'promote[] safer and more effective use of prescription drugs in the pediatric population'" and that "'a drug product that is not in compliance with [the

revised regulation] would be considered to be misbranded and an unapproved new drug under the act." *Id.* (citing 59 Fed. Reg. 64,240 (Dec. 13, 1994); 57 Fed. Reg. 47,423, 47,425 (Oct. 16, 1992)).

The effect of this 1994 regulatory requirement, as the legislative history makes clear, was to afford BMS an extended period of total marketing exclusivity, a result that Congress intended to eliminate by directing FDA's approval authority in Section 505A(o). Referred to as the "Anti-Glucophage Bill," Section 505A(o) was enacted specifically to fix the BMS problem. *Id.* at H10210 ("[T]he proposed legislation would eliminate the marketing exclusivity that BMS currently enjoys as a result of its exclusive right to the pediatric use labeling for Glucophage."); 147 Cong. Rec. H8105-06 ("[T]he proposed legislation would, as a practical matter, eviscerate the exclusive right to pediatric labeling that BMS obtained under federal law."); *Id.* at H8105 ("H.R. 2887 closes this potential loophole *by instructing the FDA to approve generic drugs* without proprietary pediatric labeling awarded to product sponsors under the Hatch-Waxman Act." (emphasis added)); 147 Cong. Rec. H8551-08 (Nov. 28, 2001) ("Let us fight against [BMS] ad close the Hatch-Waxman loophole.").

The fix "over[o]de," 147 Cong. Rec. H10210, FDA's pediatric labeling requirements only where patents and three-year exclusivity were at issue. The legislative history has repeated references to three-year exclusivity, as that was the exclusivity protection afforded BMS. *See* 147 Cong. Rec. H8105 ("H.R. 2887 closes this potential loophole by instructing the FDA to approve generic drugs without proprietary pediatric labeling awarded to product sponsors under the Hatch-Waxman Act."); 147 Cong. Rec. H10205 ("[T]his legislation contains a provision which will result in generic drugs being approved when their labeling omits the pediatric indication or other aspect of labeling which is protected by the patent exclusivity."); *Id.* at H10210 ("[T]he bill we will vote on today and send to the President closes the 'Glucophage loophole' which allowed one company

to get an additional 3 years of marketing exclusivity."); *see also* H.R. Rep. No. 277 (Nov. 9, 2001) ("[Section 11] does make clear that if a manufacturer does claim supplemental exclusivity under section 505(j), the terms of that exclusivity will not prevent generic competition for the indications or aspects of labeling which are not protected.").[4]

In sum, Congress enacted Section 505A(o) to direct FDA to approve generics that omitted pediatric labeling information protected by patent or three-year exclusivity, and nothing more. The legislative history makes clear that Congress intended to fix the BMS loophole, and not to address orphan drug exclusivity.

3. **The Arguments Set Forth By Intervenor-Defendants Are Unavailing.**

(a) **Section 505A(o) Applies Here.**

Contrary to the arguments set out by the intervenor-defendants in their earlier oppositions, ECF No. 53, at 30; ECF No. 51, at 8, Section 505A(o) applies here. There is nothing in the text of the statute to support the proposition that 505A(o) applies only where information protected by pediatric exclusivity is involved. The text of the statutory provision speaks broadly of "pediatric indication[s]" and "other aspect[s] of labeling pertaining to pediatric use." 21 U.S.C. § 355a(o)(1); *see also id.* (titled "Prompt approval of drugs under section 355(j) when pediatric information is

[4] Congress could have simply said, broadly, "exclusivity" and covered orphan drug exclusivity, rather than "exclusivity under clause (iii) or (iv) of section 355(j)(5)(F)." Congress has done so elsewhere, *see* 21 U.S.C. § 355(j)(10)(A)(i) (a drug shall not be considered misbranded if "the application is otherwise eligible for approval under this subsection but for expiration of patent, *an exclusivity period*, or of a delay in approval . . ." (emphasis added)), but Congress did not do so here. Or, Congress could have been more specific and included orphan drug exclusivity, as it has elsewhere, *see id.* § 355(j)(5)(B)(iv)(II)(dd)(AA) ("The term 'tentative approval' means notification to an applicant by the Secretary that an application under this subsection meets the requirements of paragraph (2)(A), but cannot receive effective approval because the application does not meet the requirements of this subparagraph, there is a period of exclusivity for the listed drug under subparagraph (F) or section 355a of this title, or there is a 7-year period of exclusivity for the listed drug under section 360cc of this title." (emphasis added)), but, again, Congress did not do so.

added to labeling"). The intervenor-defendants would impermissibly have the Court read into the provision limiting language that does not exit to restrict pediatric information to "pediatric information protected by pediatric exclusivity," a limit that clearly does not appear in the text of the statute. *See 62 Cases*, 340 U.S. at 596 ("It is for us to ascertain – neither to add nor to subtract, neither to delete nor to distort."); *Ignacio v. United States*, 674 F.3d 252, 255 (4th Cir. 2012) ("Courts must construe statutes as written, and not add words of their own choosing." (internal quotation marks and brackets omitted)).

The fact that Congress elsewhere in Section 505A(o) did speak to "pediatric exclusivity," 21 U.S.C. § 355a(o)(3), suggests that Congress did not mean to limit § 355a(o)(1)'s references to "pediatric indication[s]" and "other aspect[s] of labeling pertaining to pediatric use" to pediatric indications and information *protected by pediatric exclusivity*. *Coleman v. Cmty. Trust Bank*, 426 F.3d 719, 725-26 (4th Cir. 2005) ("Where Congress includes particular language in one section of a statute but omits it in another, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion." (quoting *Keene Corp. v. United States*, 508 U.S. 200, 208 (1993)).

(b) **FDA's General Statutes And Regulations Do Not "Trump" Section 505A(o).**

General statutes and regulatory provisions that allow FDA to omit a protected indication from a generic's proposed label do not "trump" Section 505A(o). Nor does the Orphan Drug Act. Intervenor-Defendants Apotex and Teva have pressed these arguments hard. *See* ECF No. 53, at 19-29. These arguments disregard the legislative history that Section 505A(o) was intended to be a fix to the problem presented by the interaction of FDA's mandatory pediatric labeling requirements and the statutory and regulatory same labeling requirement. *See supra* Part II.A.2. These arguments are also contrary to three important canons of statutory construction.

First, a more specific statutory provision trumps a more general statute. *See Busic v. United States*, 446 U.S. 398, 406 (1980) ("[A] more specific statute will be given precedence over a more general one, regardless of their temporal sequence."), *superseded by statute as recognized by* 520 U.S. 1 (1997); *United States v. Smith*, 812 F.2d 161, 166 (4th Cir. 1987) (same); *Faircloth v. Lundy Packing Co.*, 91 F.3d 648, 657 (4th Cir. 1996) (applying that concept; "However inclusive may be the general language of a statute, it 'will not be held to apply to a matter specifically dealt with in another part of the same enactment.'"). Section 505A(o) deals with the specific situation in which FDA can approve a generic drug with a label that omits certain pediatric information. Neither the general "same labeling" statutes or regulations or orphan drug statutes govern that particular situation. Rather, the general labeling statute instructs that 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). And the orphan drug statutes say simply that FDA "may not approve another application . . . for such disease or condition . . . until the expiration of seven years from the date of the approval of the approved application." *Id.* § 360cc(a)(2). These more general statutes do not address the specific situation in which pediatric information, though required to be included on a label, 21 C.F.R. § 201.57(c)(2)(i)(B); (c)(3)(C); (c)(9)(iv)(B)-(C), may be omitted. That is the topic to which Congress directed its attention in Section 505A(o). And Congress provided a specific answer.

Second, in any event, FDA's general labeling regulations, whatever they may say, cannot override Section 505A(o). "Regulations cannot trump the plain language of statutes." *Robbins v. Bentsen*, 41 F.3d 1195, 1198 (7th Cir. 1994); *Furlow v. United States*, 55 F. Supp. 2d 360, 364-65 (D. Md. 1999) ("It is a fundamental principle of American law that legislative statutes take

precedence over conflicting administrative regulations."). The legislative judgment of Congress controls over any contrary judgment of FDA.

Third, Congress is presumed to legislate against the background of existing law. *See 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))). Section 505A(o) was enacted in 2002, *after* the enactment of the Orphan Drug Act (in 1983) and *after* FDA's regulations requiring generic versions of brand drugs to bear the same pediatric labeling for pediatric indications (1994). *See* 65 Fed. Reg. 81083 ("[Regulations finalizing §§ 201.56 and 201.57] were revised in 1994 by amending the requirements relating to the inclusion of data relevant to use in pediatric populations . . ."). Congress could have included the omission of pediatric labeling covered by orphan drug exclusivity as a permissible exclusion from the otherwise applicable same labeling requirement, but Congress chose not to. Congress chose not to do so and that choice must be respected.

(c) **The Agency's Past Practice Does Not Establish Lawfulness.**

Any argument that "FDA has done this in the past, so it is permissible here" is equally unavailing. *See* ECF No. 53, at 23, 27; ECF No. 54, at 30 n.24 (noting in passing that FDA has allowed carve-outs "in other contexts"). Asserting that "FDA has done it before" does not make a policy lawful nor does past practice authorize the agency to act contrary to a statute.

In *Teva Pharmaceuticals USA, Inc. v. Sebelius*, 595 F.3d 1303, 1318 (D.C. Cir. 2010), the court declared FDA's interpretation of a statute unlawful under *Chevron* step one, despite the fact that the interpretation had been set out by the agency twice before. *In re Old Fashioned Enters., Inc.*, 236 F.3d 422 (8th Cir. 2001), illustrates the same point. The dispute there centered on

whether a restaurant chain was a "dealer" under the Perishable Agricultural Commodities Act. *Id.* at 424. The courts below ruled that the chain was not, relying in part on the USDA's 70-year practice of excluding restaurants from the Act's provisions and giving *Chevron* deference to the agency's interpretation. *Id.*at 425. The Eighth Circuit reversed, stating that it would not defer to an agency position that was contrary to the plain meaning of the statute, notwithstanding the agency's practice. *Id.* at 425-27.

(d) **The "Carve-Out" Cases Cited By Intervenor-Defendants Are Inapposite.**

Cases in which courts have upheld FDA's general carve-out authority under the FDCA do not address FDA's authority to carve out pediatric labeling protected by orphan drug exclusivity. *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141, 144-47 (4th Cir. 2002), for example, was a challenge brought by a drug manufacturer to the scope of FDA's drug approval as contrary to the Orphan Drug Act; the challenger argued that FDA's generic approvals were unlawful because the drugs would be used off-label for the challenger's protected indication. *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1496, 1499-1500 (D.C. Cir. 1996), was a challenge brought by a drug manufacturer to the scope of FDA's ability to carve out indications protected by three-year exclusivity.

Neither case considered the effect of Section 505A(o) on FDA's ability to carve-out pediatric information protected by orphan drug exclusivity. Otsuka is not arguing, as in either of those cases, that FDA cannot approve generics because they will, in actuality, be used in an off-label way for the protected carved-out indication. Otsuka is arguing that FDA is precluded from approving a generic under Section 505A(o).

(e) **Otsuka's Three-Year Exclusivity Is Irrelevant.**

The fact that Otsuka received three-year new clinical studies exclusivity has no impact on the analysis here. Otsuka's pediatric indication and other information is protected by orphan drug exclusivity and Congress did not include that exclusivity in the statute. Orphan drug exclusivity is completely separate from, and operates in addition to, three-year Hatch Waxman exclusivity. Orphan drug exclusivity is seven years, while new clinical study exclusivity is three years. *Compare* 21 U.S.C. § 360cc(a)(2), *with id.* § 355(j)(5)(F)(iii)-(iv). Three-year exclusivity protects changes made to the label that meet certain specified criteria, *see* § 355(j)(5)(F)(iii)-(iv); 21 CFR 314.108(b)(4)&(5), while orphan drug exclusivity protects information on the label specific to the orphan indication regardless of how that information is derived, 21 U.S.C. § 360cc(a)(2), 21 C.F.R. § 316.3(b)(12).

FDA has itself recognized that the scopes of the exclusivities are different:

> 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., at 10 (Feb. 15, 2013), http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-1018-0003.

B. Absent Preliminary Relief, Otsuka Will Be Irreparably Harmed Without Any Adequate Remedy.

1. Standard

This Court's immediate intervention is necessary to prevent irreparable harm to Otsuka. Otsuka fully expects that, notwithstanding the law to the contrary, FDA will approve generic

versions of aripiprazole on April 20, 2015. FDA has already tentatively approved eight generics,[5] and it is clear that the generics fully expect to come to market on April 20. *See* ECF No. 53 (Apotex/Teva), at 17; ECF No. 9-1 (Apotex), at 3; ECF No. 29-1 (Teva), at 2; ECF No. 41-1 (Alembic), at 3; ECF No. 65-1 (Zydus), at 3.

Absent the Court's intervention, on April 20, the generics will flood the market with generic versions of Abilify within minutes of receiving FDA approval. In similar cases, generics have had their trucks loaded prior to receiving approval and ready to roll at the moment of approval. The same will occur here. *See* ECF No. 29-1, at 6 ("Teva expects to receive final approval for the ANDAs from FDA on or around April 20, 2015 . . . . Once Teva obtains FDA approval, it will be ready to launch shortly thereafter, allowing it to enter the market and make potentially many millions of dollars in sales . . . .").

Irreparable harm is demonstrated where any calculation of damages is "'difficult to ascertain or are inadequate'" or where "the failure to grant preliminary relief creates the possibility of permanent loss of customers to a competitor or the loss of goodwill." *Multi-Channel TV Cable Co. v. Charlottesville Quality Cable Operating Co.*, 22 F.3d 546, 551-52 (4th Cir. 1994) ("Irreparability of harm includes the impossibility of ascertaining *with any accuracy* the extent of the loss." (quoting *Blackwelder Furn. Co. v. Seilig Mfg., Inc.*, 550 F.2d 189, 197 (4th Cir. 1977))), *abrogated on other grounds by Audiology Dist., LLC v. Hawkins*, 578 F. App'x 260 (4th Cir. 2014). The "irreparable harm to the plaintiff 'must be neither remote nor speculative, but actual and imminent.'" *Nicklas Assocs. v. Zimet*, No. GJH-14-3777, 2014 WL 6984138, *4 (D. Md. Dec.

[5] To view tentative approvals, the following website can be used, by searching for and clicking on "aripiprazole": http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=ARIPIPRAZOLE.

9, 2014) (internal quotation marks omitted).

2. Otsuka Cannot Recover Money Damages For FDA's Unlawful Action.

The harm in this case is truly irreparable. This is a case against FDA, alleging that FDA has unlawfully allowed generics onto the market in violation of Otsuka's statutory right to exclusivity. FDA's actions will result in Otsuka's lost statutory right to exclusivity.[6] Because FDA enjoys sovereign immunity, Otsuka is without a remedy to recover money damages from the agency. *See, e.g.*, *Smoking Everywhere, Inc. v. FDA*, 680 F. Supp. 2d 62, 77 n.19 (D.D.C. 2010) (claimed economic injury is irreparable because plaintiffs cannot recover damages against FDA because it is shielded by sovereign immunity), *aff'd sub nom. Sottera, Inc. v. FDA*, 627 F.3d 891 (D.C. Cir. 2010). *Senior Executives Association v. United States*, 891 F. Supp. 2d 745 (D. Md. 2012), demonstrates this point. There, a group of associations filed suit against the United States and the Acting Director of the Office of Government Ethics, alleging that a law's disclosure requirements would "compromise their confidential financial information and jeopardize their personal security." *Id.* at 748. The court, ruling on the plaintiffs' motion for a temporary preliminary injunction, found that plaintiffs had shown they were likely to suffer irreparable harm without relief. *Id.* The court explained that "monetary damages are an inadequate remedy for several reasons, *including that they are unavailable*," citing cases about the government's

[6] *See Hospira*, 2014 U.S. Dist. LEXIS 115393, at *11 (noting Sandoz's claimed lost statutory right to a six month period of exclusivity); *see also Mylan Labs., Ltd. v. FDA*, 910 F. Supp. 2d 299, 313 (D.D.C. 2012) ("[C]ourts have held that a first applicant's loss of its statutory entitlement to 180-day exclusivity period is irreparable because once lost 'it cannot be recaptured' . . . ." (citing *Apotex, Inc. v. FDA*, No. 06-627, 2006 WL 1030151, *17 (D.D.C. Apr. 19, 2006)); *Mova Pharm. Corp. v. Shalala*, 955 F. Supp. 128, 131 (D.D.C. 1997) ("[D]epriving [first-filer] Mova of a 180-day statutory grant of exclusivity and giving [later-filer] Mylan an officially sanctioned head start in the market . . . will cause injury to Mova."); *cf. Johns Hopkins Univ. v. Datascope Corp.*, 513 F. Supp. 2d 578, 586 (D. Md. 2007) (granting permanent injunction because the value of a patent is its statutory right to exclude, which "weighs against holding that monetary damages will always suffice to make the patentee whole"), *rev'd*, 543 F. 3d 1342 (Fed. Cir. 2008).

sovereign immunity. *Id.* (emphasis added; citing *FDIC v. Meyer*, 510 U.S. 471, 475 (1994); *United States v. Mitchell*, 445 U.S. 535, 538-39 (1980); *Smoking Everywhere*, 680 F. Supp. 2d at 77 n.19); *see also N.C. Growers' Ass'n v. Solis*, 644 F. Supp. 2d 664, 670-71 (M.D.N.C. 2009) ("Plaintiffs' economic losses are unrecoverable in that suits for economic damages against the federal government and federal agencies are barred by the sovereign immunity doctrine. Likewise, plaintiffs will not be able to recover their losses from H-2A workers." (citation omitted)); *cf. Hospira, Inc. v. Burwell*, No. GJH-14-02662, 2014 U.S. Dist. LEXIS 115393, *11-12 (D. Md. Aug. 19, 2014) ("[T]he government's contention at oral argument that there is no remedy the Court could fashion to address Plaintiff's harm only highlights the irreparability of the harm being suffered by Plaintiff's as a result of the FDA's ruling.").

Similarly, Otsuka's lost exclusivity is irreparable because money damages cannot be recovered from the generics. The FDCA expressly precludes private litigants from enforcing its provisions. *See* 21 U.S.C. § 337(a); *Mylan Labs., Inc. v. Matkari*, 7 F.3d 1130, 1139 (4th Cir. 1993) ("Mylan, in short, is not empowered to enforce independently the FDCA."). Thus, the injuries Otsuka will suffer at the moment of generic loss are irreparable because they cannot be remedied.

3. Price Erosion, Loss Of Market Share, Loss Of Profits, Discontinued Or Undercut Research And Educational Opportunities, Consideration Of Layoffs, Lost Goodwill

"Depending on circumstances, evidence of price erosion, loss of market share, loss of profits, loss of research opportunities, and possible layoffs may constitute irreparable harm," *Research Found. of State Univ. of New York v. Mylan*, 723 F. Supp. 2d 638, 658-59 (D. Del. 2010); *see also Par Pharms., Inc. v. TWi Pharms., Inc.*, No. CCB-11-2466, 2014 U.S. Dist. LEXIS 110963, *12-14 (D. Md. Aug. 12, 2014) (finding irreparable harm where, among other things, "the price erosion and revenue losses [Par's medication] would suffer would be impossible to reverse

completely" and there would be lost goodwill among patients);[7] they do so here because they will be exceedingly difficult, if not impossible, to quantify with any accuracy and will not be fully compensable by money damages. Harm can be irreparable where it "destroys a division of a company." *Par Pharms*, 2014 U.S. Dist. LEXIS 110963, at *10-11 ("TWi points to no authority for the position that harm is not irreparable where it only destroys a division of a company instead of the entire entity.").

Abilify is of enormous importance to Otsuka. The company has no product of comparable importance in terms of contribution to Otsuka's revenue and profit, either globally or in terms of its U.S. operations. Ex. A ¶ 2. Unlike other brand companies with multiple blockbuster products to at least partially offset the loss of a product going generic, Otsuka has no "back up" large revenue pharmaceutical products. *Id.* ¶ 4. The drug is one of the largest selling prescription drug products in the U.S., with annual gross sales exceeding $8.2 billion in 2014. *Id.* ¶ 3. These sales generated about $4.9 billion in net sales to Otsuka America Pharmaceutical, Inc. ("OAPI") in 2014 and accounted for over 90% of OAPI's net revenues.[8] *Id.* The average selling month for 2014 was

[7] *See also Hospira*, 2014 U.S. Dist. LEXIS 115393, at *11 (lost customers; lost market share); *Bayer Healthcare, LLC v. FDA*, 942 F. Supp. 2d 17, 26 (D.D.C. 2013) (decline in market share, price erosion, loss of customer good will, loss of research and development funding); *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1049 (Fed. Cir. 2010) (damage from layoffs caused by generic entry would be significant and unquantifiable); *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1382 (Fed. Cir. 2006) (price erosion); *Purdue Pharma L.P. v. Boheringer Ingelheim GmbH*, 237 F.3d 1359, 1368 (Fed. Cir. 2001) (price erosion; loss of market position); *Allergan, Inc. v. Apotex Inc.*, No. 1:10-cv-681 et al., 2013 U.S. Dist. LEXIS 57656, at *19-21 (M.D.N.C. Apr. 23, 2013) (loss of market share; loss of revenue where Allergan would not recoup its expenditures), *vac'd by* 754 F.3d 952 (Fed. Cir. 2014); *King Pharms., Inc. v. Corepharma, LLC*, No. 10-1878, 2010 U.S. Dist. LEXIS 45660, *9-12 (D.N.J. May 7, 2010) (price erosion; lost market share); *Pharmacia & Upjohn Co. v. Ranbaxy Pharms., Inc.*, 274 F. Supp. 2d 597, 614 (D.N.J. 2003) (price and market erosion), *aff'd in part and vac'd in part*, 85 F. App'x 205 (Fed. Cir. 2003); *see generally Signature Flight Support Corp. v. Landow Aviation Ltd. P'ship*, 442 F. App'x 776, 785 (4th Cir. 2011) (lost customer base; loss of goodwill).

[8] A portion of the net sales generated by Abilify are shared with another company pursuant to an agreement that terminates on April 20, 2015. Ex. A ¶ 3.

approximately $686 million in gross sales. *Id.* If four or more generics enter the market after April 20, it is estimated that after 30 days, Abilify would only maintain 17% of its monthly sales volume, and after 90 days, only 10%. *Id.* ¶ 5. That decrease is hugely significant. Even if only one generic company enters the market at risk after April 20, the loss of Abilify's market share would be very substantial. *Id.*

Besides a very significant reduction in OAPI's revenues and sales volume, generic entry will be devastating because of its impact on U.S. operations. The severe reduction in Otsuka's revenue that would inevitably occur upon generic launch would require OAPI to consider a significant reduction in its approximately 430 person sales force who currently spend 100% of their time on Abilify and one of Otsuka's much smaller revenue producing products. *Id.* ¶ 14. Otsuka's sales force is highly trained and skilled and is a valuable corporate asset. *Id.* ¶ 16. While the Abilify sales team may be used to promote other products in the future, because these will be much smaller-selling products, any sales force devoted to marketing them will have to be appropriately sized. *Id.* ¶ 14. Even if generics are later pulled from the market, it would be impossible to hire back all members who left the company due to the generic approvals. *Id.* ¶ 15. In addition to significantly affecting its U.S. operations financially and in terms of personnel, if generics entered the market, educational programs and similar programs would be discontinued and research and development efforts would be significantly undercut. *Id.* ¶¶ 17-18. OAPI and Otsuka would also lose goodwill from physicians and patients. *Id.* ¶ 19.

Otsuka would suffer price erosion in the event of generic launch, as well. *Id.* ¶ 6; *Par Pharms.*, 2014 U.S. Dist. LEXIS 110963, at *11-12. In anticipation of generic entry, some payers have already moved Abilify from the second pricing tier (generally includes preferred branded drugs) into the third pricing tier (for non-preferred branded drugs), and with generic entry,

formularies would be incentivized to move Abilify to the third tier. Ex. A ¶¶ 6-7. Otsuka could attempt to seek to counteract this by offering substantial incentives and rebates contingent on placement of Abilify in a favored tier, but this would have the effect of lowering the net effective price of Abilify. *Id.* ¶ 7. If generics were later forced off the market, OAPI would have to attempt to negotiate for more favorable tiering status and price increases based on elimination of rebates, which Otsuka expects would be futile. *Id.* ¶ 8. Otsuka would expect great resistance to efforts to restore more favorable tiering status and prices at pre-generic market entry levels, and would not expect OAPI to be successful in withdrawing incentives and rebates. *Id.* The longer the generic products are on the market, the greater the cost of payer rebate programs, the lower OAPI's bargaining power to resist further concession demands, and the harder it would be to obtain price increases after the subsequent removal of generic products. *Id.* ¶ 9. Even if generics were forced to withdraw from the market, a substantial amount of generic inventory would still exist and would have to be drawn down before OAPI could attempt to renegotiate pricing. *Id.*

A different approach would be to maintain prices with payers, accept placement in a lower tier, and try to stimulate demand for Abilify with patients through end-user rebate programs. *Id.* ¶ 10. To be even partially successful, the rebates would need to present the consumer with end use costs after rebates that are the same, or close to the same, as the cost for the generic. *Id.* Otsuka has recently implemented such a plan for Abilify. *Id.* This approach also results in price erosion. *Id.* ¶ 11. For these and other reasons, Abilify sales volumes and net effective prices would still decline substantially even with a patient rebate program. *Id.* ¶ 12. Even if generic products were later removed from the market, Otsuka expects that it would be very difficult to restore Abilify to a tier two position. *Id.*

The price erosion, lost profits, and lost sales following generic entry will be exceedingly

difficult, if not impossible, to quantify with any accuracy. *Id.* ¶ 13. All of these injuries are irreparable because there is no party from which Otsuka can recover; FDA is protected by sovereign immunity and violations of the FDCA are not privately actionable. Moreover, they are inadequate because the appearance and disappearance of generic products would result in lost goodwill, which can translate into lost future business, the dollar amount of which cannot be quantified and generic entry will require OAPI to consider a significant reduction in its sales force, a valuable corporate asset, and it would be impossible to hire back all members who left the company due to generic approvals, *id.* ¶¶ 14-16, 19.

C. The Balance Of Hardships Tips Strongly In Otsuka's Favor.

The balance of hardships tips heavily in favor of Otsuka. *E.g.*, *Bayer Healthcare*, 942 F. Supp. 2d at 26 (issuing temporary restraining order where brand drug owner challenged approval of generic; hardship tipped in favor of brand owner rather than FDA and generic company); *Hospira*, 2014 U.S. Dist. LEXIS 115393, at *12 ("Additionally, any harm suffered by Myland, and entities similarly situated, based upon a stay of FDA's twenty-four hour old decision would pale in comparison to the harm Plaintiff would suffer as a result of generic versions of its products being widely distributed to Plaintiff's customers."). To begin with, FDA will not be harmed at all by an injunction. The balance between Otsuka and FDA tips entirely in Otsuka's favor.

Absent action by this Court, Otsuka will be severely and irreparably prejudiced on April 20, 2015. There is no question that, as soon as they are approved, generics will pump product into the market, causing severe and irreparable harm to Otsuka while Otsuka waits for a resolution of the underlying question of the illegality of FDA's action. When a resolution that is favorable to Otsuka is reached, it will be impossible for that harm to be remedied. On the other hand, granting the limited interim relief requested will not prejudice FDA at all. FDA has dragged its feet on

issuing a decision on Otsuka's entitlement to exclusivity, and then insisted that it would only make a decision in tandem with generic approvals; it cannot now cry "hardship," when it has no hardship and any hardship is of its own making.

Nor will it prejudice intervenor-defendants, which will only be required to wait for a final, expedited decision from this Court. *See Par Pharms.*, 2014 U.S. Dist. LEXIS 110963, at *14-15 (dismissing arguments about delayed launch of product because "any revenue from that [exclusivity] period is only time-shifted by the imposition of an injunction"). Temporary or preliminary injunctive relief will only maintain the status quo while this Court reviews the agency's actions.

Otsuka fully supports expediting proceedings on the merits of this case. This matter should proceed quickly to the merits, with the parties' filing cross-motions for judgment. There is no discovery to be conducted and a "record to date" has already been filed; it need only be supplemented. Otsuka would be harmed seriously, however, if FDA's decision were to go unstayed in the meantime, if approvals were to go ahead, and generics were to flood the market.

D. The Public Interest Favors Granting The Limited Relief Requested.

The public interest strongly favors granting a preliminary injunction. Not only is the public interest best served "by ensuring [agency] compliance with [its governing] statute," *Bayer*, 942 F. Supp. 2d at 27, but that is particularly true in the case of FDA. "Following its own statute is important as the FDA's mission, in part, is to protect the public health by ensuring that products are safe and effective." *Hospira*, 2014 U.S. Dist. LEXIS 115393, at *12-13.

In summary, Otsuka satisfies all four factors and is entitled to injunctive relief.

III. Any Security Bond Should Be Waived Or, Alternatively, Further Submissions And Briefing Will Be Necessary To Determine Any Bond Amount.

The Court should waive the Rule 65(c) requirement for a bond. Doing so is well within the Court's discretion. *Pashby*, 709 F.3d at 331-32 ("The district court retains the discretion to set the bond amount as it sees fit or to waive the security requirement."); *Hoechst Diafoil Co. v. Nan Ya Plastics Corp.*, 174 F.3d 411, 421 & n.3 (4th Cir. 1999) ("The amount of the bond, then, ordinarily depends on the gravity of the potential harm to the enjoined party[.]"); *see also Potomac Conf. Corp. v. Takoma Acad. Alumni Ass'n*, No. DKC-12-1128, 2014 U.S. Dist. LEXIS 27123 (D. Md. Mar. 4, 2014) ("The district court has discretion in fixing the amount for the security bond, and in circumstances where the risk of harm is remote, a nominal bond may suffice.").

Here, waiver or a nominal bond is appropriate because the "risk of harm is remote" given the strength of Otsuka's claim on the merits. There is no harm to FDA so its risk of harm is zero. As to the intervenor defendants (generics), an injunction would simply deny them the "right" to immediate pre-judicial review market entry when, as a matter of law, they have no such "right" by reason of Otsuka's exclusivity rights. Any claimed harm presupposes a non-existent right.

Alternatively, if the Court determines that a more than nominal bond is required, a temporary or preliminary injunction should be entered followed by expeditious factual and legal submissions upon which the Court could properly determine the amount of a bond. The generics must offer evidence to support a claim of injury in the event of entry of a brief injunction (*e.g.*, what and how much do they allegedly stand to lose and when is this likely to occur?). *Potomac Conf.*, 2014 U.S. Dist. LEXIS 27123, at *74-75 ("Defendant does not provide any input as to the amount of damages it would sustain should it later be determined that Defendant was wrongfully enjoined. There does not seem to be a substantial risk of harm to Defendant and Plaintiff has demonstrated likelihood of success on the merits.").

IV. Otsuka Respectfully Requests That The Court Establish An Expedited Schedule And, Pursuant To Rule 65(a)(2), Consolidate Hearing On Otsuka's Motion For A Preliminary Injunction With The Trial (Hearing) On The Merits.

The factual predicate for judicial review of FDA's final decision is the administrative record; there are no facts in dispute. There is no reason for the Court to go deeply into the merits twice, first at the preliminary injunction stage and then a second time on cross-motions for summary judgment. Accordingly, pursuant to Federal Rule 65(a)(2), Otsuka respectfully requests consolidation of preliminary injunction and final merits proceedings and that those consolidated proceedings occur pursuant to an expedited schedule. Otsuka's proposed schedule is as follows: filing of the administrative record three business days following FDA's decision; simultaneous filing of dispositive motions for summary judgment five business days following the filing of the record; filing of any replies three business days after the filing of cross-motions for summary judgment motions; and then a hearing.

Conclusion

Otsuka satisfies the requirements to warrant the grant of temporary or preliminary injunctive relief to protect Otsuka for the short period of time between issuance of FDA's final decision and the hearing and determination of this case on the merits. Accordingly, Otsuka respectfully requests that the Court grant its motion for a temporary or preliminary injunction.

Respectfully submitted,

Dated: April 15, 2015

/s/ Ralph S. Tyler

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CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on this 15th day of April, 2015, a copy of the foregoing PLAINTIFFS' MOTION FOR TEMPORARY RESTRAINING ORDER AND/OR PRELIMINARY INJUNCTION is available for viewing from the Court's ECF system. Notice of this filing will be sent to all counsel of record via the Court's ECF system.

/s/ Ralph S. Tyler
Ralph S. Tyler

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

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

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

TEMPORARY RESTRANING ORDER AND/OR PRELIMINARY INJUNCTION

Pending before the Court is the motion of Plaintiff Otsuka Pharmaceutical Development & Commercialization, Inc. ("Otsuka") for a temporary restraining order and/or preliminary injunction. Having reviewed the motion and any opposition thereto and for good cause shown, and for the reasons stated on the record, the motion is hereby GRANTED this __ day of March, 2015 at ____; and, therefore, it is now hereby ORDERED that:

1. The U.S. Food and Drug Administration's ("FDA") decision denying Otsuka's entitlement to exclusivity is hereby STAYED;
2. Any additional actions that FDA has taken or is proposing to take in reliance upon its decision are similarly STAYED; specifically, FDA shall stay the effectiveness of any approvals granted prior to the entry of this Order and FDA shall not grant any further approvals of generic versions of Otsuka's prescription brand drug aripiprazole;
3. Intervenor-Defendants shall not distribute and/or shall cease distribution of their generic versions of Abilify during the pendency of this order; and
4. Nothing herein shall effect FDA's authority to grant approval to a particular generic for aripiprazole where that generic holds a license from Otsuka.

It is further ORDERED that the security bond has been considered and WAIVED, pending further order of the Court.

This Order shall continue in full force and effect until the ___ day of ____, 2014, unless extended.

SO ORDERED.

_____
George J. Hazel
United States District Judge