IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND
Southern Division

OTSUKA PHARMACEUTICAL CO., LTD.,	*	
Plaintiff,	*	
v.		**Case No.: GJH-15-852**
SYLVIA MATHEWS BURWELL, ET AL.,	*	
Defendants.	*	

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MEMORANDUM OPINION

On April 28, 2015 at 1:30 pm, Defendant Food and Drug Administration ("FDA") granted approval of the sale of four generic versions of the prescription brand drug aripiprazole, which is marketed and sold under the brand name of Abilify® by Plaintiffs Otsuka America Pharmaceutical, Inc., Otsuka Pharmaceutical Development and Commercialization, Inc., and Otsuka America Pharmaceutical Inc. (collectively, "Otsuka"). In this action, Otsuka challenges FDA's[1] approval of these generic drugs pursuant to the Administrative Procedure Act ("APA"), 5 U.S.C. § 701, *et seq*. Specifically, Otsuka seeks a temporary restraining order and/or preliminary injunction to stay the effectiveness of these approvals, to prohibit FDA from granting any further approvals of generic versions of Abilify®, and to prohibit the recent recipients of FDA-approvals from selling the generic versions of Abilify®. At 3:15 pm on April 28, 2015, just two hours after FDA approved generic versions of Abilify®, the Court conducted a hearing on Otsuka's motion for a temporary restraining order and/or preliminary injunction

[1] In addition to naming the FDA as a defendant, Otsuka has also named Sylvia Mathews Burwell, Secretary of the U.S. Department of Health and Human Services, and Drs. Margaret Hamburg and Stephen Ostroff as defendants. Because the allegations against these four defendants are the same, the Court will refer to them collectively as the "FDA."

during which Otsuka, FDA, and Defendant-Intervenors[2] presented their respective arguments for or against the issuance of injunctive relief. Based on these arguments, as well as the arguments presented in the parties' respective briefs, the Court will DENY Otsuka's motion for a temporary restraining order and/or preliminary injunction.

I. BACKGROUND

This case involves the interplay between statutory exclusivities, particularly orphan drug exclusivity, statutory and regulatory mandates that require labels of generic drugs to contain the same information as their brand counterpart, and requirements that pediatric information be included on drug labels. Specifically, Otsuka, the new drug application holder for Abilify®, contends that, as a result of FDA's recent approval of a pediatric indication for Abilify® that is protected by orphan drug exclusivity, FDA is precluded from approving an ANDA for a generic version of Abilify® until its orphan drug exclusivity expires in December 2021 because section 505A(o) of the Federal Food, Drug, and Cosmetic Act ("FDCA") does not permit this type of pediatric information to be omitted from a generic's label.

A. Statutory and Regulatory Framework

1. New Drug Applications and Supplemental New Drug Applications

Under the FDCA, pharmaceutical companies seeking to market the initial version of a drug (also known as the "innovator" or "pioneer" drug) must first obtain FDA approval by filing a new drug application ("NDA") containing extensive scientific data demonstrating the safety and effectiveness of the drug. *See* 21 U.S.C. § 355(a), (d). A sponsor may thereafter submit a supplemental new drug application ("sNDA") seeking FDA's approval of a new indication of an

[2] Defendant-Intervenors include Apotex Inc., Apotex Corp., Teva Pharmaceuticals USA, Inc., Alembic Pharmaceuticals Ltd., Alembic Ltd., Alembic Global Holdings S.A., Alembic Pharmaceuticals, Inc., Zydus Pharmaceuticals (USA) Inc., Torrent Pharma Inc., Torrent Pharmaceuticals Ltd., and Sandoz, Inc. (although Sandoz's motion to intervene has not yet been formally granted).

already approved drug. *See* 21 C.F.R. § 314.70(b). Drug sponsors must justify the labeling change proposed in the supplement by submitting data supporting the safety and effectiveness of the drug for the new indication. *See* 21 U.S.C. § 355(a) and (d); *see also* 21 C.F.R. § 314.70(b)(3)(iv)-(v). FDA will refuse to approve the sNDA if, among other reasons, the sponsor's investigations do not show that the drug is safe or effective for "the conditions of use prescribed, recommended, or suggested in the proposed labeling." 21 U.S.C. § 355(d)(1), (2), (5).

2. Abbreviated New Drug Applications

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments), codified at 21 U.S.C. § 355 and 35 U.S.C. §§ 156, 271, & 282, permits a drug manufacturer to submit an abbreviated new drug application ("ANDA") requesting approval of a generic version of an already approved drug product. See 21 U.S.C. § 355(j). ANDA applicants need not submit clinical data to demonstrate the safety and efficacy of the generic product, as with an NDA. See id. Rather, an ANDA relies on FDA's previous findings that the product approved under the NDA is safe and effective. Among other information, an ANDA must include data showing that the generic drug product is bioequivalent to the innovator product. *See* 21 U.S.C. § 355(j)(2)(A)(iv), (j)(4)(F); *see also* 21 C.F.R. § 314.127(a)(6)(i), 314.94(a)(7).

3. Orphan Drug Exclusivity

To justify the costly and risky investment of time and money in preparing and submitting NDAs and sNDAs, Congress has provided these applicants with certain periods of statutory exclusivity during which they can sell their product without generic competition. 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. One of the incentives that Congress provided in the ODA is a seven-year period of market exclusivity for approved orphan drugs. *See* 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).

4. Labeling Requirements

FDA has promulgated regulations requiring certain pediatric information to be included on a prescription drug's label.[3] For example, in the "Indications and Usage" section of the Full Prescribing Information portion, "[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." § 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*." §

[3] 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).

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." § 201.57(c)(9)(iv)(B).

The regulations require that the labeling also includes 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 . . . ." § 201.57(c)(9)(iv)(C).

5. The "Same Labeling" Requirement

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). Nonetheless, there are situations where ANDA applicants may carve out from proposed labeling patent or exclusivity-protected conditions of use and obtain approval for the remaining non-protected conditions of use. For example, the FDCA allows for exceptions if "the new [ANDA] drug and the listed drug are produced or distributed by different manufacturers." 21 U.S.C. § 355(j)(2)(A)(v); see also 21 C.F.R. §§ 314.94(a)(8)(iv), 314.92(a)(1), 314.127(a)(7). In such cases, ANDA applicants may, for example, carve out indications protected by patent or exclusivity in certain circumstances.

Additionally, Congress enacted section 505A(o) of the FDCA which identifies certain situations where the FDA cannot deny approval based on the omission of pediatric information on a brand's label, from the generic's label. 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). According to Otsuka, "[t]he 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)." ECF No. 77 at 22.[4] Otsuka therefore maintains that FDA cannot omit pediatric labeling information that is protected by orphan drug exclusivity. See id. FDA, on the other hand, contends that section 505A(o) "does not limit [its] authority to carve out pediatric labeling where a carve-out would otherwise be appropriate; instead, it provides FDA with additional authority to retain Hatch-Waxman-protected pediatric information in ANDA labeling where a carve-out would not be appropriate (because such information is necessary for safe use of the product)." Ltr. from J. Peters to R. Tyler, Apr. 28, 2015, at 11.

B. Case-Specific Background

Otsuka is the NDA holder for Abilify®. *See* ECF No. 77-2 at ¶ 4. FDA first approved Abilify® on November 15, 2002, then for schizophrenia, and FDA has since approved it for schizophrenia in adolescents, acute treatment of manic and mixed episodes associated with

[4] For the citations in this Memorandum Opinion, the Court uses the page numbers assigned to the document from CM/ECF or PACER.

Bipolar I Disorder in both adult and pediatric patients, irritability associated with autistic disorder in pediatric patients, and as an add-on treatment for depression in adults. *See id*. at ¶ 7. In 2005, Otsuka submitted an application to FDA requesting orphan drug designation for Abilify® "for the treatment of Tourette Syndrome in children and adolescents." *Id*. at ¶ 10.

In 2006, FDA granted Otsuka orphan drug designation for the use of Abilify® for the treatment of Tourette's Disorder. *See id.* at ¶ 11. This designation meant, among other things, that Otsuka would be entitled to a seven-year period of market exclusivity running from the date of FDA's approval of the use of Abilify® for the treatment of Tourette's Disorder. *See id*. During that seven-year period, FDA would be precluded from approving a drug for the same use or indication. *Id*. When the FDA awarded Abilify® orphan designation for the treatment of Tourette's Disorder, no sNDA had been submitted and no safety and efficacy studies had been conducted in any population group. As such, Otsuka initiated clinical trials which ultimately demonstrated the safety and efficacy of Abilify® to treat Tourette's Disorder in the pediatric population. *See id*. at ¶¶ 14-15, 24. Following the conclusion of these trials, Otsuka submitted a sNDA to FDA seeking approval for the new indication of the treatment of Tourette's Disorder in pediatric patients. *See id*. at ¶ 16. After either changing its mind or dealing with internal confusion, FDA ultimately approved Otsuka's sNDA for Abilify® for treatment of Tourette's Disorder in the pediatric population. *See* ECF No. 77-3. As a result of FDA's decision, Otsuka obtained approval for a pediatric Tourette's Disorder indication for Abilify® that is protected by orphan drug exclusivity.

Otsuka contends that by receiving this pediatric approval, which is protected by orphan drug exclusivity, it is entitled to a seven-year period of total market exclusivity (until December 2021). During that time, Otsuka argues that the law precludes FDA from approving any generic

version of Abilify® for any of its FDA-approved indications (absent a license from Otsuka). It is against this backdrop that Otsuka filed a complaint, along with a motion for a temporary restraining order and/or preliminary injunction, against FDA seeking to stay the effect of FDA's approvals of generic versions of Abilify® that occurred on April 28, 2015, to prevent FDA from issuing any further approvals prior to the expiration of Otsuka's seven year period of orphan drug exclusivity, and to prohibit the recipients of generic approvals from distributing their respective versions of generic Abilify®.

Just hours after FDA's approval of four generic versions of Abilify®, the Court held a hearing on April 28, 2015, on Otsuka's motion for a temporary restraining order and/or preliminary injunction. At the hearing Otsuka, FDA, and Defendant-Intervenors were all given an opportunity to present their respective arguments. Based on those arguments, as well as those arguments presented in the various briefs, the Court denies Otsuka's motion for a temporary restraining order and/or preliminary injunction, for the reasons explained more fully below.

II. DISCUSSION

A temporary restraining order or preliminary injunction is an "'extraordinary remedy that may only be awarded upon a clear showing that the plaintiff is entitled to such relief.'" *Dewhurst v. Cnty. Aluminum Co.*, 649 F.3d 287, 290 (4th Cir. 2011) (*quoting Winter v. Natural Resources Defense Council*, 555 U.S. 7, 22 (2008)). The Fourth Circuit recognizes four requirements in conjunction with the Supreme Court's ruling in *Winter v. Natural Resources* that a party must show in order to be granted a TRO or a preliminary injunction:

> (1) likelihood of success on the merits; (2) likelihood the movant will suffer irreparable harm in the absence of preliminary relief; (3) that the balance of equities tips in movant's favor; and (4) the injunction is in the public interest.

The Real Truth About Obama, Inc. v. Fed. Election Comm'n, 575 F.3d 342, 347 (4th Cir. 2009) (citing *Winter*, 555 U.S. at 20); *see also Dewhurst*, 649 F.3d at 290 (reaffirming the four requirements set forth in *The Real Truth About Obama*). According to *The Real Truth About Obama* and *Dewhurst*, the Fourth Circuit has determined that all four requirements must be met in order for a temporary restraining order or a preliminary injunction to be granted.

A. Likelihood of Success of the Merits

Otsuka claims that section 505A(o) of the FDCA directly addresses the question of when generics can omit from their labels the pediatric information that is included in the brand's label. See ECF No. 77 at 10. According to Otsuka, section 505A(o) permits FDA to approve generic drugs that omit pediatric labeling in only two circumstances – (1) when that information is protected by patent; and (2) when that information is protected by three-year new clinical study exclusivity; it does not, according to Otsuka, allow for the omission of labeling information protected by pediatric orphan drug exclusivity. See id. By approving Otsuka's sNDA for Abilify® to treat Tourette's Disorder in pediatric patients – an indication which is indisputably covered by orphan drug exclusivity – Otsuka argues that FDA was precluded from approving an ANDA for a generic version of Abilify® for any of its approved indications because section 505A(o) does not allow for the omission of this type of pediatric information from the generic's label. Thus, when FDA did approve generic versions of Abilify® on April 28, 2015, Otsuka argues it did so in contravention of section 505A(o). FDA, on the other hand, contends that while section 505A(o) limits its ability to deny approvals in two specified circumstances, it does not limit its ability to grant approvals in others. The Court must therefore address the scope of section 505A(o) of the FDCA. Ordinarily, a court reviews "an agency's construction of the

statute which it administers" under the familiar two-step process of Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc., 467 U.S. 837, 842 (1984).

1. Chevron—Step One

As the Fourth Circuit has explained, the first step in the Chevron analysis is to ask whether "Congress has directly spoken to the precise question at issue," such that "the intent of Congress is clear." *Nat'l Elec. Mfrs. Ass'n v. Dept. of Energy*, 654 F.3d 496, 504 (4th Cir. 2011) (quoting Chevron, 467 U.S. at 842-43). If the intent of Congress is clear, "that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." Chevron, 467 U.S. at 842-43. If, however, "the statute is silent or ambiguous with respect to the specific issue," id. at 843, Congress has not spoken clearly, and a permissible agency interpretation of the statute merits judicial deference. Thus, "[t]he objective of Chevron step one is not to interpret and apply the statute to resolve a claim, but to determine whether Congress's intent in enacting it was so clear as to foreclose any other interpretation." King v. Burwell, No. 14-1158, 2014 WL 3582800, at *5 (4th Cir. July 22, 2014) (citing Grapevine Imports, Ltd. v. United States, 636 F.3d 1368, 1377 (Fed. Cir. 2011)).

Under the first step of Chevron, "a reviewing court is to 'employ [ ] traditional tools of statutory construction' to determine whether Congress addressed 'the precise question at issue.'" *Nat. Elec. Mfrs. Ass'n.*, 654 F.3d at 504 (quoting Chevron, 467 U.S. at 842, 843 n. 9). Thus, courts begin this analysis with the text and structure of the statute. Id. (citing Cabell Huntington Hosp. Inc. v. Shalala, 101 F.3d 984, 986 (4th Cir. 1996)). After all, "the plain language of the statute" is "the most reliable indicator of Congressional intent." Schafer v. Astrue, 641 F.3d 49, 54 (4th Cir. 2011). Additionally, the Fourth Circuit has "described legislative history as one of the traditional tools of interpretation to be consulted at Chevron's step one." Nat. Elec. Mfrs.

Ass'n., 654 F.3d at 504–05 (citing Elm Grove Coal Co. v. Dir., O. W.C.P., 480 F.3d 278, 293-94 (4th Cir. 2007)).

Thus, the Court begins its Chevron step one inquiry into Congress's intent, as it must, from "the fundamental canon that statutory interpretation begins with the language of the statute itself." Butler v. West, 164 F.3d 634, 639 (D.C. Cir. 1999). Here, as mentioned, the relevant statute is section 505A(o) of the FDCA, which addresses certain situations where pediatric information on a brand's label may be omitted from the generic's label. Specifically, 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).

According to Otsuka, this language "directs FDA's approval authority by limiting the agency's ability to disapprove a generic drug based on specific pediatric labeling omissions." ECF No. 77 at 22. Because the statute does not expressly permit pediatric labeling protected by orphan drug exclusivity to be omitted from a generic label, FDA cannot, according to Otsuka, "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." Id. To do so, would, according to Otsuka, "require[] adding text to the statute that Congress adopted." Id. at 22.

In reaching this conclusion, however, Otsuka ignores the critical fact that section 505A(o) sets forth circumstances where FDA cannot deny approval for a labeling carve-out; it does not, as Otsuka contends, address situations where FDA can or cannot grant approval. Otsuka's effort to

turn section 505A(o) into a restriction on FDA's carve-out authority relies primarily on the principle of statutory construction known as expressio unius est exclusio alterius (the expression of one thing is the exclusion of another). See ECF No. 77 at 33. According to Otsuka, "[w]hen 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)." Id. at 23. The Court does not believe that, under the present circumstances, the expressio unius canon can be, or should be, applied to find the statute can only be interpreted as Otsuka suggests.

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) (finding expressio unius is not absolutely applied; there must be a "sensible inference that the term left out must have been meant to be excluded").

Here, Otsuka cites no evidence that Congress even contemplated orphan drug exclusivity at the time section 505A(o) was proposed and enacted, much less that Congress expressly considered orphan drug exclusivity and purposefully excluded it. In fact, at the April 28, 2015 hearing, the Court explicitly asked Counsel for Otsuka whether, in his obviously thorough research of the legislative history surrounding the enactment of section 505A(o), he or his

colleagues encountered any evidence to suggest that Congress expressly considered orphan drug exclusivity, to which he candidly replied that he had not. See ECF No. 99 at 17:8-15. In the absence of such evidence, Otsuka cannot rely on the expressio unius canon to turn section 505A(o) into a restriction on FDA's carve-out authority. See e.g., 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."); 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."); Greene v. United States, 79 F.3d 1348, 1355 (2d Cir.1996) ("The ancient maxim expressio unius est exclusio alterius . . . cautions us against engrafting an additional exception to what is an already complex [statutory scheme].").

To be sure, "the canon's relevance and applicability must be assessed within the context of the entire statutory framework." Adirondack Med. Ctr. v. Sebelius, 740 F.3d 692, 697 (D.C. Cir. 2014); *see Am. Bankers Ass'n v. Nat'l Credit Union Admin*., 271 F.3d 262, 267 (D.C. Cir. 2001) ("[W]e must not 'confine [ourselves] to examining a particular statutory provision in isolation. The meaning – or ambiguity – of certain words or phrases may only become evident when placed in context.'") (quoting FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 132 (2000))). Here, when the Court considers the statutory framework, as a whole, it cannot say that Otsuka's reading of section 505A(o) reflects Congress's clear intent in enacting the statute.

First, FDA has broad authority to approve ANDAs carving out exclusivities under the FDCA, including orphan drug exclusivity. That authority does not appear to be abrogated by section 505A(o), which, by its terms, constrains FDA's authority to refrain from approving an

ANDA, instead of, as Otsuka urges, constraining its authority to approve ANDAs. While it is generally true that generic drugs must contain the same information on their labels as the label of their respective brand-name pioneer drug, this principle does not require a generic drug's labeling to be identical to that of the listed drug it references in every respect. Instead, the same labeling rules contained in the Hatch-Waxman Amendments "reflect Congress's intent that the generic drug be safe and effective for each condition of use prescribed, recommended, or suggested in the generic drug labeling but do not require that an ANDA be approved for each condition of use for which the listed drug is approved." Ltr. from J. Peters to R. Tyler, Apr. 28, 2015, at 8. Indeed, the legislative history of these amendments demonstrates Congress's desire to permit ANDA applicants to carve out from their labels otherwise protected information. Specifically, Congress acknowledged that "[t]he bill permits an ANDA to be approved for less than all of the indications for which the listed drug has been approved. . . . [T]he applicant need not seek approval for all of the indications for which the listed drug has been approved." H.R. REP. NO. 98-857(I), at 21 (1984).

FDA's own regulations also demonstrate the authority granted by the FDCA to permit 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). The regulations permit FDA to 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). Additionally, section 314.94(a)(8)(iv) of the regulations also sets forth specific examples of permissible differences in labeling that may result because the generic drug product and listed drug product are produced or distributed by different

manufacturers. These differences 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 section 505(j)(5)(F) of the act." 21 C.F.R. § 314.94(a)(8)(iv) (emphasis added).

Finally, the Orphan Drug Act also confirms FDA's authority to approve ANDAs carving out an orphan drug exclusivity. Specifically, 21 U.S.C. § 360cc(a) 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" (emphasis added). Interpreting this language in Sigma-Tau Pharms., Inc. v. Schwetz, 288 F.3d 141 (4th Cir. 2002), the Fourth Circuit opined:

> By using the words 'such drug for such disease or condition,' Congress made clear its intention that [section 360cc] 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 360cc] 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.

Id. at 145. As such, the Fourth Circuit upheld the right of an ANDA to carve out an indication protected by orphan drug exclusivity as a permissible difference between the generic's label and the pioneer's label due to a difference in manufacturer. The Court noted that if it adopted Sigma-Tau's argument, this could mean that once FDA approves an orphan drug for a protected indication, "generic competitors might be prohibited from the market for almost any use." Id. at 147. The court further stated that "[Sigma-Tau's theory] to bar the approval of generic drugs, even for unprotected indications . . . [would add] a huge evidentiary hurdle to the generic drug

approval process [and] would be profoundly anti-competitive." Id. Accordingly, the Court rejected Sigma-Tau's argument and concluded that the statutory scheme permitted an ANDA applicant to carve out the orphan-protected indication at issue. See also Bristol Myers Squibb v. Shalala, 91 F.3d 1493, 1500 (D.C. Cir. 1996) (recognizing that the Orphan Drug Act "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).

Based on the statutory framework as a whole (as opposed to section 505A(o) in isolation), as well as relevant case law, the Court cannot conclude that section 505A(o) clearly proscribes FDA's ability to omit from a generic's label information pertaining to pediatric orphan drug exclusivity. Thus, if the Court's role here was simply to "interpret and apply the statute to resolve a claim," the Court would side with the interpretation of FDA and Defendant-Intervenors. See *Chevron,* 467 U.S. at 842. However, the Court cannot find that Congress's intent in enacting 505A(o), as it relates to its impact on orphan drugs, if any, is so clear as to completely foreclose Otsuka's interpretation.[5] The Court must therefore proceed to Chevron step two.

2. *Chevron*—Step Two

Finding that Congress has not "directly spoken to the precise question at issue," the Court moves to *Chevron*'s second step. *Chevron,* 467 U.S. at 842. At step two, the Court asks whether the "agency's [action] is based on a permissible construction of the statute." *Id.* The Court may

[5] There can be no debate that section 505A(o) does not address orphan drug exclusivities. Whether that was intentional in the manner Otsuka suggests, an oversight, or deemed unnecessary because of existing authority granted to the FDA to address the issue, is unclear from the text of the statute and the legislative history provided to the Court. Thus, while the Court has interpreted section 505A(o) in light of relevant authority, it also recognizes ambiguity in Congress's intent.

overturn the FDA's interpretation under *Chevron* step two only if the statute "unambiguously foreclosed the agency's statutory interpretation." Catawba Cnty., N.C. v. E.P.A., 571 F.3d 20, 35 (D.C. Cir. 2009). Thus, the Court will not "usurp an agency's interpretive authority by supplanting its construction with our own, so long as the interpretation is not 'arbitrary, capricious, or manifestly contrary to the statute.'" Philip Morris USA, Inc. v. Vilsack, 736 F.3d 284, 290 (4th Cir. 2013) (quoting Chevron, 467 U.S. at 844, 845). "A construction meets this standard if it 'represents a reasonable accommodation of conflicting policies that were committed to the agency's care by the statute.'" Id. Courts have been clear that "[r]eview under this standard is highly deferential, with a presumption in favor of finding the agency action valid." Ohio Vall. Envt'l Coalition v. Aracoma Coal Co., 556 F.3d 177, 192 (4th Cir. 2009).

Moreover, an agency's construction of its own regulations is entitled to "substantial deference," Thomas Jefferson Univ. v. Shalala, 512 U.S. 504, 512 (1994), and is accorded "controlling weight unless it is plainly erroneous or inconsistent with the regulation." Id. Broad deference to an agency is especially appropriate where, as here, "a complex and highly technical regulatory program" is concerned, requiring "significant expertise" and the "exercise of judgment grounded in policy concerns." Id. (citing Pauley v. BethEnergy Mines, Inc., 501 U.S. 680, 697 (1991)).

Here, as discussed above, the Court finds that the statute, case law, and FDA regulations all support the FDA's construction of the statute that allows it to carve out an indication or other information from ANDA labeling when that indication or information is protected by orphan drug exclusivity as long as the ANDA with that carved out label remains safe and effective for the remaining non-protected conditions of use. To be sure, Otsuka's reading of section 505A(o) would nullify the limitation expressly written into section 360cc – that the exclusivity is given to

a drug "for [the orphan] disease or condition" – and instead treat the orphan drug exclusivity as extending to the drug for any and all diseases and conditions, directly contradicting that provision's text and the Fourth Circuit's holding in Sigma-Tau. If that was Congress's intent, it is certainly left unclear by the statute.

Furthermore, the interpretation Otsuka seeks is directly contrary to FDA's prior decisions on orphan drug exclusivity carve-outs where that exclusivity incorporated pediatric information. In fact, FDA has, on multiple occasions over the past decade, 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. See ECF No. 82 at 27-28. Because "FDA has been consistent in how it has interpreted" the carve-out provisions over an extended period of time, the deference afforded to FDA's interpretation of its statute is particularly high. Hospira, Inc. v. Burwell, No.14-02662, 2014 WL 4406901, at *13 (D. Md. Sept. 5, 2014); see also Kasten v. Saint-Gobain Performance Plastics Corp., 131 S. Ct. 1325, 1336 (2011) (noting that the "length of the time the agencies have held" their position "suggests that [the position] reflect[s] careful consideration" and is entitled to deference). The Court therefore would likely find FDA's interpretation of the statute to be permissible. As such, the Court concludes that Otsuka is not likely to succeed on the merits and therefore denies Otsuka's motion for temporary restraining order and/or preliminary injunction. For the sake of completeness, the Court will also address the remaining factors for injunctive relief, which Otsuka also has not satisfied.

B. Irreparable Harm

Otsuka contends that, as a result of FDA's recent approvals, ANDA sponsors will flood the market with generic versions of Abilify® causing immediate and irreparable harm in the form of price erosion, loss of market share, loss of profits, discontinued or undercut research and educational opportunities, consideration of layoffs, and lost goodwill. See ECF No. 77 at 34.

While it is true that "'[p]rice erosion, loss of goodwill, damage to reputation, and loss of business opportunities'" all constitute potential and "'valid grounds for finding irreparable harm,'" the Court finds that these harms are not irreparable under the circumstances presented here. Aria Diagnostics, Inc. v. Sequenom, Inc., 726 F.3d 1296, 1304 (Fed. Cir. 2013) (quoting Celsis in Vitro, Inc. v. CellzDirect, Inc., 664 F.3d 922, 930 (Fed. Cir. 2012)).

Otsuka's main argument in support of irreparable harm is that it cannot recover monetary damages against FDA or Defendant-Intervenors in this action and that, as a result, their damages are irretrievable and irreparable. See ECF No. 77 at 33-34. That Otsuka is unable to recover monetary damages from FDA or Defendant-Intervenors does not, however, automatically make its harm irreparable. See N. Air Cargo v. USPS, 756 F. Supp. 2d 116, 125 n.6 (D.D.C. 2010) ("[P]rosepective injunctive relief would often cease to be an 'extraordinary remedy' in cases involving government defendants" if it were available whenever the plaintiff cannot recover damages from the defendant due to the defendant's sovereign immunity.). Instead, courts that have evaluated cases involving a company's irretrievable monetary loses typically find irreparable harm only where the monetary losses are so severe that they threaten the very existence of the company. See e.g., *Gulf Oil Corp. v. Dep't* of Energy, 514 F. Supp. 1019, 1026 (D.D.C. 1981) ("[I]njury must be more than simply irretrievable; it must also be serious in terms of its effect on the plaintiff."); *Sociedad Anonima Viña Santa Rita v. Dep't of Treasury*, 193 F. Supp. 2d 6, 14 (D.D.C. 2001) ("[F]inancial harm alone cannot constitute irreparable injury unless it threatens the very existence of the movant's business"); Mylan Labs., Inc. v. Thompson, 139 F. Supp. 2d 1, 27 (D.D.C. 2001) (recognizing that to satisfy the standard of irreparable injury to

justify a preliminary injunction, the movants' loss must be "more than simply irretrievable"). Otsuka has not met this burden here. [6]

For a long time now, Otsuka has been aware that it would eventually face generic competition for Abilify® and, like any other sophisticated pharmaceutical company, has prepared itself for the day when its exclusivity expired. Indeed, just recently at an Otsuka earnings presentation discussing its 2015 consolidated performance estimate, it was stated: "As you can see, we estimated the FY15 consolidated net sales JPY1.370 billion; operating income JPY110 billion; and net income JPY80 billion. Net sales i[s] forecasted to decline significantly as our overall performance driver, Abilify's patent will expire in the US."[7] As the company noted, however, "[n]eedless to say, Abilify is an important product for Otsuka Group. But in the past several years, sales of products we launched in Japan have been steadily increasing and contributing to the performance of the pharmaceuticals business." Id. (explaining "in terms of the pharmaceuticals business we have long prepared and accumulated assets and they are showing very good results"). Thus, far from sounding the death knell of Otsuka, the long expected loss of Otsuka's exclusivity of Abilify® has simply caused the company to launch other products that are "steadily increasing and contributing to the performance of the pharmaceuticals business." As such, the Court cannot find under these circumstances that Otsuka will suffer irreparable

[6] In its brief and at the hearing, Otsuka cited Smoking Everywhere, Inc. v. FDA, 680 F. Supp. 2d 77 (D.D.C. 2010) to support its argument that irretrievable economic harm equates to irreparable harm in the context of sovereign immunity. But, just like the cases cited above, the Smoking Everywhere court recognized economic harm as irreparable only because it was substantial enough to meet the standard adopted by the majority of courts (i.e., because plaintiff's entire product line was at stake under FDA's regulatory decision). On appeal, the D.C. Circuit affirmed the District Court's finding of irreparable harm, not because it was per se irreparable due to sovereign immunity, but because the FDA's action had "obviously destroyed the firm's ability in the United States to cover its costs for purchase or production of e-cigarettes." Sottera, Inc. v. FDA, 627 F.3d 891, 898 (D.C. Cir. 2010).

[7] See Full Year 2014 Otsuka Holdings Co. Ltd. Earnings Presentation Webcast—Final, FD (Fair Disclosure) Wire, Feb. 13, 2015 (available in LEXIS Current News file).

harm from its loss of exclusivity, pending resolution of this lawsuit, since the concomitant monetary losses are not severe in nature given Otsuka's business and planning and preparation for this occurrence.

Nor is the Court convinced that Otsuka will experience irreparable harm with respect to potential price erosion. Given the expedited nature of this case and the fact that it will likely be resolved in a matter of weeks, the price erosion that could take place in the interim would likely be de minimis. If Otsuka prevails, it would be entitled to seven years of full market exclusivity, during which it would be able to reestablish its price points. Additionally, Otsuka admits that it can counteract price erosion by offering payers incentives and rebates. See ECF No. 77 at 37.

Otsuka also makes various arguments regarding harm to its sales force, educational and research efforts, and goodwill. Under the facts of this case, the Court finds that this alleged harm is not sufficient to support a showing of irreparable harm. The "required 'irreparable harm' must be 'neither remote nor speculative, but actual and imminent.'" Direx Israel, Ltd. v. Breakthrough Med. Corp., 952 F.2d 802, 812 (4th Cir. 1991) (quoting Tucker Anthony Realty Corp. v. Schlesinger, 888 F.2d 969, 975 (2d Cir.1989)); see also ECRI v. McGraw–Hill, Inc., 809 F.2d 223, 226 (3d Cir. 1987) ("Establishing a risk of irreparable harm is not enough. A plaintiff has the burden of proving a 'clear showing of immediate irreparable injury.'"). Here, the Court concludes that the alleged harm to Otsuka's sales force, educational and research efforts, and goodwill is too speculative to demonstrate irreparable harm.

C. Balance of Hardship

Next, the Court must balance the hardship that Otsuka will suffer if generic versions of Abilify® continue to be sold against the hardship Defendant-Intervenors would suffer if they were prohibited from continuing to sell these generic drugs. In resolving this factor, the Court

need not look any further than Judge Simandle's recent discussion of this issue in a related case from the District of New Jersey in which Judge Simandle denied Otsuka's motion for a temporary restraining order and/or preliminary injunction against Defendant-Intervenors and others. See Otsuka Pharm. Co. v. Torrent Pharm. Ltd., Inc., No. 14-1078, 2015 WL 1782653 (D.N.J. Apr. 16, 2015).

Judge Simandle observed that "[t]he hardship on a preliminarily enjoined generic which has taken affirmative steps to enter the market can be devastating." *Otsuka Pharm. Co.*, No. 14-1078, 2015 WL 1782653, at *30. Judge Simandle further recognized that "Defendants[8] have all taken affirmative steps to enter the aripiprazole market, by developing and testing aripiprazole products, preparing ANDAs, seeking regulatory approval from the FDA, ordering raw materials, and preparing manufacturing and supply pipelines." *Id.* As such, Judge Simandle concluded that "[t]he issuance of an injunction would seriously erode these and related efforts" and that "Defendants would face the loss of all of the 'costly enterprises' made to prepare their products 'in readiness of ultimate FDA approval and commercial launch' on April 20, 2015." *Id.* (quoting *Graceway Pharm., LLC v. Perrigo Co.*, 697 F. Supp. 2d 600, 605 (D.N.J. 2010)). Additionally, Judge Simandle found that "the issuance of a TRO would deprive these Defendants of the advantage of being an early market entrant, and may force these Defendants to ultimately launch with competitors that would otherwise have only been able to launch *after* these early entrants." *Otsuka Pharm. Co.*, No. 14-1078, 2015 WL 1782653, at *30. (emphasis in original); *see Bracco Diagnostics, Inc. v. Shalala,* 963 F.Supp. 20, 29 (D.D.C. 1997) ("[T]here is a significant economic advantage to receiving first approval and being the first company to enter the market, an advantage that can never be fully recouped through money damages or by 'playing catch-

[8] The Court notes in that case the "Defendants" included all of the Defendant-Intervenors in this case, as well as others parties who have not intervened here.

up.'"); *see also Mova Pharm. Corp. v. Shalala,* 140 F.3d 1060, 1066 n.6 (D.C. Cir. 1998) (finding that party will be "harmed by the loss of its 'officially sanctioned head start'"); *Sandoz, Inc. v. FDA,* 439 F.Supp.2d 26, 32–33 (D.D.C. 2006) (finding that delayed entry to market tilts the balance of hardships). Based on these findings, Judge Simandle held "that the balance of hardships tips in favor of these generic Defendants." *Otsuka Pharm. Co.*, No. 14-1078, 2015 WL 1782653, at *31. The Court sees no reason to depart from this well-reasoned conclusion, especially given Otsuka's weak showing of likelihood of success, which tips the balance of hardships towards Defendant-Intervenors. *See Illinois Tool Works, Inc. v. Grip-Pak, Inc.*, 906 F.2d 679, 683 (Fed. Cir. 1990) ("In the present case, as the district court found, ITW's weak showing of likelihood of success tips the balance of hardships toward Grip–Pak.").

D. Public Interest

Finally, the Court concludes that Otsuka has failed to demonstrate how the public's interest would be served by the issuance of a temporary restraining order. If anything, the public's interest would be disserved by such relief. Again, Judge Simandle's recent discussion on this factor is on point. Judge Simandle observed that:

> In enacting the Hatch–Waxman Act, Congress 'struck a balance between two competing policy interests: (1) inducing pioneering research and development of new drugs and (2) enabling competitors to bring low-cost, generic copies of those drugs to market.' *Dey Pharma, LP v. Sunovion Pharm. Inc.*, 677 F.3d 1158, 1159 (Fed. Cir. 2012) (quoting *Andrx Pharm., Inc. v. Biovail Corp.,* 276 F.3d 1368, 1371 (Fed. Cir. 2002)).

Otsuka Pharm. Co., No. 14-1078, 2015 WL 1782653, at *31. Here, Otsuka has already benefited from over twelve years of market exclusivity for Abilify®. As such, Judge Simandle concluded that:

> Otsuka has long enjoyed the exclusive rights to the aripiprazole market in the United States and has, in turn, been duly rewarded

> for bringing its innovation to market. In fact, Otsuka's aripiprazole exclusivity has generated, in the last eight years alone, over $100 billion in revenue. The public's interest in encouraging and rewarding innovation has been well served already. Given this, Otsuka has had ample opportunity to fully and completely realize a return on its investment, many times over, and to adjust its business as it deemed necessary in order to address the loss of exclusivity it knew, for years, rested upon the horizon.

Id. Again, the Court sees no reason to depart from Judge Simandle's conclusion. Under these circumstances then, the Court is not convinced that Otsuka's desire to obtain an additional seven years of exclusivity should yield to the public's interest in bringing lower-cost generic versions of Abilify® to the market. Nor is the Court persuaded by Otsuka's argument that "the public interest [is] best served by ensuring agency compliance with its governing statute" (*see* ECF No. 77-39), since the Court has already concluded that Otsuka is unlikely to succeed on the merits. Otsuka has therefore failed to satisfy the fourth prong for injunctive relief. Accordingly, the Court will deny Otsuka's request for a temporary restraining order and/or preliminary injunction.

III. CONCLUSION

For the reasons stated above, the Court will DENY Otsuka's motion for temporary restraining and/or preliminary injunction.

Dated: April 29, 2015

/S/
George J. Hazel
United States District Judge