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 SUMMARY JUDGMENT

Pursuant to Fed. R. Civ. P. 56, plaintiffs Otsuka Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Development & Commercialization, Inc., and Otsuka America Pharmaceutical, Inc. (collectively, "Otsuka") respectfully move for summary judgment on their claim that the April 28, 2015 final agency decision of the United States Food and Drug Administration ("FDA") (AR 488-502) is arbitrary, capricious, and contrary to law. The material facts are not in dispute and Otsuka is entitled to a judgment reversing and vacating FDA's decision. Otsuka's motion relies upon the administrative record and the attached memorandum. A proposed form of Final Judgment is attached.

Respectfully submitted,

Dated: May 11, 2015

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MEMORANDUM IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT

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Introduction

In this action, plaintiffs Otsuka Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Development & Commercialization, Inc., and Otsuka America Pharmaceutical, Inc. (collectively, "Otsuka") challenge the lawfulness of the April 28, 2015 final agency decision of the defendant United States Food and Drug Administration ("FDA"). FDA determined "that generic versions of [Otsuka's prescription brand drug] Abilify that otherwise meet the standards for approval may be approved during the orphan drug exclusivity period for Abilify." AR 488. This decision is unlawful and should be vacated. FDA is without authority to approve generic versions of Abilify in violation of the limited circumstances in which a generic's label may omit pediatric information present on Abilify's label.

In 2001, Congress became acutely aware of how two basic drug labeling principles operate to prevent certain generic approvals and, in response to this problem, Congress crafted the solution that is at the heart of this case. The relevant background labeling principles are that (1) generally a generic's label must be the same as its predicate reference listed drug, *see* 21 U.S.C. § 355(j)(2)(A)(v), (j)(4)(G); 21 C.F.R. §§ 314.94(a)(8)(iv), 314.127(a)(7); and (2) pediatric information, including information related to pediatric use, must be included in the label, *see* 21 C.F.R. § 201.57(c)(2)(i)(B), (c)(3)(C), (c)(9)(iv)(B)-(C); *see also* 21 U.S.C. § 352(f). Congress recognized that FDA's own regulation prohibited the agency from carving out pediatric information which, in turn, meant that FDA was precluded from approving a generic version of a brand drug where the brand's label included pediatric information. To address this issue, while leaving in place FDA's pediatric labeling regulation, Congress enacted Section 505A(o) of the Federal Food, Drug and Cosmetic Act ("FDCA"), 21 U.S.C. § 355a(o). Section 505A(o) allows certain defined categories of pediatric information to be omitted from the label of a generic (*i.e.*, where it is protected by patent and three-year Hatch Waxman exclusivity) notwithstanding the

same labeling rule and FDA's pediatric labeling regulations. Congress left undisturbed FDA's pediatric labeling regulations, and those regulations remain in effect.

When the Senate Health, Education, Labor, and Pension ("HELP") Committee was working on a predecessor bill for what was ultimately enacted as the Best Pharmaceuticals for Children Act ("BPCA") and included Section 505A(o), the Committee was also then considering orphan drug issues, and specifically orphan drug exclusivity. No serious argument can be made that Congress was unaware of orphan drug exclusivity. Notwithstanding this awareness, Congress chose to omit from Section 505A(o) orphan drug exclusivity as a category of pediatric information that can be omitted from a generic's label.

Rather than giving proper effect to Section 505A(o), FDA's expressly stated positions range from "we don't even need to look at 505A(o)," Transcript, at 36 (Apr. 28, 2015), to Section 505A(o) is merely "complementary to FDA's longstanding approach to labeling carve outs." AR 499. FDA ignores the plain text of Section 505A(o); ignores the statute's legislative history and context; ignores the relationship between the statute and FDA's own pediatric labeling regulations; and ignores controlling principles of statutory construction. In place of and in violation of the statute Congress enacted, FDA invokes the truly novel doctrine that it can disregard a statute to pursue a favored policy of carving out anything, as much as it wants, and without limitation, so long as safety and efficacy are not affected. The law with respect to pediatric labeling is to the contrary.

Statement Of Undisputed Material Facts

A. Abilify's FDA-Approved Orphan Drug Protected Indication For The Treatment Of Tourette's Disorder In Pediatric Patients

Otsuka is the New Drug Application ("NDA") holder for the drug aripiprazole, which it markets under the brand name Abilify. AR 488-89. FDA first approved Abilify on November 15,

2002, and on December 12, 2014, FDA approved Abilify for a new indication for the treatment of Tourette's Disorder in the pediatric population. *Id.* 170, 489. After issuing that approval, FDA engaged in a series of regulatory twists and turns with respect to the scope of the approval, vacillating back and forth between whether the approved indication was limited to pediatric patients or included the population at large. Presumably, the agency was trying to figure out how to avoid Section 505A(o). In any event, FDA has failed to proffer an alternative explanation for its odd behavior, including first concluding that generics did not need to include a pediatric disclaimer as provided for in Section 505A(o)(2)(A), *id.* 768-73, and then changing its mind after this litigation was filed, *id.* 854-934.

The first of FDA's twists on the scope of Abilify's Tourette's indication followed a January 2015 request to FDA's Chief Counsel from counsel for Otsuka for a meeting to discuss issues arising from the approval of Abilify for the pediatric Tourette's indication. *Id.* 274. In a letter, counsel set forth briefly Otsuka's position that FDA's approval of the pediatric Tourette's indication 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 exclusivity for the new indication. *Id.* 274-75. Counsel requested a meeting to discuss the issue, *id.* 276, but FDA never granted that request.

Not long after receiving notice of Otsuka's position, however, FDA, on February 24, sent Otsuka a "corrected" approval letter in which FDA stated that its earlier December 12 approval letter "contained an error in the 'indications' section." *Id.* 364. FDA purported to correct the "error" by broadening the indication from treatment "in pediatric patients with Tourette's Disorder" to treatment of "patients with Tourette's Disorder." *Id.* 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***." *Id.* 453. On March 9, Otsuka inquired as to whether FDA "consider[s] the supplemental approval to be for the treatment of Tourette's disorder in the general population, or [whether] . . . the approval [is] limited to the pediatric population in which Otsuka demonstrated safety and efficacy." *Id.* 455. FDA responded two days later: "We consider the supplemental approval to be for the treatment of Tourette's disorder in the general population." *Id.* 456.

Because the broad "general population" indication was not supported by the clinical trials conducted in patients ages 6-18, *id*. 434, 456, on March 18, Otsuka asked FDA to rescind the broadened approval granted in the February 24 letter. *Id.* 456. When FDA did not respond, Otsuka filed this lawsuit on March 24. Count one of Otsuka's complaint challenged the lawfulness of FDA's broadened approval decision of Abilify for the treatment of Tourette's Disorder in the general population. ECF No. 1. Count two sought a declaratory judgment that, assuming without conceding the validity of the broadened approval, FDA was nevertheless precluded as a matter of law from approving generic versions of Abilify. *Id.*

On March 27, after Otsuka commenced this litigation, 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. This claimed "confusion" was a smokescreen. Prior to February 24, FDA had not communicated that it had ever considered the approval for the new Tourette's indication to be for the general population; rather, the December 12 letter informed Otsuka, consistent with its clinical data and Otsuka's FDA-approved labeling, that Otsuka's approval was for a pediatric Tourette's indication. Nevertheless, FDA's March 27 letter claimed, contrary to the text of FDA's December 12 and February 24 letters, that "the corrected approval did not broaden the indication or the scope of the underlying approval." AR 465-66. FDA's March 27 letter went on to state unequivocally

that there is no limitation of use based on age and that "[t]he indication was . . . unchanged when the approval letter was corrected." *Id.* FDA quickly abandoned this position. Late in the day on Friday, April 10, as FDA faced an imminent deadline to comply with a Court order to supplement the administrative record, FDA issued yet another letter. In that letter, FDA reversed field and concluded that "the approval of Abilify for Tourette's Disorder is only for the pediatric population," *id.* 468, directly contrary to its March 27 "age unlimited" position.

Otsuka filed immediately a motion to stay this case pending FDA's decision on Otsuka's exclusivity, ECF No. 59, and, with leave of Court, Otsuka filed its present amended complaint. ECF No. 76-1. Otsuka also filed a motion for a temporary restraining order and/or preliminary injunction. ECF No. 77. The Court ordered FDA to notify the Court *ex parte* 24 hours prior to the agency's decision to approve or reject ANDAs for generic Abilify, as well as its decision on Otsuka's exclusivity. ECF No. 64. On April 27, the Court notified the parties that a hearing would be held the following afternoon, April 28. Following that hearing, the Court denied Otsuka's motion. ECF No. 100.

B. FDA's April 28, 2015 Decision

Shortly before the scheduled hearing on April 28, FDA sent Otsuka a letter denying its exclusivity rights. FDA determined that Section 505A(o) is inapplicable to the present situation. Transcript, at 32, 35 (Apr. 28, 2015) ("There is no need to reference 505A(o)" and "505A(o) is not relevant to this analysis."). FDA decided that Section 505A(o) did not prevent the agency from approving generic versions of Abilify that omitted, or carved out, references to Abilify's pediatric Tourette's Disorder indication. AR 488-502. FDA interpreted Section 505A(o) as applying only "where a listed drug is approved in adults and pediatric patients for the same indication but protected by HW exclusivity for that use in pediatric patients." *Id.* 497.

Moreover, FDA concluded that Section 505A(o) is just an "additional tool[]" that is applicable only where there is a safety issue. *Id.* 497 ("Section 505A(o) . . . gave FDA additional tools to ensure that ANDAs are adequately labeled and not unnecessarily blocked in cases where pediatric labeling is protected by HW exclusivity and absence of this information has safety implications and the potential to misbrand the product."); *id.* 498 ("This provision does not limit FDA's authority to carve out pediatric labeling where a carve-out would otherwise be appropriate; instead, it provides FDA with additional authority to retain HW-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)."). In the agency's view, "[Section 505A(o)] does not limit but, in fact, is complementary to FDA's longstanding approach to labeling carve-outs under section 505(j)." *Id.* 499.

FDA made two additional points. First, if Section 505A(o) did apply, which FDA denies, Otsuka's orphan drug exclusivity would be subsumed by Section 505A(o)'s reference to three-year new clinical studies exclusivity. *Id.* 500. Second, if orphan drug exclusivity is not subsumed by three-year exclusivity, FDA's general carve-out authority would nevertheless allow the omission of orphan drug protected information from a generic's labeling. *Id.* 500-01.

C. FDA's Final Approval Of Generic Versions Of Abilify

The content of FDA's generic approvals and the administrative record contradict the stated conclusion in FDA's decision that Section 505A(o) does not apply here because Abilify is not indicated for the adult population for the treatment of Tourette's Disorder in addition to the pediatric population. In December 2014, FDA requested an internal consultation "on the carve-out or retention of protected pediatric information from generic aripiprazole tablets." AR 767-68. On February 23, 2015 (only one day before FDA sent Otsuka its "corrected" broadened approval

decision, *see id.* 364-452), FDA concluded that Section 505A did not require generic labels to include a disclaimer about omitted pediatric labeling under Section 505A(o)(2). *Id.* 771-72. FDA then changed its mind in late April (after finally agreeing with Otsuka that the Tourette's indication was for the pediatric population only, *id.* 468-70), concluding that Section 505A applied and that a disclaimer in the generics' labels would be required. *Id.* 858-59.

Simultaneous with FDA's denial of Otsuka's exclusivity rights on April 28, FDA issued final approvals for aripiprazole to four generic pharmaceutical companies. AR 643-45, 660-62, 678-80, 696-98, 714-16, 733-35, 750-52. Tellingly, the FDA-approved labels for these generics confirm that 505A(o)(1) & (2) does apply here, despite the absence of an adult indication for Tourette's. The generic labels include a pediatric disclaimer as contemplated by Section 505A(o)(2)(A). *Id.* 663-65 (Teva 10mg tablets); *id.* 681-83 (Teva 15mg, 20mg, and 30mg tablets); *id.* 699-701 (Torrent 2 mg, 5mg, 10mg, 15mg, 20mg, and 30mg tablets); *id.* 717-20 (Alembic 2 mg, 5mg, 10mg, 15mg, 20mg, and 30mg tablets); *id.* 736-39 (Alembic 10mg and 15mg orally disintegrating tablets).[1] The disclaimer FDA required states: "Additional pediatric use information is approved for Otsuka America Pharmaceutical, Inc.'s ABILIFY® (aripiprazole) product. However, due to Otsuka America Pharmaceutical, Inc.'s marketing exclusivity rights, this drug product is not labeled with that information." *Id.* 858-59.

The generic labels also include other safety information required by Section 505A(o)(2)(B). The generic labels include safety information related to the omission of the Tourette's indication as follows: "**Less Common Adverse Reactions in Pediatric Patients (6 to 18 years) with Schizophrenia, Bipolar Mania *or Other Indications*** Table 20 enumerates the

[1] The version of Hetero USA, Inc.'s label that FDA has included in the administrative record is not readable. AR 753-74.

pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks in schizophrenia, up to 4 weeks in bipolar mania, up to 8 weeks in one indication, and *up to 10 weeks in another indication*) . . . ." AR 646, 663, 681, 699, 717, 736 (italics added). In Otsuka's Abilify label, the reference to 10 weeks is to Tourette's Disorder. *Id.* 398. Again, though the Tourette's indication is not for the adult population, the generic labels include safety information as required by Section 505A(o)(2).

Argument

FDA's letter decision lacks any serious analysis of the statutory text and the legislative history of Section 505A(o). In addition, and perhaps most significantly, FDA's decision makes no attempt to square the decision's ultimate conclusion that pediatric information on Abilify's label may be omitted from the label of generics with FDA's own regulation requiring all prescription drugs (generics included) to include pediatric information on their labels. Without reference to statutory text or legislative history, and without any reasoned basis, FDA boldly interprets Section 505A(o) as applying only "where a listed drug is approved in adults and pediatric patients for the same indication but protected by HW [Hatch-Waxman] exclusivity for that use in pediatric patients only" and as an "additional tool[] to ensure that ANDAs are adequately labeled and not unnecessarily blocked in cases where pediatric labeling is protected by HW exclusivity and absence of this information has safety implications and the potential to misbrand the product."

All of the tools applicable to determining Congress's intent – statutory text, context, and legislative history – make clear that Congress enacted Section 505A(o) to speak directly to the question of when a brand drug's pediatric labeling, which FDA's regulations otherwise require to be included, may be omitted from a generic's label. FDA's interpretation of Section 505A(o) cannot stand because it reaches a conclusion directly contrary to the one Congress directed.

I. Otsuka's Administrative Procedure Act Claim Is Properly Resolved On Cross-Motions For Summary Judgment.

Otsuka's complaint challenges final agency action under the Administrative Procedure Act ("APA"). Summary judgment under Fed. R. Civ. P. 56(a) is the proper "mechanism for deciding, as a matter of law, whether the [challenged] agency action is supported by the administrative record and otherwise consistent with the APA standard of review." *Roberts v. United States*, 883 F. Supp. 2d 56, 62-63 (D.D.C. 2012); *see also Hospira, Inc. v. Burwell*, No. GJH-14-02662, 2014 U.S. Dist. LEXIS 123972, *26 (D. Md. Sept. 5, 2014) ("'[T]he function of the district court is to determine whether or not as a matter of law the evidence in the administrative record permitted the agency to make the decision it did.'" (quoting *Kaiser Found. Hosps. v. Sebelius*, 828 F. Supp. 2d 193, 198 (D.D.C. 2011))).

II. Otsuka Is Entitled To Judgment Because FDA's Decision Is Contrary To Law.

A. *Chevron* Does Not Apply.

As a threshold matter, the Court must determine the level of deference to give FDA's April 28 decision. While the Court previously indicated that its analysis would proceed under *Chevron*, ECF No. 100, at 9-10, an approach with which Otsuka's counsel agreed, Transcript, at 16, 21-22 (Apr. 28, 2015), the receipt of FDA's decision (which Otsuka received shortly before the April 28 hearing) and further research establish that *Chevron* deference is inapplicable.

"*Chevron* deference is generally reserved for agency interpretations set forth after notice-and-comment rulemaking or a formal adjudication under 5 U.S.C. § 556-557." *Medicines Co. v. Kappos*, 731 F. Supp. 2d 470, 475 (E.D. Va. 2010) (citing *United States v. Mead*, 533 U.S. 218, 231-34 (2001)). Agency actions falling short of *Chevron* warrant the less restrictive deference under *Skidmore v. Swift & Co.*, 323 U.S. 134 (1944). *See id.* at 477; *cf. Christensen v. Harris County*, 529 U.S. 576, 587 (2000) ("Interpretations such as those in opinion letters – like

interpretations contained in policy statements, agency manuals, and enforcement guidelines, all of which lack the force of law – do not warrant *Chevron*-style deference."); *U.S. v. Undetermined Quantities of Articles of Drug*, 145 F. Supp. 2d 692, 697 (D. Md. 2001) (FDA guidance warranted *Skidmore* deference). Under *Skidmore*, an agency interpretation "receives weight in proportion to its 'power to persuade,' as measured by factors like 'the thoroughness evident in its consideration, the validity of its reasoning, [and] its consistency with earlier and later pronouncements." *Shipbuilders Council of Am., Inc. v. U.S. Dep't of Homeland Security*, 673 F. Supp. 2d 438, 453 (E.D. Va. 2009).

Whether a court should give *Chevron* deference depends on whether "Congress delegated authority to the agency generally to make rules carrying the force of law, and . . . the agency interpretation claiming deference was promulgated in the exercise of that authority." *Mead*, 533 U.S. at 226-27. Relevant considerations are "the interstitial nature of the legal question, the related expertise of the Agency, the importance of the question to the administration of the statute, the complexity of that administration, and the careful consideration the Agency has given the question over a long period of time." *Barnhart v. Walton*, 535 U.S. 212, 222 (2002).[2] In *Innovator Enterprises v. Jones*, 28 F. Supp. 3d 14, 22-24 (D.D.C. 2014), for example, the court concluded that *Chevron* did not apply to a "brief and informal" agency letter that, among other things, "contain[ed] hardly any reasoning," "ma[de] no reference to prior agency regulations or interpretations that support its conclusion," "appear[ed] to be a non-binding statement of the

[2] *See generally Innovator Enters. v. Jones*, 28 F. Supp. 3d at 22 ("The D.C. Circuit has recently confirmed that Barnhart now supplies the determinative analysis at Chevron step zero."). *But see Shipbuilders Council*, 673 F. Supp. 2d at 453 (rejecting position that *Barnhart* has replaced *Mead*); *Co. Doe v. Tenenbaum*, 900 F. Supp. 2d 572, 589 n.6 (D. Md. Oct. 16, 2012) (applying *Mead* at *Chevron* step zero but not considering whether *Barnhart* clarified that standard), *rev'd sub nom. Doe v. Tenenbaum*, 749 F.3d 246 (4th Cir. 2014).

agency's position on [the issue], which will not bear the force of law as applied in future classifications of different devices," and "the relevant legal question present[ed] a fairly conventional statutory interpretation issue."

Here, FDA's interpretation of Section 505A(o) is only entitled to the more limited *Skidmore* level "power to persuade" deference. FDA issued a plainly inadequate, rushed decision a mere three months after Otsuka notified FDA of its position in letter containing an abbreviated two page argument meant only to set the stage for a meeting. Rather than engage with Otsuka and hear its views in full or solicit a range of comments through a public docket, as FDA has done on prior occasions, FDA ignored Otsuka's request for a meeting. FDA's sole response to Otsuka's letter was its April 28 decision, a letter that is long on background and short on analysis (a mere four pages, AR 496-99), and the few pages in which FDA sets forth its interpretation of Section 505A(o) lack any careful analysis of the statutory text or legislative history as well as being thin on legal authority. FDA's decision demonstrates that this issue is unprecedented, so FDA has no prior decisions to guide it. FDA's inexperience with this exact issue has resulted in an inconsistent decision: FDA's decision states that 505A(o) only applies where there is an adult and pediatric indication for the same use (*i.e.*, not here), yet FDA actually applies 505A(o)(2) in this case to require certain generic labeling regarding the Tourette's indication.

Given the highly informal nature of FDA's decision-making process, the Court should afford FDA's decision only *Skidmore* deference and hold that it lacks the "power to persuade."[3]

[3] Cases from the D.C. Circuit are not precedential here or are distinguishable. *E.g.*, *Mylan Labs., Inc. v. Thompson*, 389 F.3d 1272, 1277-78, 1280 (D.C. Cir. 2004) (two parties sought a determination from FDA, FDA issued a decision in two letters, and "FDA's decision made no great legal leap but relied in large part on its previous determination of the same or similar issues and on its own regulations"); *ViroPharma, Inc. v. Hamburg*, 898 F. Supp. 2d 1, 13 (D.D.C. 2012) (challenge to "comprehensive letter ruling" denying citizen petition).

B. Under *Skidmore* Or *Chevron*, FDA's Interpretation Fails Because Section 505A(o) Is Clear.

In Section 505A(o), Congress "directly spoke[] to the precise question" of when pediatric indications and other information pertaining to pediatric use may be omitted from a generic's label. *See Nat'l Elec. Mfrs. Ass'n v. U.S. Dep't of Energy*, 654 F.3d 496, 504 (4th Cir. 2011) (quoting *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 842-43 (1984)). Congress provided that only pediatric labeling protected by patent and three-year new clinical studies exclusivity could be omitted from a generic's label. Even if the Court determines that "the statute is silent or ambiguous with respect to the specific issue," *Nat'l Elec. Mfrs.*, 654 F.3d at 504-05, FDA's interpretation is not a permissible or reasonable construction of Section 505A(o) and lacks any power to persuade.

1. Section 505A(o) Prohibits FDA From Approving A Generic Drug That Omits Pediatric Labeling Protected By Orphan Drug Exclusivity.

Congress enacted Section 505A(o) to address when and what kinds of pediatric information may be omitted from a generic's label. "[T]hat is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Nat'l Elec. Mfrs.*, 654 F.3d at 504-05 (noting that, "in consulting legislative history at step one of *Chevron*, we have utilized such history only for limited purposes, and only after exhausting more reliable tools of construction").

a. The Text Of Section 505A(o)

Section 505A(o)(1) 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 exclusivity under [21 U.S.C.

§ 355(j)(5)(F)(iii) or (iv)]." 21 U.S.C. § 355a(o)(1). By its plain terms, the statute defines FDA's approval authority by expressly limiting the agency's authority to disapprove a generic drug based on specific pediatric labeling omissions.

i. Section 505A(o) Defines FDA's Approval Authority With Respect To Pediatric Labeling.

In Section 505A(o), Congress expanded FDA's carve-out authority with respect to pediatric labeling by limiting the agency's generic disapproval authority. Prior to the enactment of Section 505A(o), FDA's pediatric labeling regulations, which mandate that pediatric information be included on every label, prevented FDA from approving a generic version of a drug omitting pediatric labeling. That is, FDA could not, under its general carve-out authority, permit a generic to omit pediatric labeling because of the agency's own pediatric labeling requirements. *See* Part II.B.1.b. In Section 505A(o), Congress expanded FDA's carve-out authority with respect to pediatric labeling, but only to the extent of patent and three-year Hatch-Waxman exclusivity.

Section 505A(o) addresses, as its title states, the "[p]rompt approval of drugs under section 355(j) *when pediatric information is added to labeling*." (emphasis added). Acting in response to FDA's inaction and failure to approve a generic version of Bristol Myers Squibb's ("BMS") drug Glucophage, Congress enacted Section 505A(o) to require FDA to approve generic versions of the drug (and, as such, expanded FDA's carve-out authority). *See infra* Part II.B.1.c. The plain text of the statute requires FDA to approve generic drugs notwithstanding the omission of pediatric labeling by limiting FDA's authority to disapprove generic drugs – *i.e.*, "A drug for which an application has been submitted or approved under section 355(j) . . . shall not be considered ineligible for approval . . . or misbranded." Thus, FDA shall approve a generic where pediatric labeling information protected by patent or Hatch-Waxman exclusivity is omitted, because FDA cannot declare it ineligible for approval under § 355(j) or misbranded under § 352.

In denying Otsuka's motion for injunctive relief, the Court concluded that "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." ECF No. 100, at 11. Respectfully, that linguistic distinction is not a substantive difference. The absence of the words "FDA shall grant approval where 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" does not mean that the statute fails to "address situations where FDA can or cannot *grant* approval." Congress's negative phrasing defines FDA's approval authority no less than positive phrasing would have. *See, e.g.*, *Marine Space Enclosures, Inc. v. Fed. Maritime Comm'n*, 420 F.2d 577, 583-84 (D.C. Cir. 1969) (interpreting a statute that required a hearing prior to the Commission's decision to "disapprove, cancel or modify any agreement" to require a hearing prior to approval of an agreement); *Colon v. U.S. Dep't of State*, 2 F. Supp. 2d 43, 45 (D.D.C. 1998) ("[T]he absence of language pertaining to the denial of a certificate rather than approval of one in the last sentence of § 1501 cannot be construed to mean what Plaintiff argues: that while the approval of certification is an appealable final agency determination, the disapproval of certification is not.").

Here, Congress simply chose, as it was free to do, to define FDA's approval authority by limiting when FDA cannot deny approval when it comes to pediatric labeling, rather than when FDA shall grant approval. Under either formulation, however, the outcome is the same. Congress directed when FDA shall approve generic drugs (*i.e.*, "shall not be declared ineligible or misbranded"), assuming, of course, other conditions for approval are satisfied. In any event, when the statute directs FDA not to disapprove an ANDA that omits certain pediatric labeling, FDA has no license to grant approvals omitting, as here, pediatric indications or information beyond the

categories expressed in Section 505A(o). *See* 147 Cong. Rec. H8105 (daily ed. Nov. 13, 2001) ("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)).[4]

Congress expressed its definition of FDA's approval authority with a double negative (*i.e.*, "shall not be considered ineligible or misbranded"). This double negative acts as a positive constraint; that is, in the absence of satisfying the double negative condition, FDA cannot grant approval. *Adams v. State Livestock Facilities Siting Review Bd.*, 2010 WI App. 88, 787 N.W.2d 941 (Wisc. Ct. App. 2010), demonstrates this point. There, the court interpreted a law stating, "Notwithstanding [statutory provisions], a political subdivision may not disapprove or prohibit a livestock facility siting or expansion unless at least one of the following applies . . . ." *Id.* at ¶ 17. The court rejected an argument that the statute did not "apply when a municipality *approves* a permit" because "[t]he double negative 'may not disapprove' necessarily means 'must approve.'" *Id.* ¶¶ 18-19. Thus, "[p]roperly read," the statutory provision "directs that a political subdivision must approve a livestock siting or expansion application, unless a listed exception applies." *Id.* ¶ 19; *cf. Ford Motor Co. v. Kahne*, 379 F. Supp. 2d 857, 861 n.3 (E.D. Mich. 2005) (interpreting contract provision with double negative, "Ford has the right to deny participation where Ford feels the team is incompatible . . . , but *disapproval* will not be unreasonably withheld" as meaning, "[b]y not withholding disapproval, Ford would be giving its approval").

ii. Section 505A(o) Does Not Permit FDA To Omit Pediatric Labeling Information Protected By Orphan Drug Exclusivity.

[4] Directing FDA to approve generics when these precise circumstances exist with respect to pediatric labeling does not ignore the other reasons why FDA could refuse to approve a generic drug (*e.g.*, manufacturing deficiencies). Otsuka's construction is consistent with the framework of the rest of the FDCA in that, as instructed in Section 505A(o)(3)(D), "the operation of section 355" is not otherwise affected, including FDA's approval authority, *see* § 355(j).

(a) **The Text Only Refers To Patent Protection And Three-Year Exclusivity.**

Orphan drug exclusivity is granted pursuant to Section 527 of the FDCA, *see* 21 U.S.C. § 360cc. Section 505A(o), however, mentions only "pediatric indication[s] 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 [Section 505(j)(5)(F)(iii) or (iv)]." *Id.* § 355a(o)(1).

It is well settled that courts shall construe what Congress has written without adding words to the statutory text. *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."); *United States v. Sonmez*, 777 F.3d 684, 688 (4th Cir. 2015) ("We will not construe the statute in such a manner, because we are required to interpret statutory language as written and are not permitted to add words of our own choosing."); *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)). Congress only provided for the omission of pediatric labeling protected by patent and three-year exclusivity; reading Section 505A(o) to allow the omission of pediatric labeling protected by orphan exclusivity requires adding text to the statute. That is impermissible.[5]

[5] The *expressio unius est exclusio alterius* canon provides additional support for this conclusion. *See Leatherman v. Tarrant Narcotis Intelligence & Coordination Unit*, 507 U.S. 163, 168 (1993); *Andrus v. Glover Constr. Co.*, 446 US. 608, 616-17 (1980); *TRW Inc. v. Andrews*, 534 U.S. 19, 28-29 (2001); *Shays v. FEC*, 528 F.3d 914, 933-34 (D.C. Cir. 2008); *NRDC v. EPA*, 489 F.3d 1250, 1259-60 (D.C. Cir. 2007); *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). Further, as discussed *infra* Part II.B.1.c.ii, Otsuka has learned that the Senate HELP committee was actively considering orphan drug issues, and specifically orphan drug exclusivity, at the same time as it was working on one of the predecessor bills to what ultimately was passed as the BPCA and included Section

The absence of any reference to orphan drug exclusivity in Section 505A(o) reflects an intentional congressional choice not to include orphan drug exclusivity. This is particularly clear because orphan drug exclusivity long predated Section 505A(o). *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.'"). Moreover, statutory text elsewhere demonstrates that Congress was well aware of orphan drug exclusivity, and thus Congress would have specifically included orphan drug exclusivity in Section 505A(o) had Congress intended orphan exclusivity to be a category of exclusivity permitted to be omitted. Congress was not picking from a large universe of patent and regulatory protections; the only relevant protection omitted from Section 505A(o) is orphan drug exclusivity, and, indeed, that type of exclusivity is specifically mentioned elsewhere in Section 505A itself. Section 505A(b)&(c), in addressing the interaction of pediatric exclusivity with patent and regulatory protections, specifically mention orphan drug exclusivity. 21 U.S.C. § 355a(b)(1)(A)(ii); *id.* § 355a(c)(1)(A)(ii). Of note, Section 505A(b)&(c) were reauthorized in section 8 of the BPCA by the same Congress that passed Section 505A(o) (section 11 of the BPCA). *See* Pub. L. No. 107-277, 155 Stat. 1408 (Jan. 4, 2002).[6]

505A(o). Moreover, FDA and the intervenor-defendants have not pointed to "contrary indications that adopting a particular rule or statute was probably not meant to signal any exclusion" of orphan drug exclusivity. ECF No. 100, at 12 (quoting *Marx v. Gen. Revenue Corp.*, 133 S. Ct. 1166, 1175 (2013); internal quotations omitted).

[6] Congress has included specific references to orphan drug exclusivity elsewhere as well. *See* 21 U.S.C. § 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.").

Alternatively, had Congress intended that all exclusivities could be omitted from a generic's label, rather than specifically mentioning "orphan drug exclusivity," Congress could have spoken broadly and used the term "exclusivity." Congress did not do so in Section 505A(o) while it has done so elsewhere.[7] *See* 21 U.S.C. § 355(j)(10)(A)(i) (a drug shall "be eligible for approval and 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)). Congress intended to omit orphan exclusivity from the statutory text and thereby not allow FDA to approve a generic where its label would omit an orphan protected pediatric indication or related pediatric label information.

(b) **The Absence Of A Specific Mention Of Orphan Drug Exclusivity In The Legislative History Does Not Abrogate The Plain Text.**

The Court earlier concluded that Otsuka's argument failed because it relied primarily on the *expressio unius* canon of construction and because the legislative history contains no express reference to orphan drug exclusivity. ECF No. 100, at 12-13. Respectfully, Otsuka's argument is not so limited,[8] nor is the absence of a specific mention of orphan drug exclusivity in the legislative history dispositive.

"It is not the law that a statute can have no effects which are not explicitly mentioned in its

[7] The fact that the statute references pediatric labeling "protected by patent" is itself a good indication that Congress was thinking more broadly about the statutory scheme and what the agency wanted to include. There were no patents listed in the Orange Book for Glucophage. *See* 147 Cong. Rec. H8551 (daily ed. Nov. 28, 2001) ("There are no patents blocking the approval of generics in this case.").

[8] Otsuka's memorandum in support of its motion for a temporary restraining order and/or preliminary injunction contained a single paragraph on this canon, ECF No. 77, at 15, as part of a much larger argument about the statutory text, context, and legislative history and responses to arguments set out by the intervenor-defendants. *Id.* at 14-23.

legislative history." *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 669 n.2 (1990) (quoting *Pittston Coal Group v. Sebben*, 488 U.S. 105, 115 (1988)); *Albany Eng'g Corp. v. FEC*, 548 F.3d 1071, 1077 (D.C. Cir. 2008) ("FERC evidently believes that the legislative history's failure to mention 'disruption' of the sort it espies here renders its interpretation of § 10(f) reasonable. But it is simply 'not the law that a statute can have no effects which are not explicitly mentioned in its legislative history.'"); *see, e.g.*, *United States v. Blackwood*, 913 F.2d 139, 147 (4th Cir. 1990) ("Although, as noted, the legislative history of these provisions does not directly speak to the problem of treating related convictions separately, that history gives some indications of the intent and expectation that § 841(b)'s increased punishments would turn on criminal episodes that occurred at distinct *times*."); *Aponte v. United States*, 940 F. Supp. 898, 902 (E.D.N.C. 1996) ("It is true that the legislative history of Section 8191 does not explicitly state that the coverage is an exclusive remedy. However, the legislative history, case law interpretation, and overall purpose of the entire FECA has the effect of leaving no question about Section 8191 being an exclusive remedy for plaintiffs such as the Apontes.").

In *United States v. Lund*, 853 F.2d 242 (4th Cir. 1988), for example, the Fourth Circuit reversed a district court's interpretation of a statute that was based in part on the absence of an express mention in the legislative history of the specific issue at hand. *Id.* at 244. There, the district court found, in interpreting the federal conflict of interest statute, *see* 18 U.S.C. § 208(a), that the legislative history showed "that Congress intended § 208(a) to apply only to conflicts of interest in matters involving 'outside suppliers of goods and services to the government,' and thus, by implication, not to those arising in internal personnel matters." *Id.* The Fourth Circuit reversed, explaining, *inter alia*, "[t]hat the legislative history contains no specific mention of conflicts of interest in internal personnel matters cannot be taken as affirmative evidence that it did not intend

the statute's sweeping language to reach them, for 'it is not necessary for Congress in its committee reports to identify all the "weeds" which are being excised from the garden.'" *Id.* at 246 (quoting *Standefer v. United States*, 447 U.S. 10, 20 (1980)).

The dispositive point is that Congress referenced patent and three-year exclusivity in Section 505A(o) and nothing else, and Congress did not have to mention orphan drug exclusivity in the legislative history for it to be impacted by Section 505A(o). Put another way, the absence of a specific mention of orphan drug exclusivity in the legislative history provides no basis or authority for the agency to add orphan drug exclusivity to the statute's identified categories of pediatric information that may be omitted.

b. The Statutory And Regulatory Context Demonstrate The Precise Need For Section 505A(o).

The statutory and regulatory context demonstrates why Congress needed to enact Section 505A(o). Without Section 505A(o), FDA's own regulations preclude FDA from approving a generic that omits pediatric labeling information, and that is precisely is why Congress enacted Section 505A(o).

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) ("An [ANDA] shall contain information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug . . . ."); *see also id.* (j)(4)(G) ("Subject to paragraph 5, the Secretary shall approve an application for a drug unless the Secretary finds information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the application . . . ."). The statute, however, allows for an exception to the general rule of "sameness" where "the new drug and the listed drug are produced or distributed by different manufacturers." *Id.* § 355(j)(2)(A)(v); *see also id.*

§ 355(j)(4)(G) ("except for changes required because of differences approved under a petition filed under paragraph (2)(C) or because the drug and the listed drug are produced or distributed by different manufacturers").

In 1992, FDA promulgated its general "carve-out" regulations allowing a generic drug label to differ from the label of the reference listed drug by the "omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the act" so long as "such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use." 21 C.F.R. § 314.94(a)(8)(iv), 314.127(a)(7); 57 Fed. Reg. 17950, 17984-86, 17992 (1992) (final rule).

In 1994, FDA created an "exception" to its regulation concerning proper labeling omissions. *See* 147 Cong. Rec. H10209 (daily ed. Dec. 18, 2001; memorandum on proposed amendment (H.R. 2887)); 59 Fed. Reg. 64240, 64247 (1994) (final rule).[9] In promulgating the regulations, FDA relied on its authority under 21 U.S.C. § 352(f). 57 Fed. Reg. 47423, 47425 (1992) (proposed rule); 59 Fed. Reg. 64247. Under § 352(f), a drug is misbranded "[u]nless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions *or by children where its use may be dangerous to health*, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users, except that where any requirement of clause (1) of this paragraph, as applied to any drug or device, is not necessary for the protection of the public health, the Secretary shall promulgate regulations exempting such drug or device from such requirement."

[9] *See* 147 Cong. Rec. 10209 ("In 1994, the FDA created an exception to the above regulation, concerning acceptable label omissions, affording pioneer drug manufacturers extended total marketing exclusivity based on the development of new pediatric use indications. In particular, the FDA adopted regulations requiring that pediatric information be included in the labeling of every prescription drug. See 21 C.F.R. § 201.57(f)(9)(ii).").

(emphasis added). The misbranding statute mandates that labeling include adequate warnings against use by children where it may be dangerous to health; that labeling requirement, under the statute's terms, cannot be excepted by FDA regulation. *Id.* ("except that where any requirement of clause (1) of this paragraph, as applied to any drug or device, is not necessary for the protection of the public health, the Secretary shall promulgate regulations exempting such drug or device from such requirement" (emphasis added)).

FDA, acting in reliance on its authority under this statute, and others, adopted regulations requiring that pediatric information be included in the labeling of prescription drugs. That rule as promulgated provided: "If there is a specific pediatric indication (*i.e.*, an indication different from those approved for adults) that is supported by adequate and well-controlled studies in the pediatric population, it shall be described under the 'Indications and Usage' section of the labeling, and appropriate pediatric dosage information shall be given under the 'Dosage and Administration' section of the labeling.'" 59 Fed. Reg. 64249 (promulgating 201.57(f)(9)(ii)).[10] FDA's pediatric labeling regulation was meant to "'promote[] safer and more effective use of prescription drugs in the pediatric population.'" *Id.* at 64240. In proposing the regulations, FDA expressly noted that

[10] There has been no material change to the regulation as it reads today: "If 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, and appropriate pediatric dosage information must be given under the 'Dosage and Administration' section." 21 C.F.R. § 201.57(c)(9)(iv)(B).

FDA's other regulations require that, "[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 of usefulness of the drug and any uncertainty about anticipated clinical benefits, with reference to the 'Clinical Studies' section for a discussion of the available evidence." 21 C.F.R. § 201.57(c)(2)(i)(B). They also require that the label include "[d]osages for each indication and subpopulation." *Id.* (c)(3)(C).

"'a drug product that is not in compliance with revised § 201.57(f)(9) would be considered to be *misbranded and an unapproved new drug under the act*." 57 Fed. Reg. 47425 (emphasis added).

This context makes clear both why Section 505A(o) was necessary and how the statute operates within the framework of FDA's overall drug labeling regime. Section 505A(o) was enacted because FDA's carve-out authority was limited by operation of FDA's own regulations governing pediatric labeling. On the one hand, FDA has authority to omit certain information on its label in contravention of the same labeling requirement, but on the other hand, the FDCA and FDA's later-in-time pediatric labeling regulations require pediatric information to be included on the label or the drug will be considered "misbranded and an unapproved drug." Congress faced and solved this problem when it enacted Section 505A(o)(1). Congress there answered the question of when pediatric labeling information may be omitted from a generic's labeling without violating § 355(j) and § 352. FDA's reading of the statute, that Section 505A(o) is an "additional tool" and is merely "complementary" to the agency's general carve-out authority, renders Section 505A(o) meaningless and fails to account for why it was enacted.

The Orphan Drug Act ("ODA") is another aspect of this context. The ODA has always provided a seven-year period of exclusivity for approved orphan drugs. Pub. L. No. 97-414, § 527, 96 Stat. 2049, 2051 (1983) (codified at 21 U.S.C. § 360cc). FDA's regulations have always provided 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); 57 Fed. Reg. 62076, 62086 (1992) (final rule) (promulgating 21 C.F.R. § 316.3(b)(12): "[N]o approval will be given to a subsequent sponsor of the same drug product for the same indication for 7 years, except as otherwise provided by law or in this part."); 78 Fed. Reg. 35117, 35132-33 (2013) (final rule) (revising 21 C.F.R. § 316.3(b)(12): "[N]o approval will be given to a subsequent

sponsor of the same drug for the same use or indication for 7 years, except as otherwise provided by law or in this part."). These provisions, including the incentives provided to drug companies to develop drugs for the treatment of rare diseases and the policy reasons for those incentives, are well known to Congress and were in the background when Section 505A(o) was enacted.

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

i. Section 505A(o)'s Legislative History Demonstrates That Section 505A(o) Was Intended To Fix The Glucophage Loophole.

Congress did not act in a vacuum when it enacted Section 505A(o). Rather, in late 2001, Congress confronted a specific situation that demonstrated the need for a change in the law and that situation drove the enactment of Section 505A(o).

BMS had conducted pediatric studies for an oral type 2 diabetes treatment, and the company submitted a sNDA seeking approval to add pediatric use information to its label. 147 Cong. Rec. H10210 (memorandum). 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, as described above, 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. See 21 C.F.R. § 201.57(f)(9)(iv); 147 Cong. Rec. H8105 ("Because FDA has granted three-year exclusivity to the pediatric label of Glucophage, Bristol has argued that no generic may be marketed during the pendency of its labeling exclusivity."). Congress acted to close the BMS "loophole." 147 Cong. Rec. H8105; 147 Cong. Rec. H8551 ("Mr. Speaker, there is currently a legislative fix in place in

the House and Senate version of the pediatric exclusivity bill that would close this loophole and allow generic versions of this diabetes drug to compete with Bristol's Glucophage.").

Congress understood clearly that the Glucophage problem arose in the context of the above-referenced statutes and regulations. A memorandum in the Congressional Record recounts that FDA promulgated its general carve-out 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." 147 Cong. Rec. H10209 (memorandum; citing 21 C.F.R. §§ 201.57(f)(9)(ii), 314.94(a)(8)(iv), 314.127(a)(7)). The effect of this 1994 requirement, as the memorandum reflects, was to afford BMS an extended period of total market exclusivity. *Id.*; 147 Cong. Rec. H8105 ("Bristol has apparently succeeded in convincing at least some of the decisionmakers in FDA that the differential labeling regarding pediatric use may constitute a safety risk if not found on equivalent generic products. Because FDA has granted three-year exclusivity to the pediatric label of Glucophage, Bristol has argued that no generic may be marketed during the pendency of its labeling exclusivity.").[11]

Notably, in 2001, FDA retained its general carve out authority and the Orphan Drug Act

[11] Contrary to FDA's present altogether unsubstantiated assertion that Glucophage was about safety, AR 497 n.27, Congress understood that the problem was the product of statutes and regulations: "The FDA's Office of Generic Drugs has numerous generic versions of this diabetes drug awaiting approval. However, the office is unable to allow these generics onto the market due to Bristol's monopoly. There are no patents blocking the approval of generics in this case. *The only obstacle is a result in the loophole in the Waxman-Hatch exclusivity. It allows Bristol to obtain 3 years of Waxman-Hatch exclusivity in addition to 6 months of pediatric exclusivity for a new indication, the use of this drug for treatment of Type 2 diabetes in pediatric patients ages 10 to 16 years*." 147 Cong. Rec. H8551 (emphasis added). When FDA was asked to supplement the administrative record to substantiate any safety basis with respect to Glucophage, FDA refused to do so, stating that Otsuka should cite, as Otsuka has, "to the Congressional Record." *See* Ex. A (email exchange between counsel for Otsuka and counsel for FDA).

was enacted long before that (having been enacted in 1983). FDA's carve out authority, however, was plainly insufficient to cure the loophole BMS had discovered. *Cf.* H.R. Rep. No. 107-277, 107th Cong. (Nov. 9, 2001) ("Amendments to the Generic Drug Approval Process. H.R. 2887 *would amend the approval process for generic drugs when pediatric information is added to the labeling*. The bill would require prompt approval of a generic drug that otherwise meets all other applicable requirements even when its labeling omits pediatric information that is protected by patent or other market exclusivity protections." (emphasis added)).

Referred to as the "Anti-Glucophage Bill," Section 505A(o) was enacted 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 (memorandum; "[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 ("Let us fight against [BMS] and close the Hatch-Waxman loophole."); *see also* H.R. Rep. No. 107-277 ("[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. This provision allows the Secretary to require that drugs approved under section 505(j) and that omit protected pediatric labeling include a statement that the drug is not labeled for the protected pediatric use and any warnings against unsafe pediatric

use.").[12] The provision "direct[ed] the FDA to approve generic applications lacking pediatric labeling under certain circumstances." H. R. Rep. No. 107-277.

The fix was a deliberate and carefully crafted one that "over[o]de," 147 Cong. Rec. H10210 (memorandum), FDA's pediatric labeling requirements but 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. H10210 (memorandum; "[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. 107-277 ("[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.").

Importantly, though, Congress in Section 505A(o) went beyond the BMS scenario. Congress included patent protection as an additional category of pediatric labeling that could be omitted despite the fact that Glucophage had no patent protection. *See* 147 Cong. Rec. H10205 ("[T]his legislation contains a provision which will result in generic drugs being approved when

[12] *See also* Transcript of Record of Markup on H.R. 2985 American Spirit Fraud Prevention Act of 2001, H.R. 2887, Best Pharmaceuticals for Children Act, and H.R. 2983 Price-Anderson Reauthorization Act of 2001, House of Representatives, Committee on Energy and Commerce, at 76 (Oct. 11, 2011) ("[I]f we really want to go after something, let us go after any company – and there is one, in particular, with the product of Glucophage, where the company got six months of exclusivity and then an additional three years, and that is, I think, really a bastardization of the Wax-Hatchman legislation. We should close that loophole. We should close that loophole . . . . We should close that loophole."); H.R. Rep. No. 107-277 ("The objective of H.R. 2887 is to ensure that drugs used in children are properly studied *and labeled for pediatric use*." (emphasis added)).

their labeling omits the pediatric indication or other aspect of labeling which is protected by the patent exclusivity."); 147 Cong. Rec. H8551 ("There are no patents blocking the approval of generics in this case [Glucophage]."). Again, this reflects careful congressional attention to the problem of pediatric labeling and clear congressional intent as to the types of pediatric information that may be omitted from a generic's label.

ii. When Section 505A(o) Was Enacted, The Senate HELP Committee Was Aware Of Orphan Drug Exclusivity.

Congress was considering orphan exclusivity contemporaneously with the debate over Section 505A(o). These contemporaneous legislative activities also support the conclusion that the omission of orphan drug exclusivity from Section 505A(o) was deliberate and intentional. On August 1, 2001, the Senate Health, Education, Labor and Pensions ("HELP") Committee held a markup of the BPCA (S. 838, 107th Cong. (2001)).[13] S. Rep. No. 107-79, at 5. Two days later, on August 3, Senator Kennedy, the Chairman of the HELP Committee, introduced a bill entitled "Rare Diseases Act of 2001," to provide statutory authorization for the existing Office of Rare Diseases at the National Institutes of Health ("NIH") and to increase the funding for FDA's Orphan Product Research Grant program. S. 1379, 107th Cong. (2001); 147 Cong. Rec. S8952 (daily ed. Aug. 3, 2001). In commenting on the bill, Chairman Kennedy noted "that Congress has had a longstanding interest in rare diseases" and "[i]n 1983, . . . enacted the Orphan Drug Act ["ODA"] to promote the development of treatments for rare diseases and disorders." 147 Cong. Rec. S8952.

The bill text itself reflects an understanding of the need to incentivize drug manufacturers

[13] There were two legislative vehicles known as the BPCA, one in the House, H.R. 2887, and one in the Senate, S. 838. *See* H. Rep. No. 107-277; S. Rep. No. 107-79, 107th Cong. (Oct. 4, 2001). The bills each passed their respective chambers, and after being informally conferenced were melded into the ultimate vehicle that was enacted, S. 1789, which was introduced and passed by both chambers and then signed by the President in 2002. Pub. L. No. 107-109, 115 Stat. 1408 (Jan. 4, 2002).

to develop drugs for orphan diseases. The findings in the bill stated,

- "For many years, the 25,000,000 Americans suffering from the over 6,000 rare diseases and disorders were denied access to effective medicines because prescription drug manufacturers could rarely make a profit from marketing drugs for such small groups of patients. The prescription drug industry did not adequately fund research into such treatments." S. 1379, at 2.

- "The Orphan Drug Act created financial incentives for the research and production of such orphan drugs. New federal programs at the National Institutes of Health and the Food and Drug Administration encouraged clinical research and commercial product development for products that target rare diseases." *Id.* at 3.

The legislation recognized that, "[d]espite the tremendous success of the [ODA], rare diseases and disorders deserve greater emphasis," and so the legislation had the purpose of establishing an Office of Rare Diseases at the NIH and "increas[ing] the national investment in the development of diagnostics and treatments for patients with rare diseases and disorders." *Id.* at 3-4.

On October 4, 2001, the HELP Committee issued a report on the BPCA (S. 838) without Section 505A(o). S. Rep. No. 107-79, 107th Cong. (Oct. 4, 2001). Shortly thereafter, on October 16, 2001, the HELP Committee marked up the Rare Diseases Act. S. Rep. No. 107-129, 107th Cong., at 5 (Dec. 18, 2001). Only two days later, on October 18, 2001, the Senate passed S. 838 with the amendment containing Section 505A(o). 147 Cong. Rec. S10816-19 (daily ed. Oct. 18, 2001); 147 Cong Rec. S10844-46 (daily ed. Oct. 18, 2001). On December 12, 2001, the Senate considered and passed S. 1789 (the ultimate BCPA vehicle that was enacted), containing Section 505A(o). 147 Cong. Rec. S13070-76 (daily ed. Dec. 12, 2001). Six days later, on December 18, 2001, the Senate HELP Committee issued a report on the Rare Diseases Act, which was later enacted in 2002. S. Rep. No. 107-129; Rare Diseases Act of 2002, Pub. L. No. 107-280, 116 Stat. 1988 (Nov. 6, 2002).

The first paragraph of the December 18 Committee Report clearly evidences the committee's understanding and recognition of the importance of the Orphan Drug Act, including

the market exclusivity incentive afforded to drug manufacturers:

> To address a longstanding unmet need to develop new treatments, diagnostics, and cures for rare diseases and disorders, Congress enacted the Orphan Drug Act of 1983 (Pub. L. 97-414). **This Act created financial incentives, such as *market exclusivity*,** tax credits, and research grants, for the research and production of orphan drugs, and established the Orphan Products Board at the [FDA]. Congress sought through the Act to encourage the development of new "orphan" treatments, diagnostics, and cures for the millions of Americans with rare diseases who did not have access to effective medicines because prescription drug manufacturers were unlikely to develop and market drugs for such small groups of patients. . . .

S. Rep. No. 107-129, at 1-2 (emphasis added). The report notes that "[t]he Orphan Drug Act *provided seven years of market exclusivity* and expanded tax credits to companies for the development and marketing of orphan drugs." *Id.* at 3 (emphasis added).

In sum, the Senate HELP committee was actively considering orphan drug issues, specifically including orphan drug exclusivity, at the same time as it was working on the Section 505A(o) bill. The senators enacting Section 505A(o) knew what they were doing by limiting it to patent protection and three-year exclusivity, and not including orphan drug exclusivity.

On the House side, during the October 11, 2001 markup of H.R. 2887 by the House Committee on Energy and Commerce, Congressman Waxman noted that drug manufacturers "get even more exclusivity" for orphan drugs. Ex. B, Transcript of Record of Markup on H.R. 2985 American Spirit Fraud Prevention Act of 2001, H.R. 2887, Best Pharmaceuticals for Children Act, and H.R. 2983 Price-Anderson Reauthorization Act of 2001, House of Representatives, Committee on Energy and Commerce, at 68 (Oct. 11, 2011). Congressman Waxman, of course, had special knowledge and expertise in all matters involving generic approvals and exclusivities as he and Senator Hatch authored the 1984 Hatch-Waxman Amendments to the FDCA.

For all these reasons, FDA's April 28 decision violates the plain meaning of Section

505A(o). The Court should reverse and vacate FDA's decision.

2. Alternatively, FDA's Interpretation Fails Under *Skidmore* And *Chevron* Step Two.

FDA's decision is contrary to Section 505A(o)'s statutory text and legislative history, contrary to FDA's own regulations, and is itself internally inconsistent. Thus, even if the Court determines the statute is ambiguous, FDA's construction should not be upheld because it is unreasonable and lacks any power to persuade. An agency's construction of a statute is arbitrary, capricious, or manifestly contrary to law where "it [does not] 'represent[] a reasonable accommodation of conflicting policies that were committed to the agency's care by the statute.'" *King v. Burwell*, 759 F.3d 358, 372 (4th Cir. 2014) (considering these factors under *Chevron* step one), *cert. granted* 135 S. Ct. 475 (2014).

a. FDA's Interpretation That Section 505A(o) Does Not Apply Because It Applies Only Where A Drug Is Approved In Adults And Pediatric Patients For The Same Indication Is Entitled To No Deference.

FDA's interpretation that Section 505A(o) does not apply here because the statute supposedly applies only "where a listed drug is approved in adults and pediatric patients for the same indication but protected by HW exclusivity for that use in pediatric patients only," AR 497, is contrary to the statute and FDA's regulations and is inconsistent with FDA's application of Section 505A(o) here.

FDA's reading of Section 505A(o) conflicts with the text of the statute. *See, e.g.*, *Mohamed v. Holder*, 769 F.3d 885, 888-89 (4th Cir. 2014) (holding that BIA's construction of statute was unreasonable because it conflicted with the statute); *Haddam v. Holder*, 547 F. App'x 306, 310-11, 313 (4th Cir. 2013) ("The Attorney General's definition does away with this nexus requirement [of the statute], and for this reason, it is impermissible under the INA."). Section 505A(o)'s text speaks broadly and, indeed, comprehensively 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 added to labeling"). FDA's interpretation impermissibly reads into the provision limiting language that does not exist to restrict pediatric information to "pediatric information protected by pediatric exclusivity." FDA's added limitation impermissibly adds words not found in the statutory text. *See 62 Cases*, 340 U.S. at 596-99; *Ignacio*, 674 F.3d at 255.

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, as FDA claims, to limit § 355a(o)(1)'s references to "pediatric indication[s]" and "other aspect[s] of labeling pertaining to pediatric use" to situations where a brand drug is approved in adults and pediatric patients for the same indication but only protected by three-year exclusivity for the pediatric use. *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)).

Moreover, FDA's interpretation is inconsistent with FDA's regulations. 21 C.F.R. § 201.57(c)(9)(iv)(B), one of FDA's pediatric labeling provisions, requires "specific pediatric indication[s that are] different from those approved for adults" to be included on drug labeling. And 21 C.F.R. § 201.56(d)(5) states that "*[a]ny* risk information that is required under § 201.57(c)(9)(iv) is considered 'appropriate pediatric contraindications, warnings, or precautions' within the meaning of section 505A(1)(2) of the [FDCA]." (emphasis added). Thus, all situations contemplated under 21 C.F.R. § 201.57(c)(9)(iv) are applicable to Section 505A(o), because "any" risk information required under the pediatric labeling requirement is an appropriate

contraindication, warning, or precaution to be included in Section 505A(o). FDA's conclusion that Section 505A(o) applies only where the brand drug has identical adult and pediatric indications is contrary to its own regulations.

Further, as noted above, the undisputed agency record in this case demonstrates that FDA actually applied 505A(o) here, despite the absence of an adult indication for Tourette's Disorder. FDA concluded that the generics must include a pediatric disclaimer as contemplated by Section 505A(o)(2)(A). AR 858-59; *e.g.*, AR 663-65; *id.* 681-83; *id.* 699-701; *id.* 717-20; *id.* 736-39.[14] As required by Section 505A(o)(2)(B), the labels also include other safety information related to the Tourette's Disorder indication: "**Less Common Adverse Reactions in Pediatric Patients (6 to 18 years) with Schizophrenia, Bipolar Mania *or Other Indications*** Table 20 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks in schizophrenia, up to 4 weeks in bipolar mania, up to 8 weeks in one indication, and *up to 10 weeks in another indication*) . . . ." AR 646, 663, 681, 699, 717, 736 (italics added). In Otsuka's label, the reference to 10 weeks is to Tourette's Disorder. *Id.* 398.

FDA's interpretation should receive no deference because it is inconsistent with the statute, FDA's own regulations, and with FDA's application of the statute in this matter.

b. FDA's Interpretation Of Section 505A(o) As "Complementary" To Its General Carve-Out Authority Is Entitled To No Deference.

FDA interprets Section 505A as an "additional tool[] to ensure that ANDAs are adequately labeled and not unnecessarily blocked in cases where pediatric labeling is protected by HW exclusivity and absence of [pediatric labeling] has safety implications and the potential to misbrand

[14] The disclaimer, as contemplated by Section 505A(o)(2)(A), provides: "Additional pediatric use information is approved for Otsuka America Pharmaceutical, Inc.'s ABILIFY® (aripiprazole) product. However, due to Otsuka America Pharmaceutical, Inc.'s marketing exclusivity rights, this drug product is not labeled with that information." AR 859.

the product." AR 497. Rather than considering, as a first proposition, whether Section 505A(o) applies, FDA treats Section 505A(o) as an "additional tool" to aid its carve-out authority. FDA's rather convoluted position is that the agency could always omit this pediatric information, and Section 505A(o) is necessary only as a "carve-in" when an omission of information would make the generic less safe and effective. This reading is unreasonable and lacks the power to persuade for it renders the statute meaningless, it allows a more general statute to trump a more specific statute, and it ignores the legislative history and background.

First, FDA's conclusion that Section 505A(o) is an additional tool or is merely complementary to its general carve-out authority renders Section 505A(o) meaningless and unnecessary, a plainly inappropriate way to read a statute. *Mohamed*, 769 F.3d at 888 ("[B]y using the phrase 'involving moral turpitude' to define a qualifying crime, Congress meant to refer to more than simply the wrong inherent in violating the statute. Otherwise, the requirement that moral turpitude be involved would be superfluous."). The first question here, given the "same labeling" requirement and FDA's pediatric labeling regulations, is whether the pediatric information from Otsuka's label can be omitted. FDA's decision avoids or misses this point, concluding that the agency can carve-out Otsuka's orphan-protected pediatric labeling under its general carve-out authority. If FDA's carve-out authority were as broad as FDA asserts, there would have been no need for Section 505A(o). FDA could have simply omitted the pediatric labeling from generic versions of Glucophage. But, as the legislative history makes clear, Section 505A(o) was necessary. FDA was stuck. It could not approve generic versions of Glucophage, so Congress stepped in to fix the problem that FDA's carve out authority could not fix.

Second, FDA's interpretation totally disregards the principle that 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 pediatric information. Neither the general same labeling requirements nor the orphan drug statute address 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). The orphan drug statute says 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. An agency interpretation that allows a more general reading of a statute to trump a more specific one is unreasonable under *Chevron* step two. *Nutritional Health Alliance v. FDA*, 318 F.3d 92, 102-03 (2d Cir. 2003) (agency's construction is impermissible under *Chevron* step two where "a later-enacted, more specific, comprehensive statute that targets the specific subject matter at issue in the case" was involved).

Third, 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. 81082, 81083 (2000) (proposed rule) ("[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 is presumed to legislate against the background of existing law. *See Langley*, 62 F.3d at 605. Further, the Senate HELP Committee was actively considering orphan drug issues, and orphan drug exclusivity, specifically, at the same time it was working on the Section 505A(o) bill. *See supra* Part II.B.1.c.ii. Congress, assisted by FDA,[15] could have included the omission of pediatric labeling covered by orphan drug exclusivity as a permissible label exclusion, but Congress chose not to do so.

c. FDA's Interpretation Of Section 505A(o) Ignores The Reference to "Misbranded Under Section 352."

FDA's interpretation of Section 505A(o) focuses totally on the phrase "shall not be considered ineligible for approval under [§ 355(j)]," and as such, FDA wholly and intentionally disregards the statute's reference to "misbrand[ing] under section 352." That omission is fatal to FDA's interpretation. Section 352 states that a product is misbranded unless "its labeling bears . . . adequate warnings against use . . . by children where its use may be dangerous to health" regardless of the uses approved for adults. The statute expressly prohibits FDA from promulgating

[15] FDA participated in the legislative process. *See* 147 Cong. Rec. H10818 (daily ed. Oct. 18, 2001) ("I also commend the expert staff of the Food and Drug Administration, including Melinda Plaisier, Jarilyn DuPont, Liz Dickinson, and Kim Dettelbach for their hard work on this legislation."); 147 Cong. Rec. H8105 ("Several potential, and very serious, abuses of the Hatch-Waxman procedures have been uncovered during the course of the discussions with the FDA regarding the technical provisions of this bill."). Notably, at least two of the FDA experts cited, Ms. Dickinson and Ms. Dettelbach, both lawyers in FDA's Office of Chief Counsel, are Hatch-Waxman experts.

regulations abolishing this requirement. 21 U.S.C. § 352(f) ("[A product is misbranded u]nless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users, except that where any requirement of clause (1) of this paragraph, as applied to any drug or device, is not necessary for the protection of the public health, the Secretary shall promulgate regulations exempting such drug or device from such requirement.").

Because Section 505A(o) does not provide a statutory exemption to this requirement when the pediatric labeling is protected by orphan drug exclusivity, generic aripiprazole products omitting safety information in children are misbranded. By omitting safety information in contravention of the statute, FDA approved misbranded generics and is permitting misbranded generics to remain on the market.

d. FDA's Interpretation That Three-Year Exclusivity Subsumes Orphan Drug Exclusivity Is Entitled To No Deference.

FDA's thin "fall back" argument that, if Section 505A(o) applies, Otsuka's orphan drug exclusivity would be subsumed by Section 505A(o)'s reference to three-year new clinical studies exclusivity, AR 500, is contrary to the statute and entitled to no deference. FDA's brief one paragraph treatment of this argument is understandable; Otsuka's three-year exclusivity has no impact here.

Otsuka's pediatric Tourette's labeling is protected by orphan drug exclusivity, which is completely separate from, and operates in addition to, Hatch-Waxman exclusivity. While orphan drug exclusivity is seven years, 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 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), *available at* http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-1018-0003.

Further, interpreting the statute, as FDA does, leads to absurd results. Orphan drug exclusivity can exist in the absence of three-year exclusivity (*e.g.*, where orphan approval is based purely on literature or bioequivalence data). If having three-year exclusivity is all that is relevant here, then the conclusion must be that Congress intended for labeling protected by pediatric orphan exclusivity to be carved out if the information came from a new, essential clinical trial, but not if the information came solely from literature or bioequivalence data. That is an absurd result.

e. FDA's Decision That Section 505A(o) Is An "Additional Tool" and "Complementary" To Its General Carve-Out Authority Is Contrary To FDA's Pediatric Labeling Regulation.

There is simply no way to reconcile FDA's conclusion that Section 505A(o) is "additional" and "complementary" to the agency's carve-out authority with FDA's own pediatric labeling

regulation. Notably, FDA's decision does not address this critical regulation.[16] This absence is extremely telling for FDA's pediatric labeling requirements drove the enactment of Section 505A(o). For the same reason that Section 505A(o) was necessary for FDA to approve generic versions of Glucophage, a statutory vehicle is necessary for FDA to authorize the omission of pediatric labeling protected by orphan drug exclusivity and for FDA to lawfully approve generic aripiprazole. FDA's writ alone is legally insufficient.

In Glucophage, FDA could not approve generic versions of Glucophage because, though it had carve-out authority, *see* 21 U.S.C. § 355(j)(2)(A)(v), (j)(4)(G), 21 C.F.R. § 314.94(a)(8)(iv), 314.127(a)(7), the agency had promulgated a later rule, pursuant to its misbranding authority under 21 U.S.C. § 352(f), requiring all prescription drugs to contain pediatric labeling, 57 Fed. Reg. 47425 (proposed rule); 59 Fed. Reg. 64247 (final rule). In proposing the regulations, FDA expressly noted that "a drug product that is not in compliance with [the revised regulation requiring the "pediatric use" subsection "to provide for the inclusion of more information about use of a drug in children"] would be considered *misbranded and an unapproved new drug under the act*." 57 Fed. Reg. 47425 (emphasis added). That scenario is still live here: FDA's general carve-out authority is limited by the agency's binding pediatric labeling regulation in the absence of a statute authorizing the omission of pediatric labeling protected by orphan drug exclusivity.

f. FDA Ignores The Legislative History.

FDA's construction of the statute as an "additional" and "complementary" tool to its general carve-out authority totally disregards the legislative history, *see supra* Part II.B.1.c, and it

[16] FDA only references 21 C.F.R. 201.57(c)(9)(iv)(C), AR 496, which discusses when pediatric information needs to be summarized in the pediatric use subsection of the label because there are "specific statements on pediatric use of the drug for an indication also approved for adults." FDA totally disregards 21 C.F.R. § 201.57(c)(2)(i)(B), (c)(3)(C), and (c)(9)(iv)(B).

is entitled to no deference for that reason. *Chevron*, 467 U.S. at 845 ("'If this choice represents a reasonable accommodation of conflicting policies that were committed to the agency's care by the statute, we should not disturb it unless it appears from the statute or its legislative history that the accommodation is not one that Congress would have sanctioned.'"); *see also, e.g.*, *Wassenaar v. Office of Personnel Mgmt.*, 21 F.3d 1090, 1095 (Fed. Cir. 1994) ("[N]either the statutory language nor the legislative history reveals any intent by Congress to impose the retirement-specific requirements . . . ."). The legislative history shows that Congress intended to fix a "loophole" to which FDA's general carve-out authority provided no solution. Congress enacted Section 505A(o) as a legislative fix that allowed FDA to carve-out pediatric labeling in specific circumstances. Reading the statute as an "additional" tool or "complementary" to FDA's general carve-out authority totally disregards that history and congressional intent.

g. FDA's Past Practice Does Not Establish Lawfulness.

FDA's citation to meloxicam as "precedent," AR 499-500, is equally unavailing. First, past practice does not make a policy lawful or authorize the agency to act contrary to a statute. *See, e.g.*, *Teva Pharmaceuticals USA, Inc. v. Sebelius*, 595 F.3d 1303, 1318 (D.C. Cir. 2010) (holding that FDA's interpretation of a statute was 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, 425-27 (8th Cir. 2001) (reversing, stating that it would not defer to an agency position contrary to the plain meaning of the statute, notwithstanding agency's practice). Second, there is no evidence (and FDA has offered none) to suggest that in the meloxicam example the agency even considered or was asked to consider the argument made here; the agency memorandum there contains no discussion as to whether Section 505A(o) precludes FDA as a matter of law from omitting pediatric labeling protected by orphan drug exclusivity. At most, the

meloxicam "precedent" is only an example of where FDA took an action never subjected to judicial review and where FDA's authority to act as it did was not raised or challenged.

h. Otsuka's Position Is Not Contrary To The Ruling In *Sigma-Tau*.

This case is not *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141 (4th Cir. 2002). Otsuka is not arguing that the Orphan Drug Act blocks generic competition for any of its unprotected FDA-approved indications. Otsuka is arguing that, when pediatric labeling is involved, FDA, for good reason, required by regulation that pediatric information be retained on all drug labeling, thereby limiting its carve-out authority. To fix that problem, Congress enacted Section 505A(o), but that "fix" did not (does not) cover orphan drug exclusivity. *Sigma Tau* has no impact on this argument because neither pediatric labeling nor Section 505A(o) was at issue there.

Here, Otsuka invested time and money, after product development and FDA approval for its original application, to focus on developing a new use for its drug for a pediatric use in an orphan population. Such an investment is unusual. As a 2012 article concluded, from 2000 to 2009, 1138 orphan drugs were designated and only 148 received marketing approval, of which only 38 were for pediatric diseases that have an onset only in childhood (*i.e.*, less than 17 years of age). Chandana Thorat et al., *What the Orphan Drug Act Has Done Lately for Children with Rare Diseases: A 10-year Analysis*, Pediatrics 518 (2012).[17] That study does not account for, as here, pediatric orphan uses that were approved for pediatric use in orphan populations as an additional indication (*i.e.*, after original development and approval).

Under whatever standard of deference this Court applies, FDA's decision should be reversed and vacated.

[17] *Available at* http://pediatrics.aappublications.org/content/early/2012/02/22/peds.2011-1798.

Conclusion

For the reasons stated, the Court should (a) grant Otsuka's motion for summary judgment; (b) enter final judgment for Otsuka and against FDA; (c) vacate FDA's April 28 decision and direct FDA to vacate forthwith any and all generic approvals granted in accordance with that decision; (d) issue a permanent injunction in accordance with the Court's final judgment enjoining FDA from granting any further approvals for generic versions of Abilify and ordering Intervenor-Defendants to cease distributing their generic products; and (e) grant such other and further relief as the Court determines necessary. A proposed form of Final Judgment is attached.

Respectfully submitted,

Dated: May 11, 2015

/s/ Ralph S. Tyler

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CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on this 11th day of May, 2015, a copy of the foregoing PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT 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.	*	

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

[PROPOSED] FINAL JUDGMENT AND ORDER

Pending before the Court are the parties' respective cross-motions for summary judgment. Having reviewed the motions and the oppositions thereto and having heard the oral arguments of counsel at a hearing on May 20, 2014, and finding that the material facts are not in dispute and that for the reasons stated on the record [and in the Court's Memorandum Opinion, ECF No. __], plaintiffs Otsuka Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Development & Commercialization, Inc., and Otsuka America Pharmaceutical, Inc. (collectively, Otsuka) are entitled to judgment as a matter of law, Otsuka's motion for summary judgment is hereby GRANTED, and the cross-motions of the federal defendants, including the U.S. Food and Drug Administration ("FDA"), and intervenor defendants Apotex Inc. and Apotex Corporation; Teva Pharmaceuticals USA, Inc.; Alembic Pharmaceuticals Limited, Alembic Limited, Alembic Global Holdings SA, and Alembic Pharmaceuticals, Inc.; Zydus Pharmaceuticals (USA) Inc.; Torrent Pharma Inc. and Torrent Pharmaceuticals Ltd.; and Sandoz Inc. are hereby DENIED.

Accordingly, FINAL JUDGMENT is hereby entered FOR Otsuka and AGAINST all defendants on Otsuka's complaint, and it is further ORDERED and DECLARED that:

1. The April 28, 2015 decision of Defendant FDA is declared unlawful and, accordingly, FDA's decision is hereby VACATED and shall be given no further force or effect;

2. FDA shall withdraw any and all approvals of abbreviated new drug applications for a generic version of Abilify, and FDA shall not issue any further approvals of an abbreviated new drug application allowing the marketing or sale of a generic version of Abilify.

3. Alembic Pharmaceuticals Ltd., Teva Pharmaceuticals, Torrent Pharmaceuticals, affiliated companies, and any other parties in this proceeding that have been granted final approval, shall cease distribution, sale, and marketing of generic versions of Abilify.

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

Dated: May _, 2015

Hon. George Jarrod Hazel
United States District Judge