IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

OTSUKA PHARMACEUTICAL CO., LTD., *et al.*, Plaintiffs, v. SYLVIA MATHEWS BURWELL *Secretary of Health and Human Services*, *et al.*, Defendants, APOTEX, INC., *et al.*, Intervenor-Defendants.	Civil Action No. 15-cv-00852-GJH

INTERVENOR-DEFENDANTS' MEMORANDUM IN SUPPORT OF THEIR MOTION FOR SUMMARY JUDGMENT

TABLE OF CONTENTS

Page

Introduction 1
Background 3
I. Statutory and Regulatory Background 3
A. The NDA Process Under the Food, Drug, and Cosmetic Act 3
B. The ANDA Process Pursuant to the Hatch-Waxman Amendments to the FDCA 4
C. The Orphan Drug Act 7
D. Pediatric Studies and the Best Pharmaceuticals for Children Act 8
II. Factual Background 10
A. Background on Abilify® 10
B. FDA's Approval of ANDAs for Generic Abilify® and Response to Otsuka's Demand To Block Generic Competition to Abilify® 11
C. Procedural History 14
Argument 16
I. Standard of Review 17
II. The FDCA Unambiguously Provides FDA With Authority To Carve Out Pediatric Information Protected by Orphan Drug Exclusivity 18
A. FDA Has Clear and Unambiguous Authority To Approve Generic Drugs With Labeling That Carves Out Approved Uses of a Brand-Name Drug 19
1. The Hatch-Waxman Amendments to the FDCA 19
2. The Orphan Drug Act 22
B. 21 U.S.C. § 355a(*o*) Does Not Limit FDA's Authority To Approve Labeling Carve-Outs 23
1. Section 355a(*o*) Enhances, Rather than Diminishes, FDA's Authority To Permit Labeling Carve-Outs 23
2. Otsuka's Negative Implication Argument Is Contrary to Section 355a(*o*)'s Text, History, and Purpose. 24
3. Other Canons of Construction That Otsuka Has Invoked Do Not Apply 29
C. Otsuka's Claim Fails Even Under Its Cramped Reading of Section 355a(*o*) 31
III. At a Minimum, FDA's Construction of the Statute Is Reasonable and Entitled to Deference 33
A. The FDCA Does Not Foreclose FDA's Interpretation Under Chevron 33
B. FDA's Construction Harmonizes Various Provisions of the FDCA While Otsuka's Interpretation Nullifies Statutory Text and Frustrates Congress's Objectives 34

C. FDA Has Consistently Exercised Its Authority To Permit Labeling Carve-Outs Pursuant to Established Regulations 35

Conclusion 39

TABLE OF AUTHORITIES

Page(s)

Cases

Adirondack Med. Ctr. v. Sebelius,
740 F.3d 692 (D.C. Cir. 2014) 31, 33, 34

AstraZeneca Pharms. LP v. Apotex Corp.,
669 F.3d 1370 (Fed. Cir. 2012) 18, 20

Audubon Naturalist Soc'y of the Cent. Atlantic States, Inc. v. U.S. Dep't of Transp.,
524 F. Supp. 2d 642 (D. Md. 2007) 17

Barnhart v. Peabody Coal Co.,
537 U.S. 149 (2003) 25

Bristol-Myers Squibb Co. v. Shalala,
91 F.3d 1493 (D.C. Cir. 1996) 18, 21

Brown v. Thompson,
374 F.3d 253 (4th Cir. 2004) 31

Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.,
467 U.S. 837 (1984) ..... *passim*

Chevron USA, Inc. v. Echazabal,
536 U.S. 73 (2002) 25, 34

Cutonilli v. Fed. Transit Admin.,
No. ELH-13-2373, 2015 WL 1431251 (D. Md. Mar. 30, 2015) 17

Director, Office of Workers' Comp. Programs v. Bethlehem Mines Corp.,
669 F.2d 187 (4th Cir. 1982) 24

FTC v. Actavis, Inc.,
133 S. Ct. 2223 (2013) 4

Kasten v. Saint-Gobain Performance Plastics Corp.,
131 S. Ct. 1325 (2011) 35

Marx v. Gen. Revenue Corp.,
133 S. Ct. 1166 (2013) 25

Mobile Commc'ns Corp. of Am. v. FCC,
77 F.3d 1399 (D.C. Cir. 1996) 33

Morton v. Mancari,
417 U.S. 535 (1974).....30

Motor Vehicle Mfrs. Ass'n of the U.S. v. State Farm Mut. Auto Ins. Co.,
463 U.S. 29 (1983).....17

Philip Morris USA, Inc. v. Vilsack,
736 F.3d 284 (4th Cir. 2013).....18, 33

Serono Labs., Inc. v. Shalala,
158 F.3d 1313 (D.C. Cir. 1998).....35

Sigma-Tau Pharms., Inc. v. Schwetz,
288 F.3d 141 (4th Cir. 2002)..... *passim*

Thomas Jefferson Univ. v. Shalala,
512 U.S. 504 (1994).....39

U.S. Immigration & Naturalization Serv. v. Fed. Labor Relations Auth.,
4 F.3d 268 (4th Cir. 1993).....24

United States v. Granderson,
511 U.S. 39 (1994).....32

Watt v. Alaska,
451 U.S. 259 (1981).....30

Whitman v. Am. Trucking Ass'ns., Inc.,
531 U.S. 457 (2001).....34

Statutes

21 U.S.C. § 301 et seq.....3

21 U.S.C. § 355..... *passim*

21 U.S.C. § 355(b)(1).....4

21 U.S.C. § 355(c)(3)(E)(ii).....22

21 U.S.C. § 355(d)(1).....3

21 U.S.C. § 355(d)(5).....3

21 U.S.C. § 355(j).....26

21 U.S.C. § 355(j)(2)(A).....5

21 U.S.C. § 355(j)(2)(A)(i) 5, 6, 20

21 U.S.C. § 355(j)(2)(A)(v) 5, 20, 21, 35

21 U.S.C. § 355(j)(2)(A)(viii) 5, 20

21 U.S.C. § 355(j)(4) 24

21 U.S.C. § 355(j)(4)(B) 20

21 U.S.C. § 355(j)(4)(G) 5, 12, 35

21 U.S.C. § 355(j)(5)(F)(ii) 22

21 U.S.C. § 355(j)(5)(F)(iii) 8, 9, 32

21 U.S.C. § 355(j)(5)(F)(iv) 8, 9, 21, 32

21 U.S.C. § 355a 8, 9

21 U.S.C. § 355a(b)(1) 8

21 U.S.C. § 355a(c)(1) 8

21 U.S.C. § 355a(b)-(d) 8

21 U.S.C. § 355a(*o*) ..... *passim*

21 U.S.C. § 355a(*o*)(1) 9, 12

21 U.S.C. § 355a(*o*)(2) 9, 30

21 U.S.C. § 355a(*o*)(3) 9

21 U.S.C. § 355a(*o*)(3)(D) ..... *passim*

21 U.S.C. § 360bb(a) 7

21 U.S.C. § 360bb(a)(2) 7

21 U.S.C. § 360cc(a) ..... *passim*

Pub. L. No. 107-109, 115 Stat. 1408 9

Pub. L. No. 98-417, 98 Stat. 1585 4

Pub. L. No. 87-781, 76 Stat. 780 3

Pub. L. No. 97-414, 96 Stat. 2049 7

Federal Regulations

21 C.F.R. § 201.57(f)(9)(ii) 26

21 C.F.R. § 314.92(a)(1) 6

21 C.F.R. § 314.94(a)(8)(iv) 6, 36

21 C.F.R. § 314.127(a)(7) 7, 36

21 C.F.R. § 316.3(b)(12) 7

21 C.F.R. § 316.3(b)(13) 7

21 C.F.R. § 316.31(b) 8, 36

Other Authorities

147 CONG. REC. H10209 (daily ed. Dec. 18, 2001) 26

147 CONG. REC. H10209-10 (daily ed. Dec. 18, 2001) 9

147 CONG. REC. H10210 (daily ed. Dec. 18, 2001) 27

147 CONG. REC. H10212 (daily ed. Dec. 18, 2001) 27

147 CONG. REC. H8105 (daily ed. Nov. 13, 2001) 27

74 Fed. Reg. 63,404 (Dec. 3, 2009) 10

BLACK'S LAW DICTIONARY (10th ed. 2014) 26

H.R. REP. NO. 98-857(I) (1984) 4, 6, 20

Intervenor-Defendants Apotex Inc. and Apotex Corporation (collectively, "Apotex"), Teva Pharmaceuticals USA, Inc. ("Teva"), Alembic Pharmaceuticals Limited, Alembic Limited, Alembic Global Holdings S.A., and Alembic Pharmaceuticals, Inc. (collectively, "Alembic"), Torrent Pharma Inc. and Torrent Pharmaceuticals Ltd. (collectively, "Torrent"), and Zydus Pharmaceuticals (USA) Inc. ("Zydus") respectfully submit this memorandum in support of their motion for summary judgment on all claims brought by Plaintiffs Otsuka Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Development & Commercialization, Inc., and Otsuka America Pharmaceutical, Inc. (collectively, "Otsuka").[1]

INTRODUCTION

In this case, Otsuka seeks to leverage a very narrow exclusivity, which covers at most a small fraction of all Abilify® uses, to block *all* generic competition for *seven years*. Under the Orphan Drug Act, Otsuka possesses a regulatory exclusivity for the use of aripiprazole to treat Tourette's disorder in pediatric patients, but it has no exclusivity rights with respect to the many other FDA-approved uses of aripiprazole or for the drug itself. Nevertheless, Otsuka argues that because its exclusivity pertains to a pediatric use, it precludes FDA from approving ANDAs referencing Abilify® even if they are strictly limited to uses with no remaining exclusivity and are found safe and effective for those uses. In other words, Otsuka claims that its exclusive right to market the drug to a tiny population of fewer than 120,000 pediatric patients affected by Tourette's disorder should block all generic competition for a major drug that accounted for more than $4.7 billion in U.S. sales in the 2013 fiscal year alone.

The Federal Food, Drug, and Cosmetic Act ("FDCA") does not compel, or even permit, the result that Otsuka demands. Instead, as court after court has held, the relevant laws

[1] Sandoz Inc. ("Sandoz") has also moved to intervene. Sandoz will join with the other Intervenor-Defendants in this motion for summary judgment if the Court grants Sandoz's motion to intervene.

governing FDA's authority explicitly contemplate that situations like this might arise. When a brand company obtains exclusivity for only one of several approved uses, that limited exclusivity will *not* block approval of generic products for all *other* uses. Rather, the FDCA permits what is known as a "carve-out": generic drug manufacturers are permitted to omit (or "carve out") references to the protected indication from their labeling, and to obtain approval for other uses that are not protected by the exclusivity at issue. In this way, the laws balance the interests of the brand company (by not permitting the generics to label their products for the use protected by the unexpired exclusivity) and those of the generics and the public (by permitting generics to be sold on the basis of labeling that refers only to unprotected uses).

Otsuka's argument to the contrary distorts the FDCA in several respects. Otsuka relies on a single FDCA provision adopted in a 2002 amendment, 21 U.S.C. § 355a(*o*), which Otsuka claims limits the circumstances when pediatric information may be carved out of a generic's labeling and implicitly forbids FDA from approving generic labels that carve out pediatric indications protected by orphan drug exclusivities. But section 355a(*o*) is a *pro*-carve out statute designed to facilitate generic entry, not to block it. Otsuka's reading turns the statutory provision on its head. Its reading is not based on any express text but instead on a negative implication Otsuka tries to draw from that text. But that negative implication flies in the face of the text and history of the FDCA as a whole and the clear text of the provision itself, which states that it should not be read to alter FDA's preexisting authority under the FDCA except where *expressly* stated in section 355a(*o*). *See* 21 U.S.C. § 355a(*o*)(3)(D). Otsuka's interpretation also nullifies key language in the orphan drug subchapter of the FDCA, which specifies that exclusivities may only be awarded for particular *indications* or *uses*, not for the drug as a whole. *See* 21 U.S.C. § 360cc(a).

In short, reading the relevant provisions of the FDCA together and in context leaves no doubt about the statute's plain meaning: Congress allowed the public access to lower-priced generic substitutes when those products have substantial FDA-approved uses that are not protected by any patent or regulatory exclusivity. Certainly, Otsuka has not demonstrated and cannot demonstrate that FDA's sensible interpretation of the FDCA's text, structure, and purpose is *foreclosed*, as it must do to defeat FDA's considered judgment. To the contrary, FDA, exercising its congressionally delegated responsibility to administer this Act, has long approved generic drug applications with appropriate labeling carve-outs in cases like this one rather than allow narrow exclusivities to block all generic competition. This Court should adhere to its decision at the preliminary injunction stage in this case that FDA's interpretation is at least a reasonable interpretation of its statutory authority that receives deference under *Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984). Accordingly, the Court should grant Intervenor-Defendants' motion for summary judgment.

BACKGROUND

I. Statutory and Regulatory Background

A. The NDA Process Under the Food, Drug, and Cosmetic Act

In 1962, Congress amended the FDCA to require that FDA pre-approve any new drug before a company markets it to the public. *See* Pub. L. No. 87-781, 76 Stat. 780 (codified as amended at 21 U.S.C. § 301 et seq.). Under the 1962 amendments, those seeking to market a new drug must submit a New Drug Application ("NDA") that shows to the agency's satisfaction that a drug is safe and effective—not just generally, but for the particular labeled conditions. *See* 21 U.S.C. § 355(d)(1), (5) (identifying grounds for disapproval as, *inter alia*, lack of adequate tests showing the drug is "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof" and "a lack of substantial evidence that the drug

will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof"). An NDA is a time- and cost-intensive undertaking—a voluminous filing that contains, *inter alia*, technical data on the composition of the drug and how it will be manufactured, proposed labeling, and the results of clinical studies on the safety and efficacy of the drug. *See* 21 U.S.C. § 355(b)(1). This process increased costs of generic drugs and dissuaded many generic drug manufacturers from entering the market even after a brand-name drug lost its patent protection. *See* H.R. REP. NO. 98-857(I), at 16-17 (1984) (explaining that the procedure under the 1962 amendments was "inadequate," leaving 150 off-patent drugs for which there was no generic equivalent).

B. The ANDA Process Pursuant to the Hatch-Waxman Amendments to the FDCA

In 1984, Congress passed the Drug Price Competition and Patent Term Restoration Act, more commonly known as the Hatch-Waxman Amendments to the FDCA, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended at 21 U.S.C. § 355, 35 U.S.C. §§ 156, 271, 282). The Hatch-Waxman Amendments were intended to "speed[] the introduction of low-cost generic drugs to market, thereby furthering drug competition," *FTC v. Actavis, Inc.*, 133 S. Ct. 2223, 2228 (2013) (internal quotation marks and citation omitted). And they have. In the thirty years since the law was passed, generic drugs have become the overwhelming majority of drugs dispensed in this country (nearly 80%), and their comparatively lower costs have helped slow the overall growth in healthcare spending. *Facts About Generic Drugs*, FDA, http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm167991.htm (last updated Sept. 19, 2012) ("[N]early 8 in 10 prescriptions filled in the United States are for generic drugs…. In 2010 alone, the use of FDA-approved generics saved $158 billion, an average of $3 billion every week."); *About: The*

Industry, GENERIC PHARMACEUTICAL ASSOCIATION, http://www.gphaonline.org/about/the-industry (last visited May 11, 2015) ("Generic pharmaceuticals fill 80% of the prescriptions dispensed in the U.S. but consume just 27% of total drug spending.").

The Hatch-Waxman Amendments changed the FDA approval process for generic drugs, permitting manufacturers to file Abbreviated New Drug Applications ("ANDAs") in place of NDAs. The Amendments generally provide that, as long as a generic drug is the same as a "reference listed drug," or RLD (often synonymous with the NDA drug) for "the conditions of use prescribed, recommended, or suggested in the labeling" of the ANDA, 21 U.S.C. § 355(j)(2)(A)(i), FDA may rely on its findings of safety and efficacy for the RLD in determining that the generic is safe and effective for its labeled "conditions of use." To this end, the Hatch-Waxman Amendments require ANDA applicants to make a showing of sameness: that the ANDA and RLD are bioequivalent, and that the active ingredient(s), route of administration, dosage form, strength, and—with certain relevant exceptions—labeling are the same. *See generally* 21 U.S.C. § 355(j)(2)(A).

Notably, the Hatch-Waxman Amendments do not require the generic drug's labeling to be completely identical to the RLD's labeling. While the law generally requires "information to show that the labeling proposed for the [ANDA] is the same as the labeling approved for the listed drug," it contains exceptions, including "because the [ANDA] and the [RLD] are produced or distributed by different manufacturers." 21 U.S.C. § 355(j)(2)(A)(v). A parallel provision lists reasons why an ANDA may not be approved, one of which is that the ANDA does not "show that the labeling proposed for the [ANDA] is the same as the labeling for the [RLD]"—but again, "except for changes . . . because the [ANDA] and the [RLD] are produced or distributed by different manufacturers." *See* 21 U.S.C. § 355(j)(4)(G). Section 355(j)(2)(A)(viii)

also anticipates that labeling of the ANDA and RLD will not always match, requiring ANDA applicants to provide a statement to FDA identifying those "method[s] of use" for which an ANDA applicant is not seeking approval, and which the applicant has therefore carved out of its labeling, because they are claimed in the brand company's "method of use patent." And 21 U.S.C. § 355(j)(2)(A)(i) requires that an ANDA contain "information to show that the conditions of use . . . in the labeling proposed for the [ANDA] have been previously approved for [the listed drug]," but does not require an ANDA to include every condition of use in its labeling.

The legislative history explicitly acknowledged that these Amendments permit a practice that has become known as a labeling "carve-out": "[T]he bill permits an ANDA to be approved for less than all of the indications for which the listed drug has been approved. . . . [T]he applicant need not seek approval for all of the indications for which the listed drug has been approved." H.R. REP. NO. 98-857(I), at 21 (1984); *see also id.* at 22 ("The committee recognizes that the proposed labeling for the generic drug may not be exactly the same [as the RLD].").

FDA likewise has promulgated regulations pursuant to notice-and-comment rulemaking permitting such carve-outs. Those rules allow ANDA labeling to include "differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, *or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under [the FDCA]*." 21 C.F.R. § 314.94(a)(8)(iv) (emphasis added). In addition, FDA rules explicitly acknowledge that an ANDA may omit "conditions of use for which approval cannot be granted because of exclusivity or an existing patent." 21 C.F.R. § 314.92(a)(1). And FDA will refuse to approve an ANDA if it is "insufficient to show that the labeling proposed for the [ANDA] is the same as the labeling approved for the [RLD] . . . except for changes required because . . . the [ANDA] and

the [RLD] are produced or distributed by different manufacturers or because aspects of the [RLD's] labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the [RLD] for all remaining, non-protected conditions of use." 21 C.F.R. § 314.127(a)(7). These regulations make no exceptions: they allow *any* indication or use protected by patent or FDCA exclusivity to be carved out, subject to safety and effectiveness review.

C. The Orphan Drug Act

Congress amended the FDCA again with the Orphan Drug Act. *See* Pub. L. No. 97-414, 96 Stat. 2049 (codified as amended at 21 U.S.C. §§ 360aa-360ff). This subchapter of the FDCA provides incentives to develop drugs to treat rare diseases and conditions while at the same time preserving labeling carve-outs otherwise available under the FDCA.

Among other incentives, the orphan drug subchapter generally grants seven years of orphan drug exclusivity to the first drug approved to treat a protected disease or condition. *See* 21 U.S.C. § 360cc(a). It defines a rare disease or condition as one affecting fewer than 200,000 persons in the United States, or one affecting more people but "for which there is no reasonable expectation that the cost of developing and making available [the drug] … will be recovered from sales in the United States of such drug." 21 U.S.C. § 360bb(a)(2); *see also* 21 C.F.R. § 316.3(b)(12), (13).

In line with other provisions of the FDCA, section 360cc(a) limits orphan drug status to the orphan "disease or condition" the drug is designed to treat. The statute does not measure eligibility by looking at the drug's other uses; as long as a drug treats an orphan "disease or condition," it is eligible even if the drug is in wide use for other indications. *See* 21 U.S.C. § 360bb(a). Nor does the statute award orphan drug exclusivity to the drug as a whole for all uses. *See* 21 U.S.C. § 360cc(a) (prohibiting FDA from "approv[ing] another application . . . for

such drug *for such disease or condition* . . . until the expiration of seven years from the date of" the orphan drug exclusivity approval) (emphasis added). An application that does not seek approval "for such [orphan] disease or condition"—*i.e.*, that has carved out the protected use from its proposed label—is not blocked by orphan drug exclusivity. FDA's implementing regulations confirm that limitation. *See* 21 C.F.R. § 316.31(b) ("Orphan-drug exclusive approval protects only the approved indication or use of a designated drug."); *id.* § 316.31(a) (providing "FDA will not approve another sponsor's marketing application for the same drug for the same use or indication before the expiration of 7 years from the date of such approval").

D. Pediatric Studies and the Best Pharmaceuticals for Children Act

In 1997, Congress amended the FDCA again, adding a new section that creates incentives for drug sponsors to determine the safety and efficacy of their drugs in pediatric populations. *See* 21 U.S.C. § 355a. Section 355a provides that FDA may ask an NDA sponsor to conduct studies of its drug on a pediatric population. *See* 21 U.S.C. § 355a(b)-(d). If the NDA sponsor completes those studies to FDA's satisfaction, any existing exclusivity or patent protection covering that drug is extended by six months. *See* 21 U.S.C. § 355a(b)(1), (c)(1). That exclusivity is awarded whether or not the pediatric studies lead to a new approved pediatric use or indication.

New studies (including, but not limited to, the same studies that support a six-month pediatric exclusivity) can also earn an NDA sponsor an additional three years of marketing exclusivity *if* they produce usable results. *See* 21 U.S.C. § 355(j)(5)(F)(iii), (iv). If new studies support a change in an NDA sponsor's labeling, the sponsor may be entitled to an additional three-year period of exclusivity for the approved change. 21 U.S.C. § 355(j)(5)(F)(iv); *see id.* § 355(j)(5)(F)(iii) (providing exclusivity for "conditions of approval of such drug" where the new clinical studies are performed before initial NDA approval, rather than after). Where the

change is approved in a supplemental NDA, this exclusivity blocks only those applications seeking approval "for [the] change approved in the supplement." 21 U.S.C. § 355(j)(5)(F)(iv).

Once again, as with the FDCA and the Orphan Drug Act, the law permits carve-outs. Congress further modified section 355a in the Best Pharmaceuticals for Children Act of 2002 ("BPCA"), Pub. L. No. 107-109, 115 Stat. 1408 (codified as amended at 21 U.S.C. § 355a). One new subsection, 21 U.S.C. § 355a(*o*), was enacted to provide for (as the subsection title puts it) "Prompt approval" of ANDAs containing a carve-out of pediatric information. It provides that an ANDA "shall not be considered ineligible for approval . . . 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 clause (iii) or (iv) of section 355(j)(5)(F)." 21 U.S.C. § 355a(*o*)(1). The law also gives FDA authority to require labeling information explaining that the generic drug is not labeled for pediatric use and providing appropriate pediatric warnings, contraindications, and precautions. *Id.* § 355a(*o*)(2). The text of section 355a(*o*) makes clear that Congress intended for the amendment's effect to be limited: paragraph (3) specifically disclaims any effect on "the operation of section 355 of this title"—the section from which FDA has long drawn its general carve-out authority—"except as *expressly* provided in paragraphs (1) and (2)." 21 U.S.C. § 355a(*o*)(3) (emphasis added).

The BPCA's legislative history demonstrates that subsection 355a(*o*) was intended to address a specific question that was before FDA at that time. At the time, an NDA holder was urging FDA to interpret a rule concerning pediatric labeling to not permit ANDA carve-outs of pediatric labeling information when that information is protected by a three-year marketing exclusivity under 21 U.S.C. § 355(j)(5)(F)(iii) or (iv). *See* 147 CONG. REC. H10209-10 (daily ed. Dec. 18, 2001) (memorandum to the United States Congress Re: Proposed Amendment to the

Hatch-Waxman Act (H.R. 2887)) (NDA holder arguing grant of three-year exclusivity for pediatric use labeling "resulted in total marketing exclusivity with respect to Glucophage for the applicable period because [the NDA holder] has acquired exclusive rights to the only pediatric use indication that applied under the pediatric labeling requirements"). Such an interpretation would have prevented generic drug approvals for *all* uses of a drug, and not just for those uses protected by those exclusivities. Congress quickly stepped in and passed the BPCA to prevent this result. The BPCA ensured that omitting pediatric information from a generic's label despite an unexpired period of exclusivity would not impede "Prompt approval" of the generic.

II. Factual Background

A. Background on Abilify®

Otsuka holds several NDAs for Abilify® for various strengths and dosage forms. Its first NDA was approved by FDA in 2002, and Abilify® has been marketed continuously ever since in one or more dosage forms.[2] Abilify® is currently marketed for the following five indications (all identified in the "Indications and Usage" section of its labeling):

- Schizophrenia
- Acute Treatment of Manic and Mixed Episodes associated with Bipolar I Disorder
- Adjunctive Treatment of Major Depressive Disorder
- Irritability Associated with Autistic Disorder
- Treatment of Tourette's Disorder

Administrative Record ("AR") 279, 368.

The last indication, for Tourette's disorder, is new. Abilify® was a multi-billion dollar blockbuster drug well before that indication was added, with data showing, for example, that the

[2] Otsuka never marketed the 20 mg and 30 mg orally disintegrating tablet ("ODT") and has now stopped marketing the ODT for all strengths. In 2009, FDA determined the 20 mg and 30 mg versions of the ODT were withdrawn from the market for reasons other than for safety or effectiveness, which means ANDAs may still approved for this dosage form. *See* Determination That ABILIFY DISCMELT (Aripiprazole) Orally Disintegrating Tablets, 20 Milligrams and 30 Milligrams, Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness, 74 Fed. Reg. 63,404 (Dec. 3, 2009).

drug accounted for more than $4.7 billion in U.S. sales revenue in fiscal year 2013. *See* Otsuka Holdings Co., Ltd., *Fact Book: Supplementary Materials, Financial Results FY 2014*, 6 (2014), *available at* http://www.otsuka.com/en/financial/pdf.php?financial=338. FDA added the Tourette's disorder indication and related information to the Abilify® labeling when it approved Otsuka's supplemental NDAs for Abilify® on December 12, 2014. AR 170-73. Tourette's disorder is an orphan disease or condition (whereas the other conditions that Abilify is approved to treat are not). Otsuka has been granted exclusivity until December 12, 2017 for "treatment of pediatric patients with Tourette's disorder (6-18 years)" (a new clinical studies exclusivity), and until December 12, 2021 for "treatment of pediatric patients with Tourette's" (an orphan drug exclusivity). AR 488-90.

B. FDA's Approval of ANDAs for Generic Abilify® and Response to Otsuka's Demand To Block Generic Competition to Abilify®

Otsuka's compound patent for Abilify® expired on October 20, 2014. The six-month period of pediatric exclusivity associated with that compound patent (previously awarded to Otsuka in connection with studies conducted in pediatric patients with schizophrenia and acute mania as part of bipolar I disorder) expired on April 20, 2015. As of that date, FDA was permitted to grant final approval to one or more ANDAs to market generic aripiprazole.

On January 21, 2015, Otsuka submitted a letter to FDA arguing that it lacked authority to approve any ANDAs for generic Abilify®. AR 274-76. Otsuka advanced the extraordinary proposition that, although the Orphan Drug Act only provided it with a narrow exclusivity to market Abilify® for the treatment of Tourette's disorder in pediatric patients, the exclusivity nonetheless precluded FDA from approving any ANDAs for Abilify® for any use for seven years. *Id.*

On April 28, 2015, FDA denied Otsuka's claim, concluding that Otsuka's arguments "fail on multiple counts." AR 500. It rejected Otsuka's interpretation as contrary to the agency's governing statutes and regulations, which support FDA's longstanding practice of approving ANDAs that carve out exclusivities when the resulting labeling is safe and effective for use without the omitted information. AR 500-02.

In its letter, FDA summarized the statutory and regulatory provisions establishing the agency's carve-out authority. FDA explained that the agency had long interpreted 21 U.S.C. § 355(j)(4)(G), in regulations issued through notice and comment, to authorize ANDA applicants to "carve out from proposed labeling patent or exclusivity-protected conditions of use and obtain approval for the remaining non-protected conditions of use" provided the resulting labeling differences do not render the product less safe or effective for those uses. AR 495 (citing 21 C.F.R. §§ 314.91(a)(1), 314.94(a)(8)(iv), 314.137(a)(7)).

FDA noted that, in some cases, carving out pediatric labeling information presents a challenge. That is because FDA generally presumes that drugs approved to treat a disease or condition in adults will also be used to treat pediatric patients with the same disease or condition. In that scenario, information concerning matters like dosage and safety risks for pediatric patients may need to appear in the label to ensure the drug is safe and effective for pediatric patients. AR 496-97. According to FDA, Congress resolved the potential impasse in the BPCA by adopting section 355a(*o*), which on the one hand prohibits FDA from refusing to approve an ANDA because it omits pediatric labeling information "protected by . . . exclusivity under clause (iii) or (iv) of section [355](j)(5)(F)," 21 U.S.C. § 355a(*o*)(1), while on the other hand gives the agency "additional tools" to ensure that a generic drug is safe and effective for its listed indications despite a pediatric carve-out. AR 497-98. Importantly, as FDA explained, section

355a(*o*) "does not limit FDA's authority to carve out pediatric labeling where a carve-out would otherwise be appropriate" (*i.e.*, where the drug is safe and effective as labeled with the omission). AR 498. Rather, the provision "is complementary to FDA's longstanding approach to labeling carve-outs under section [355](j)." AR 499. And under that approach, "FDA has long carved out from ANDA labeling information protected by [orphan drug exclusivity]" so long as "the drug without the protected indication will remain safe and effective for the remaining, non-protected conditions of use." *Id*. FDA further explained that it has previously carved out pediatric information protected both by three-year Hatch-Waxman exclusivity under 21 U.SC. § 355(j)(5)(F) and orphan drug exclusivity. *See* AR 499-500 (describing approval of ANDAs for meloxicam tablets as a precedent).

Turning to Otsuka's arguments, FDA first stated that Otsuka's negative-implication theory was based on a flawed premise, because the relevant information regarding the treatment of Tourette's disorder in pediatric patients is protected by both three-year Hatch-Waxman exclusivity and orphan drug exclusivity. As a result, FDA could have relied on section 355a(*o*) (which expressly refers to three-year Hatch-Waxman exclusivity) to allow applicants to carve out the Tourette's disorder indication but retain certain safety-related pediatric information in their labeling if the agency had elected to do so. AR 500. Second, FDA reasoned that even if section 355a(*o*) did not apply, it did not forbid the agency from approving carve-outs of the labeling information protected by orphan drug exclusivity if resulting labels are safe and effective for non-protected uses. And that was the case here, the agency explained, because "as a factual matter FDA has determined that it was not necessary to retain in the generic drug labeling any protected Tourette's Disorder information." AR 501. FDA noted that Otsuka's labeling includes no information for the treatment of Tourette's disorder in adults (a fact Otsuka also not only

confirmed but "strenuously argued"). *Id.* In this instance, FDA determined that the inclusion of information about treatment of Tourette's disorder in pediatric patients was not necessary to ensure the resulting ANDA labeling is safe and effective. *Id*.

FDA added in conclusion that "Otsuka's arguments regarding the meaning of section [355a](*o*) turn section [355a](*o*) on its head." AR 502. FDA explained that section 355a(*o*) was designed to ensure prompt ANDA approval, not to thwart it. Moreover, the agency observed that Otsuka's contention that "Congress intended to negate FDA's preexisting authority to carve out pediatric information protected by ODE in any circumstance" when it passed section 355a(*o*) was directly contrary to the statutory text stating that the addition of the provision "was not intended to have any effect on FDA's preexisting interpretations of the other provisions of section [355], including the provisions under section [355](j) that otherwise allow for labeling carve outs." *Id.* (citing 21 U.S.C. § 355a(*o*)(3)(D)). Accordingly, the agency concluded that its longstanding interpretation of its carve-out authority remained valid.

Concurrently with its letter decision, FDA granted ANDA approval to four manufacturers to market generic aripiprazole for indications other than Tourette's disorder: Intervenor-Defendants Alembic, Teva, and Torrent, as well as non-party Hetero Labs Ltd. *See* AR 643-45, 660-62, 678-80, 696-98, 714-16, 733-35, 750-52. The remaining Intervenor-Defendants all have ANDAs currently pending before FDA.

C. Procedural History

Before FDA made a final decision whether to approve ANDAs for generic aripiprazole, Otsuka filed a preemptive suit against the agency to block generic competition. After Otsuka's initial complaint was mooted by developments at the agency, Otsuka filed an amended complaint along with a motion for a Temporary Restraining Order and/or Preliminary Injunction. (ECF No. 77). On April 28, 2015, within hours of FDA granting final approval to several ANDAs for

generic aripiprazole, this Court held a hearing on Otsuka's motion. The Court issued a 24-page opinion the next day denying Otsuka's motion and holding that Otsuka had failed to establish *any* of the four requirements for a temporary restraining order or preliminary injunctive relief. Mem. Op. (ECF No. 100) at 2, 18.

In the memorandum opinion, this Court concluded that Otsuka was unlikely to succeed on the merits of its claim that FDA's decision to approve ANDAs for generic aripiprazole with labeling that carves out information concerning the treatment of Tourette's disorder in pediatric patients was unlawful. Applying *Chevron*'s two-step framework, the Court first considered and rejected Otsuka's argument that Congress had foreclosed FDA's interpretation. The Court concluded that Otsuka's argument that 21 U.S.C. § 355a(*o*) establishes a ceiling for FDA's carve-out authority was unconvincing for several reasons. The Court indicated that Otsuka's argument "ignores the critical fact that section [355a](*o*) sets forth circumstances where FDA cannot *deny* approval for a labeling carve-out; it does not . . . address situations where FDA can or cannot *grant* approval." Mem. Op. at 11. The Court rejected Otsuka's attempt to turn section 355a(*o*) from a pro-carve-out provision into an implied restriction on FDA's ANDA approval authority. The Court noted that the *expressio unius* canon, relied upon by Otsuka, does not apply "'unless it is fair to suppose that Congress considered the unnamed possibility and meant to say no to it.'" *Id.* at 12 (quoting *Marx v. Gen. Revenue Corp.*, 133 S. Ct. 1166, 1175 (2013)). Here, the Court reasoned, there is nothing to support such an inference. Otsuka had identified no evidence that "Congress even contemplated orphan drug exclusivity at the time section [355a](*o*) was proposed and enacted," much less purposefully chosen to exclude it. *Id.* at 12-13. And, the Court added, the statute's structure points strongly against such an inference. FDA has broad authority to approve ANDAs carving out exclusivities, including orphan drug exclusivity, which

"does not appear to be abrogated by section [355a](*o*)." *Id.* at 13. Moreover, the Orphan Drug Act itself "confirms FDA's authority to approve ANDAs carving out an orphan drug exclusivity," as courts—including the Fourth Circuit—have repeatedly held. *Id.* at 15 (discussing *Sigma-Tau Pharms., Inc. v. Schwetz*, 288 F.3d 141 (4th Cir. 2002)).

Based on these considerations, the Court concluded that section 355a(*o*) does *not* clearly proscribe FDA's ability to omit information protected by pediatric orphan drug exclusivity from a generic manufacturer's labeling, and it reasoned that if it were deciding the issue *de novo*, it "would side with the interpretation of FDA and Defendant-Intervenors." Mem. Op. at 16. The Court then stated that there appeared to be some ambiguity in Congress's intent and thus moved on to *Chevron* Step 2. Applying that highly deferential test, the Court concluded that "the statute, case law, and FDA regulations all support the FDA's construction." *Id*. at 17. The Court explained that FDA's reading was consistent with its established precedent, as the agency has "on multiple occasions over the past decade approved ANDA drug products during the NDA-holder's seven-year period of orphan drug exclusivity, despite the fact that the orphan indication covered a pediatric use." *Id*. at 18. By contrast, the Court recognized that Otsuka's proposed construction was not only inconsistent with established agency practice, but also "would nullify the limitation expressly written into section 360cc"—providing orphan drug exclusivity only for the treatment of a specific disease or condition—and thus would "directly contradict[]…that provision's text and the Fourth Circuit's holding in *Sigma-Tau*." *Id.* at 17-18.

ARGUMENT

Otsuka's suit against FDA to block *all* generic competition to Abilify® for seven years rests on a myopic view of FDA's authority to approve ANDAs that carve out portions of brand-name drug labeling—a view that is belied by the FDCA as a whole, the orphan drug provisions in particular, and controlling Fourth Circuit authority. Any doubt is squarely resolved by agency

regulations (and practices) entitled to deference. FDA has broad authority to approve ANDAs carving out exclusivities under the FDCA, including orphan drug exclusivity. That authority is not abrogated by 21 U.S.C. § 355a(*o*), which by its plain terms promotes FDA's carve-out authority, instead of, as Otsuka urges, constraining its authority to *approve* ANDAs. Otsuka's reading of section 355a(*o*) would turn the provision on its head, and it would lead to significant and unwarranted delays in generic drug entry that are antithetical to the pro-consumer, pro-competition goals of the FDCA.

FDA's recognition that it has authority to approve ANDAs that omit pediatric information protected by an orphan drug exclusivity from their labeling is the only reasonable reading of the FDCA. At a minimum, the agency's longstanding and consistent interpretation of the statute it administers is not foreclosed or otherwise unreasonable. Accordingly, the Court should grant the Intervenor-Defendants' motion for summary judgment.

I. Standard of Review

Otsuka's sole claim for relief arises under the Administrative Procedure Act ("APA"). "Because claims brought under the APA are adjudicated without a trial or discovery, on the basis of an existing administrative record, such claims are properly decided on summary judgment." *Audubon Naturalist Soc'y of the Cent. Atlantic States, Inc. v. U.S. Dep't of Transp.*, 524 F. Supp. 2d 642, 660 (D. Md. 2007). Judicial review under the APA "is highly deferential." *Cutonilli v. Fed. Transit Admin.*, No. ELH-13-2373, 2015 WL 1431251, at *17 (D. Md. Mar. 30, 2015). A party seeking to set aside agency action as arbitrary and capricious—as Otsuka does here—"has the burden" of persuasion. *Id.* The scope of the court's review "is narrow and a court is not to substitute its judgment for that of the agency." *Motor Vehicle Mfrs. Ass'n of the U.S. v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 43 (1983).

Because Otsuka is challenging FDA's "construction of the statute which it administers," the Court's review is governed by the familiar *Chevron* framework, which asks "two questions." *Chevron*, 467 U.S. at 842. The first is known as Step 1 of *Chevron*: "First, always, is the question whether Congress has directly spoken to the precise question at issue. If the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Id.* at 842-43. "If, however, the court determines Congress has not directly addressed the precise question at issue, the court does not simply impose its own construction on the statute, as would be necessary in the absence of an administrative interpretation," and instead moves to Step 2. *Id.* at 843. "[I]f the statute is silent or ambiguous with respect to the specific issue, the question for the court is whether the agency's answer is based on a permissible construction of the statute." *Id.* Under Step 2, the Court must uphold an agency's construction of the statute "so long as the interpretation is not 'arbitrary, capricious, or manifestly contrary to the statute.'" *Philip Morris USA, Inc. v. Vilsack*, 736 F.3d 284, 290 (4th Cir. 2013) (quoting *Chevron*, 467 U.S. at 844). "A construction meets this standard if it 'represents a reasonable accommodation of conflicting policies that were committed to the agency's care by the statute.'" *Id.* (quoting *Chevron*, 467 U.S. at 845).

II. The FDCA Unambiguously Provides FDA With Authority To Carve Out Pediatric Information Protected by Orphan Drug Exclusivity

Plaintiffs' argument fails at the starting gate, because far from ruling out FDA's statutory construction, the FDCA unambiguously provides FDA with authority to approve ANDAs that carve out all manner of information protected by patents and exclusivities, including orphan drug exclusivity. The Fourth Circuit and other courts have confirmed this interpretation under Step 1 of *Chevron*. *See, e.g.*, *Sigma-Tau Pharms., Inc. v. Schwetz*, 288 F.3d 141, 145, 148 n.3 (4th Cir. 2002); *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996); *AstraZeneca*

Pharms. LP v. Apotex Corp., 669 F.3d 1370, 1379 (Fed. Cir. 2012). Those decisions and the plain text of the FDCA (including the orphan drug subchapter) should decide this case.

Contrary to Otsuka's claims, nothing in section 355a(*o*) limits FDA's authority to carve out orphan drug-protected pediatric information when the resulting labeling will be safe and effective for all remaining labeled uses. Section 355a(*o*) is a *pro*-carve-out provision adopted by Congress to limit the grounds FDA may invoke to *disapprove* an ANDA; it does not constrain FDA from carving out information protected by an exclusivity in order to approve an ANDA for other, unprotected uses. *Accord* Mem. Op. at 11-12. And while Otsuka contends that section 355a(*o*) implicitly limits FDA's carve-out authority in any context that is not specifically mentioned in this single section, the text, structure, and purpose of the FDCA generally and section 355a(*o*) specifically rule out Otsuka's negative-implication argument.

A. FDA Has Clear and Unambiguous Authority To Approve Generic Drugs With Labeling That Carves Out Approved Uses of a Brand-Name Drug

1. The Hatch-Waxman Amendments to the FDCA

The FDCA provides FDA with broad, clear, and unambiguous authority to approve ANDAs that carve out labeling approved for a listed drug. Although, in general, the labeling of a generic drug must be the same as the labeling for the brand-name drug, there are exceptions. One key exception to the general rule of "sameness" has always been that ANDA applicants are permitted to seek approval for fewer than all of the FDA-approved indications and uses for the RLD, and that in such situations the labeling for the ANDA product must differ correspondingly from the RLD's labeling. *See* Mem. Op. at 14. The House Report on the Hatch-Waxman Amendments made this point explicitly: it recognized that there would be instances where "the proposed labeling for the generic drug may not be exactly the same," including, for example, situations where "an ANDA [is] approved for less than all of the indications for which the listed

drug has been approved." H.R. REP. NO. 98-857(I), at 21-22 (1984). It went on to explain that the ANDA applicant "*need not seek approval for all of the indications for which the listed drug has been approved*. For example, if the listed drug has been approved for hypertension and angina pectoris, and if the indication for hypertension is protected by patent, then the applicant could seek approval for only the angina pectoris indication." *Id*. at 21 (emphasis added).

In accordance with the drafters' clear intent, the Hatch-Waxman Amendments expressly authorize different labeling for brand and generic drugs. 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"—*but with several exceptions*, including 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 rest of the FDCA is in accord with a general rule of sameness *for a given use*, but contains no concomitant requirement that an ANDA applicant seek approval for *all* uses approved for the brand. For example, the Hatch-Waxman Amendments require an ANDA filer to provide a statement informing FDA of those uses for which it is not seeking approval due to an existing "method of use" patent—a provision that would be superfluous if ANDA applicants could not omit information from an RLD's labeling. *See* 21 U.S.C. § 355(j)(2)(A)(viii). The Amendments also list certain situations in which FDA may not approve an ANDA. One of those situations is where "information submitted with the [ANDA] is insufficient to show that each of the proposed conditions of use have been previously approved for the listed drug." 21 U.S.C. § 355(j)(4)(B). The FDCA thus does not require that an ANDA include every "condition of use" for which the RLD was approved—only that where an ANDA includes such a use, that use must have been approved for the RLD. *See* 21 U.S.C. § 355(j)(2)(A)(i); *AstraZeneca*, 669 F.3d at 1379 (noting that, "while generic applicants cannot obtain approval for uses beyond those

already approved by the FDA, nothing in the Act requires that an ANDA must encompass *every* approved indication") (internal citations omitted).

In light of this clear text and legislative history, the Fourth Circuit and other courts repeatedly have read the statute to unambiguously grant broad carve-out authority to FDA. In *Sigma-Tau*, the brand-name drug was approved for two uses, only one of which was subject to an existing orphan drug exclusivity. FDA approved ANDAs carving out the exclusivity. The Fourth Circuit rejected the brand-name drug manufacturer's argument that FDA's approval "violated the 'same labeling' requirement of the FDCA." *Sigma-Tau*, 288 F.3d at 148 n.3. The court reasoned that the FDCA expressly permits labeling differences that are required "because the new [generic] drug and the listed drug are produced or distributed by different manufacturers,'" and that exception allows FDA to approve labeling differences that carve out orphan drug exclusivity. *Id.* (quoting 21 U.S.C. § 355(j)(2)(A)(v)).

The D.C. Circuit has also held that the FDCA unambiguously gives FDA authority to approve ANDAs that carve out labeling information awarded pursuant to a three-year exclusivity under what is now codified at section 355(j)(5)(F)(iv): "[T]he statute expresses the legislature's concern that the new generic be safe and effective for each indication that will appear on its label; whether the new generic lists every indication approved for use of the pioneer is a matter of indifference." *Bristol-Myers Squibb Co.*, 91 F.3d at 1499-1500. The court reasoned that any other interpretation would turn an exclusivity awarded for a "change approved in the supplement," 21 U.S.C. § 355(j)(5)(F)(iv) (there, a new "indication"), into "three more years of protection against the approval of any ANDA based upon that pioneer drug, including one that lists only the original indication(s) of the pioneer"—"much broader protection from competition than [the statute] would otherwise confer." *Bristol-Myers Squibb Co.*, 91 F.3d at 1500.

2. The Orphan Drug Act

The orphan drug subchapter in the FDCA also provides FDA authority to approve ANDAs carving out orphan drug exclusivities. *See* Mem. Op. at 15 ("[T]he Orphan Drug Act also confirms FDA's authority to approve ANDAs carving out orphan drug exclusivity."). Section 360cc(a) provides that "for a drug designated under section 360bb of this title for a rare disease or condition, the Secretary may not approve another application under section 355 of this title . . . *for such drug for such disease or condition* . . . until the expiration of seven years from the date of the approval of the approved application" (emphasis added).

As the Fourth Circuit held in *Sigma-Tau*, "the plain language of the [Orphan Drug Act] is unambiguous." 288 F.3d at 144-45. Section 360cc "simply provides that the FDA 'may not approve' generics for a protected indication," and does not preclude ANDA approvals for other approved uses unprotected by orphan drug exclusivity:

> By using the words "such drug for such disease or condition," Congress made clear its intention that [section 360cc] was to be disease-specific, not drug-specific. In other words, the statute as written protects uses, not drugs for any and all uses. Congress could have written [section 360cc] more broadly by prescribing that the FDA "may not approve another application . . . for such drug," but it chose not to draft the statute in that way. Because Congress has spoken directly to the dispositive question before us, our inquiry is at an end.

Id. at 145.[3]

This law is controlling. As in *Sigma-Tau*, this dispute is about an exclusivity granted under the orphan drug subchapter of the FDCA. Otsuka has made no serious attempts to distinguish this authority, other than by suggesting that 21 U.S.C. § 355a(*o*) trumps it and turns orphan drug exclusivities into seven-year exclusivities *for the entire drug* whenever a pediatric

[3] By contrast, when Congress intends to provide exclusivity for *a drug*—rather than for a particular indication for a drug—it knows how to do so. *See* 21 U.S.C. § 355(c)(3)(E)(ii), 355(j)(5)(F)(ii) (providing, in the case of exclusivity for a new chemical entity, that FDA may not approve an application "which refers *to the drug*" protected by exclusivity (emphasis added)).

indication is at issue. But Otsuka's argument is completely at odds with the clear text of section 360cc(a), as interpreted in *Sigma-Tau*. And as discussed below, Plaintiffs' reading of section 355a(*o*) is unsupportable.

B. 21 U.S.C. § 355a(*o*) Does Not Limit FDA's Authority To Approve Labeling Carve-Outs

Otsuka asks this Court to set aside controlling statutory, Fourth Circuit, and regulatory authority by reading section 355a(*o*) to prohibit FDA from approving ANDAs that carve out labeling protected by orphan drug exclusivity that includes a pediatric use. Otsuka's interpretation of section 355a(*o*) is wrong. Otsuka's effort to turn section 355a(*o*) into a restriction on FDA's carve-out authority relies primarily on the *expressio unius* canon. But that canon does not apply here, and it should not be used to generate a reading of section 355a(*o*) that would contradict the law's text, history, and purpose.

1. Section 355a(*o*) Enhances, Rather Than Diminishes, FDA's Authority To Permit Labeling Carve-Outs

Section 355a(*o*) cannot properly be read to constrain FDA's broad authority to permit labeling carve-outs. The provision states that an ANDA "shall not be considered ineligible for approval" when it carves out pediatric information that "is protected by patent or by exclusivity under clause (iii) or (iv) of section 355(j)(5)(F)." Otsuka has not discussed the operative language—"shall not be considered ineligible for approval"—in its prior submissions to the Court. But that language is fatal to Otsuka's position. As this Court noted, section 355a(*o*) does not restrict FDA's ability to *approve* an ANDA (the interpretation Otsuka urges); section 355a(*o*) restricts when FDA may *disapprove* an ANDA. *See* Mem. Op. at 11 ("Otsuka ignores the critical fact that section [355a(*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.").

Other provisions in the FDCA demonstrate that Congress knew how to restrict FDA's ability to *approve* an ANDA when it wanted to do so; elsewhere the FDCA provides explicitly that FDA "*shall* approve an [ANDA] *unless* . . ." barred by one of a limited set of grounds for disapproval. 21 U.S.C. § 355(j)(4) (emphases added). Section 355(j)(4) makes clear that grounds for disapproving an ANDA are those enumerated therein, and any other grounds for disapproving an ANDA are unlawful. In light of that baseline command to FDA, Otsuka cannot turn a provision limiting FDA's *disapproval* authority into a provision limiting its *approval* authority. Similarly, at no point does section 355a(*o*) say ANDAs that omit pediatric information protected by orphan drug exclusivity "*shall*" be ineligible for approval (instead, it uses a double-negative: "shall not be considered ineligible"). This language permits FDA to approve generics by virtue of its authority under both the Hatch Waxman Amendments and the orphan drug subchapter of the FDCA, as discussed more fully above, *supra* at 19-23.

2. Otsuka's Negative Implication Argument Is Contrary to Section 355a(*o*)'s Text, History, and Purpose.

Otsuka has rested its case almost exclusively on a single canon of statutory construction: *expressio unius est exclusio alterius*. It has argued that this Court should disregard the clear authority in the FDCA to permit labeling carve-outs—which FDA has exercised consistently and which courts have repeatedly upheld. Instead, Otsuka has argued that section 355a(*o*) supersedes any other statutory grant of carve-out authority when pediatric information is implicated. But *expressio unius* cannot bear that interpretive load.

The Fourth Circuit has recognized that the *expressio unius* canon "should be applied warily," *U.S. Immigration & Naturalization Serv. v. Fed. Labor Relations Auth.*, 4 F.3d 268, 272 (4th Cir. 1993), because it is often an "unreliable" guide to congressional intent, *Director, Office of Workers' Comp. Programs v. Bethlehem Mines Corp.*, 669 F.2d 187, 197 (4th Cir. 1982).

And as the Supreme Court has "long held[,] . . . the *expressio unius* canon does not apply 'unless it is fair to suppose that Congress considered the unnamed possibility and meant to say no to it,' and [it] can be overcome by 'contrary indications that adopting a particular rule or statute was probably not meant to signal any exclusion.'" *Marx v. Gen. Revenue Corp.*, 133 S. Ct. 1166, 1175 (2013) (internal citations omitted); *see also Barnhart v. Peabody Coal Co.*, 537 U.S. 149, 168 (2003) ("We do not read the enumeration of one case to exclude another unless it is fair to suppose that Congress considered the unnamed possibility and meant to say no to it."); *Chevron USA, Inc. v. Echazabal*, 536 U.S. 73, 81 (2002) (*expressio unius* is not absolutely applied; there must be a "sensible inference that the term left out must have been meant to be excluded"); Mem. Op. at 12 (recognizing this limitation to the *expressio unius* canon).

Here, as this has Court previously noted, Mem. Op. at 12-13, Otsuka has cited no evidence that Congress even contemplated orphan drug exclusivity at the time section 355a(*o*) was proposed and enacted, let alone that Congress expressly considered orphan drug exclusivity and meant to exclude it. In fact, the text of section 355a(*o*), as well as its history and purpose, demonstrate precisely the opposite.

a. Otsuka's Negative-Implication Argument Is Foreclosed by Section 355a(*o*)'s Savings Clause

In adding section 355a(*o*) to the FDCA, Congress was careful to stipulate that the provision "does not affect . . . the operation of section 355 [of the FDCA]"— the source of FDA's general background authority to carve out labeling information, *supra* at 3, except as "*expressly* provided in paragraphs (1) and (2)" of section 355a(*o*). 21 U.S.C. § 355a(*o*)(3)(D) (emphasis added); *see also* AR 502 & n.39 (FDA letter decision making this point). Otsuka's argument disregards this savings clause. Otsuka has never claimed that paragraphs (1) and (2) of 355a(*o*) *expressly* displace FDA's authority to carve out pediatric labeling information. Nor

could it; those paragraphs only address when FDA *must* carve out pediatric information, not when it may not do so. *See* Mem. Op. at 11. Indeed, Otsuka's *expressio unius* argument, by its very nature, seeks to construe section 355a(*o*) to *implicitly* constrain FDA's carve-out authority. *See Expressio unius est exclusio alterius*, BLACK'S LAW DICTIONARY (10th ed. 2014) (defining *expressio unius* as "[a] canon of construction holding that to express or include one thing *implies* the exclusion of the other" (emphasis added)). But that sort of argument-by-implication is precisely what section 355a(*o*)(3)(D) forbids.

b. Otsuka's Argument Is Inconsistent With Section 355a(*o*)'s History and Purpose

Even without this savings clause, *expressio unius* should not be used to produce a result that Congress never contemplated and that runs directly contrary to Congress's intent. *Accord* Mem. Op. at 13-14. Congress added 21 U.S.C. § 355a(*o*) when it adopted the BPCA in January 2002. At the time, an NDA holder was urging FDA to deem misbranded any drug product that did not include pediatric labeling information (when available), thereby preventing the distribution of these products in interstate commerce. 147 CONG. REC. H10209 (daily ed. Dec. 18, 2001) (referencing 21 C.F.R. § 201.57(f)(9)(ii)). Indeed, the ranking minority member of the relevant House committee, Representative John Dingell, noted that one NDA sponsor had:

> succeeded in convincing FDA that it was entitled to [an] additional 3½ years of exclusivity for the same pediatric study of its drug, Glucophage, that . . . they had submitted to acquire the initial six months of monopoly marketing. Three of those years of alleged exclusivity were based on the company's claim that a study of some 68 pediatric patients was sufficient to merit a new indication of use claim under [21 U.S.C. § 355(j)]. *Normally, such claims only result in differential labeling between a product that was the subject of a new trial and other therapeutically equivalent products on the market.* However, [the NDA sponsor] . . . 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, [the sponsor] has argued that no generic may be marketed during the pendency of its labeling exclusivity.

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

Alarmed by the prospect that such tactics would succeed, with profound and adverse consequences to consumers, Congress added section 355a(*o*) "to override the [existing] requirement that generic versions of pioneer drugs bear labeling for pediatric indications." 147 CONG. REC. H10210 (memorandum to the United States Congress Re: Proposed Amendment to the Hatch-Waxman Act (H.R. 2887), referring to the proposal as the "Anti-Glucophage Bill"). Representative Dingell expressly noted that the misuse of pediatric information to garner three-year exclusivity for a certain indication and wholly block generic competition for *all* approved indications is "a fundamental abuse of the system and were the FDA . . . to accept the claim, consumers would be harmed." 147 CONG. REC. H8105. Representative Dingell also noted that the provision that eventually became section 355a(*o*) "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." *Id.*; 147 CONG. REC. H10212 (same); *accord id.* at H10210 (statement of Rep. Eshoo) ("Importantly the bill we will vote on today . . . closes the 'Glucophage loophole' which allowed one company to get an additional 3 years of marketing exclusivity. This bill ensures that no company will be able to take advantage of the exclusivity granted by this very important legislation.").

Given this clear and unambiguous evidence of congressional intent, it defies logic and common sense to suggest that section 355a(*o*) can be interpreted to block generic competition for all uses for an additional seven years, when Congress enacted the provision to prevent exactly this type of unwarranted extension of exclusivity. Indeed, Congress thought that an additional

three years was too long—yet Otsuka unabashedly wants *seven*. Moreover, Otsuka readily concedes that the number of pediatric patients who suffer from Tourette's disorder (and therefore qualified Otsuka to receive orphan drug exclusivity for that indication) is fewer than 120,000. Declaration of Robert D. McQuade, Ph.D. ¶ 10, ECF No. 77-2. IMS data show that even if Abilify® were prescribed to this entire pediatric population, those sales still would be only a small percentage of the more than $4.7 billion worth of Abilify® sales in the United States in fiscal year 2013. *Supra* at 11. In other words, Otsuka seeks to block the approval and marketing of generic aripiprazole products for *all* uses when its *orphan drug* exclusivity by its own admission could at the very most cover fewer than 120,000 patients.

This Court should not countenance such a result, which would destroy the careful balance Congress struck when it enacted the Orphan Drug Act and the Hatch-Waxman Amendments to the FDCA—a balance the Fourth Circuit weighed in *Sigma-Tau* and found to reinforce FDA's carve-out authority under the Orphan Drug Act. As the Fourth Circuit explained:

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

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

Otsuka has already enjoyed well over twelve years of market exclusivity for its product. Abilify® accounted for over $4.7 billion of Otsuka's U.S. revenues in its fiscal year for 2013, and $3.9 billion in Otsuka's U.S. revenues during the nine months that contributed to its fiscal year

for 2014.[4] While those revenues may represent the legitimate results Otsuka earned for the patent covering the aripiprazole compound (as extended by the associated six-month pediatric exclusivity), those exclusivity periods have now come to an end. Any additional regulatory exclusivities Otsuka may have for this product do not cover all uses, and Otsuka should not be permitted to leverage the single exclusivity for Tourette's disorder into something it is not. The statute simply will not bear such an anticompetitive and anti-consumer result.

3. Other Canons of Construction That Otsuka Has Invoked Do Not Apply

In addition to its heavy reliance on the *expressio unius* canon, Otsuka has invoked two related canons—the canon that a more specific statutory provision takes precedence over a general statute and the presumption against superfluity. *See* Pls.' Mot. for TRO (ECF No. 77) at 20; Pls.' Reply in Support of Mot. for TRO (ECF No. 90) at 3-5. But these canons are also inapposite.

First, just like Otsuka's *expressio unius* argument, these canons of construction at best support an argument that section 355a(*o*) *implicitly* contracted the scope of FDA's carve-out authority under section 355. As discussed above, however, section 355a(*o*)(3)(D) forecloses that argument. *Supra* at 25-26.

Second, the rule that a more specific statutory provision trumps a more general statute does not apply because nothing in section 355a(*o*) contradicts any of the FDCA provisions that FDA has long relied on to carve out information protected by exclusivities from a generic applicant's label. As explained above, *supra* at 5-6, 12-14, 16-17, section 355a(*o*) and these other provisions of the FDCA have different but complementary purposes. Section 355a(*o*) limits FDA's authority to deny approval to ANDA carve-outs, while the Hatch-Waxman

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

Amendments and the orphan drug subchapter affirmatively give FDA authority to permit labeling carve-outs. Where two statutes can be harmonized without invalidating one, a court should choose the reading that gives full force to congressional enactments rather than unnecessarily limiting them. *See Watt v. Alaska*, 451 U.S. 259, 267 (1981) ("[R]epeals by implication are not favored…. We must read the statutes to give effect to each if we can do so while preserving their sense and purpose.") (internal quotation marks and citations omitted); *Morton v. Mancari*, 417 U.S. 535, 551 (1974) ("[W]hen two statutes are capable of co-existence, it is the duty of the courts, absent a clearly expressed congressional intention to the contrary, to regard each as effective.").

Third, section 355a(*o*) is not superfluous under the statutory interpretation defended by Intervenor-Defendants and FDA. Otsuka claims that reading the FDCA to provide FDA with general authority to carve out pediatric information from labeling means that the BPCA was unnecessary and section 355a(*o*) is meaningless; on that reading, Otsuka argues, FDA could have simply relied on its preexisting carve-out authority to prevent a pediatric exclusivity from blocking generic competition. Pls.' Reply in Support of Mot. for TRO at 3-5. But Otsuka's argument is flawed for at least two reasons. First, the BPCA cut off any potential argument that FDA had discretion to refuse to approve ANDAs simply because they carved out certain pediatric labeling information. Second, section 355a(*o*) provides FDA with new authority to require certain pediatric labeling information for a generic drug using a carve-out, when that information is needed to ensure the drug is safe and effective. *See* 21 U.S.C. § 355a(*o*)(2). Such authority is irrelevant in this case, because FDA determined that the approved generic labeling *is already* safe and effective with the omission of information for treatment of Tourette's disorder

in pediatric patients. AR 501. But the fact that FDA did not use section 355a(*o*)'s additional authority *in this case* hardly suggests that it is meaningless.

Moreover, even if section 355a(*o*) simply confirmed that FDA has carve-out authority in a particular context that it already possessed under the best—but contested—reading of the statute, that would not make section 355a(*o*) superfluous. Congress may amend a statute not only to establish new law, but also "purely to make what was intended all along even more unmistakably clear." *Brown v. Thompson*, 374 F.3d 253, 259 (4th Cir. 2004) (internal quotation marks and citation omitted). In the administrative law context, Congress may amend a statute merely to "clarify and complement the [agency's] existing authority—*i.e.*, to make assurance double sure—not to extinguish or eliminate it." *Adirondack Med. Ctr. v. Sebelius*, 740 F.3d 692, 698 (D.C. Cir. 2014) (internal quotation marks and citation omitted). There is every reason to believe that is what took place when Congress enacted the BPCA to foreclose a particular interpretation of the FDCA that Congress believed perverted the law's structure and purpose. The fact that Congress acted to preempt an interpretation it disfavored does not establish that Congress believed that interpretation accurately captured existing law, nor does it suggest that Congress believed FDA lacked carve-out authority in other contexts. To interpret Congress's action in this way would dramatically inhibit its ability to clarify legislation. And it would be utterly perverse here, where Congress specifically guarded against this possibility by including a savings clause. *See* 21 U.S.C. § 355a(*o*)(3)(D).

C. Otsuka's Claim Fails Even Under Its Cramped Reading of Section 355a(*o*)

Otsuka's cramped reading of 21 U.S.C. § 355a(*o*) fails for the additional reason that, if it *were* applied, it would require FDA to act in violation of that very section as it relates to Otsuka's three-year exclusivity. Otsuka asserts that section 355a(*o*) cabins FDA's authority to approve drugs that carve out pediatric labeling information, *only* permitting FDA to approve

such ANDAs if the information carved out was added pursuant to a three-year marketing exclusivity awarded pursuant to 21 U.S.C. § 355(j)(5)(F)(iii) and (iv). But the record shows—and Otsuka admits, *see* Pls. Mot. for TRO at 23—that Otsuka *has* exclusivity granted under section 355(j)(5)(F)(iv) for "treatment of pediatric patients with Tourette's Disorder (6-18 years)." *See* ORANGE BOOK[5]; *see also* AR 500 ("[T]he relevant information regarding Tourette's Disorder in pediatric patients is protected by HW exclusivity so it expressly falls within the contours of section [355a](o)."). This is the same labeling information Otsuka asserts cannot be carved out—information on treatment of Tourette's disorder in pediatric patients. Section 355a(*o*) cannot be read to simultaneously restrict FDA's authority to deny approval and restrict its authority to grant approval *for the same labeling information*. FDA cannot be required to *approve and to disapprove the same carve-out*.

Otsuka's only response is that orphan drug exclusivity is different and should be treated differently in this situation. *See* Pls.' Mot. for TRO at 20. But these "differences" do not help Otsuka. Otsuka concedes that orphan drug exclusivity prevents approval only for "information on the label specific to the orphan indication." *Id.* But it is that very same indication-specific information that constitutes the changes to the Abilify® label that gave rise to Otsuka's three-year exclusivity. Otsuka's preferred reading would lead to results that are completely inconsistent with the FDCA, because it would require FDA to carve out an indication from the labeling to permit generic competition during a three-year exclusivity but tie its hands from approving *the same labeling* when an orphan drug exclusivity is also at issue and thus foreclose all generic competition for seven years. *See United States v. Granderson*, 511 U.S. 39, 56 (1994) (favoring an interpretation that produced "'a sensible construction' that avoids attributing to the legislature

[5] That exclusivity expires December 12, 2017.

either 'an unjust or an absurd conclusion'"). It also would require reading into section 355a(*o*) a restriction that does not appear on its face: that information may be carved out if it is protected by a three-year marketing exclusivity *unless* that information also is covered by orphan drug exclusivity. Otsuka's disruptive addition to section 355a(*o*)'s text is not required by the statute (or even consistent with it) and therefore must fail under Step 1 of *Chevron*.

III. At a Minimum, FDA's Construction of the Statute Is Reasonable and Entitled to Deference

Even if FDA's interpretation of its carve-out authority under the FDCA is not *compelled* (and for the reasons set forth above, it is), the agency's construction is certainly not *foreclosed*. Accordingly, if this Court concludes that the statute is ambiguous, it must defer under Step 2 of *Chevron* to FDA's interpretation of its carve-out authority "so long as the interpretation is not 'arbitrary, capricious or manifestly contrary to the statute.'" *Philip Morris USA*, 736 F. 3d at 290 (*quoting Chevron*, 467 U.S. at 844)). FDA's construction, which follows from its regulations and adheres to many years of consistent agency precedent, easily clears this low bar.

A. The FDCA Does Not Foreclose FDA's Interpretation Under *Chevron*

As discussed above, Otsuka's claim that section 355a(*o*) divested FDA of its longstanding authority to approve generic labels that carve out pediatric information protected by an orphan drug exclusivity depends heavily on the *expressio unius* canon. *Supra* at 24-25. But courts have recognized that "[t]he *expressio unius* canon is a 'feeble helper in an administrative setting, where Congress is presumed to have left to reasonable agency discretion questions that it has not directly resolved.'" *Adirondack Med. Ctr.*, 740 F.3d at 697 (quoting *Cheney R.R. Co. v. ICC*, 902 F.2d 66, 68-69 (D.C. Cir. 1990)). An argument from negative implication, like the one Otsuka presses, "is simply too thin a reed to support the conclusion that Congress has clearly resolved [an] issue." *Mobile Commc'ns Corp. of Am. v. FCC*, 77 F.3d 1399, 1405 (D.C. Cir.

1996) (internal quotation marks omitted). That is particularly true where, as here, the canon is "countervailed by a broad grant of authority [to the agency] contained within the same statutory scheme," *Adirondack Med. Ctr.*, 740 F.3d at 697, as well as by a savings clause disclaiming any implicit effect on section 355.

At best, Otsuka's arguments raise a potential ambiguity about whether Congress intended to limit FDA's ability to carve out pediatric information to the specific instances recognized in section 355a(*o*), or whether Congress instead merely wanted to clarify that ANDA approvals should not be denied in that specific context while leaving the agency's general carve-out authority intact. Otsuka cannot show that only the first interpretation is reasonable. Otsuka has pointed to *nothing* in the legislative history that would suggest Congress considered orphan drug exclusivities when it enacted the BPCA. *See* Mem. Op. at 12-13. And it has provided absolutely no explanation why the Congress that acted to prevent pediatric exclusivities from blocking generic competition for unprotected uses would have at the same time intended to prevent FDA from approving generic drug applications for *seven years* whenever an orphan drug indication included pediatric information. *Cf. Whitman v. Am. Trucking Ass'ns., Inc.*, 531 U.S. 457, 468 (2001) ("Congress . . . does not . . . hide elephants in mouseholes.").

B. FDA's Construction Harmonizes Various Provisions of the FDCA While Otsuka's Interpretation Nullifies Statutory Text and Frustrates Congress's Objectives

To the extent the scope of FDA's carve-out authority is ambiguous, the agency's reasonable effort to construe its authority in a manner that harmonizes the various components of the FDCA and furthers congressional intent should receive deference. *See Echazabal*, 536 U.S. at 79-84 (holding that, despite an argument that "*expressio unius*" made the text unambiguous, the statutory text was sufficiently equivocal that the agency's reading was entitled to deference "so long as it makes sense of the statut[e]"). FDA's interpretation gives full effect to Congress's

decision to make orphan drug exclusivity "disease-specific, not drug specific." *Sigma-Tau*, 288 F.3d at 145. The interpretation fits with the Hatch-Waxman Amendments' long-established exception to the law's general same labeling requirement. *See* 21 U.S.C. § 355(j)(2)(A)(v), (j)(4)(G). And FDA's interpretation honors the Hatch-Waxman Amendments' overall policy of getting low-cost generic drugs into the hands of consumers as soon as possible. *See, e.g.*, *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1326 (D.C. Cir. 1998).

By contrast, Otsuka's proposed interpretation would make a hash of the statute and frustrate congressional intent. As this Court recognized, under Otsuka's reading, section 355a(*o*) "would nullify the limitation expressly written into section 360cc—that the exclusivity is given to a drug 'for [the orphan] disease or condition'—and instead treat the orphan drug exclusivity as extending to the drug for *any and all* diseases and conditions, directly contradicting that provision's text and the Fourth Circuit's holding in *Sigma-Tau*." Mem. Op. at 17-18 (emphasis added). Moreover, Otsuka's interpretation is unapologetically divorced from Congress's purpose in enacting section 355a(*o*), as Otsuka would turn a pro-carve-out provision into an unprecedented seven-year barrier to generic competition for unprotected uses. FDA's decision to adopt an interpretation that avoids these consequences is plainly reasonable.

C. FDA Has Consistently Exercised Its Authority To Permit Labeling Carve-Outs Pursuant to Established Regulations

Finally, the reasonableness of FDA's decision to approve ANDAs omitting the information covered by Otsuka's orphan drug exclusivity is reinforced by the fact that "'FDA has been consistent in how it has interpreted'" the carve-out provisions over an extended period of time. Mem. Op. at 18 (quoting *Hospira, Inc. v. Burwell*, No.GJH-14-02662, 2014 WL 4406901, at *13 (D. Md. Sept. 5, 2014)); *see also Kasten v. Saint-Gobain Performance Plastics Corp.*, 131 S. Ct. 1325, 1336 (2011) (noting that the "length of the time the agencies have held"

their position "suggests that [the position] reflect[s] careful consideration" and is entitled to substantial deference).

FDA's regulations recognize the general authority granted by the FDCA to permit labeling changes based on the "omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under [the FDCA]." 21 C.F.R. § 314.94(a)(8)(iv). Under its longstanding regulations, FDA will approve an ANDA that omits "aspects of the listed drug's labeling [that] are protected by patent, or by exclusivity [if] such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use." 21 C.F.R. § 314.127(a)(7). Likewise, FDA's regulations implementing the Orphan Drug Act provide that "[o]rphan-drug exclusive approval *protects only the approved indication or use of a designated drug*," in recognition of the statute's unambiguous limitations. 21 C.F.R. § 316.31(b) (emphasis added).

FDA has consistently applied its statutory authority recognized by these regulations to approve generic drug products with labeling that omits indications protected by an RLD's statutory exclusivity—including orphan drug exclusivity based on pediatric use. *See, e.g.*, Ltr. from J. Woodcock to R. Church, at 5 n. 15, Dkt. No. FDA-2014-P-1649 (Feb. 24, 2015) ("Fusilev CP Ruling") (allowing ANDAs to carve out an orphan drug protected indication and acknowledging FDA's authority to approve generic drug products with labeling that omits protected information); Ltr. from J. Woodcock to D. Bunce, at 6, Dkt. No. FDA-2013-P-1293 ("FDA has affirmed its authority to approve generic drug products with labeling that omits protected information on many occasions."); Ltr. from J. Woodcock to G. Trout, at 6, Dkt. No. FDA-2013-P-0247 (Aug. 1, 2013) (same); Ltr. from J. Woodcock to R. Trainor, at 9 n.14, Dkt. No. FDA-2010-P-0545 (Feb. 24, 2011) ("On a number of occasions, we have affirmed our

authority to approve ANDAs with carved-out labeling.") (citing ribavirin, pregabalin, amifostine, dronabinol, and ramipril).[6]

In the letter decision to Otsuka at issue in this case, FDA specifically recognized and relied on this history. *See* AR 499-500. FDA discussed a post-BPCA precedent involving ANDAs referencing Mobic® (meloxicam tablets) (NDA No. 20-938) in which the agency approved labeling carve-outs of pediatric information protected by both three-year pediatric exclusivity *and* an orphan drug exclusivity. AR 499. As FDA explained, the agency approved multiple ANDAs referencing Mobic® that carved-out "labeling associated with the ODE" and thus "omitted certain information related to" a pediatric indication, *i.e.*, "treatment of juvenile rheumatoid arthritis." AR 500 (capitalization omitted).

In addition to the Mobic® precedent, FDA has on several other occasions also approved ANDA drug products during the NDA-holder's seven-year period of orphan drug exclusivity, *despite the fact that the orphan indication covered a pediatric use*. For example:

[6] *See also* Ltr. from J. Woodcock to S. Auten, at 8 n.11, Dkt. No. FDA-2010-P-0087 (Jul. 30, 2010) ("On a number of occasions, we have affirmed our authority to approve ANDAs with carved-out labeling) (collecting decisions); Ltr. from J. Woodcock to R. R. Wilk-Orescan, at 9, Dkt. Nos. FDA-2008-P-0343 and FDA-2008-P-0411 (Dec. 4, 2008) (collecting decisions); Ltr. from J. Woodcock to E. Lengle, at 8-9, Dkt. No. FDA-2008-P-0069 (Jul. 28, 2008) ("[W]e again reaffirm our authority to approve generic drug products with carved-out labeling.") (collecting decisions); Ltr. from G. Buehler to ANDA for Metaxalone Tablets Applicant, at 1 (Mar. 1, 2004), available at http://www.fda.gov/ohrms/dockets/dailys/04/mar04/031904/04p-0140-cp00001-07-Tab-06-vol1.pdf ("The regulatory principles governing FDA's decision on this matter are well established. FDA has authority to approve ANDAs that omit labeling carried by the listed drug, when such labeling is protected by patent or exclusivity."); Ltr. from J. Woodcock to M. Macdonald, D. Jaskot, and J. Hurst, at 6, Dkt. Nos. 01P-0495/CP1, 02P-0191/CP1, & 02P-0252/CP1 (Jun. 11, 2002) ("FDA has the authority to approve ANDAs with labeling that is not identical to that of the listed drug.").

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

  - Gilead Sciences obtained orphan drug exclusivity for Viread® for the treatment of HIV-1 infection in pediatric patients that expires on March 24, 2017. The six-month pediatric exclusivity extension for this orphan indication expires on September 24, 2017.[7]

  - FDA approved Teva's ANDA on March 18, 2015—nearly 2.5 years before Gilead's orphan drug exclusivity (as extended by pediatric exclusivity) expired.[8]

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

  - Salix Pharmaceuticals obtained orphan drug exclusivity for Colazal® for the treatment of mildly to moderately active ulcerative colitis in pediatric patients, which expired on December 20, 2013. The six-month pediatric exclusivity extension for this orphan indication expired on June 20, 2014.[9]

  - FDA approved ANDAs submitted by Roxane, Mylan, and Apotex on December 28, 2007—nearly 6.5 years before Salix's orphan drug exclusivity (as extended by pediatric exclusivity) expired.[10]

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

  - Schering Corporation received orphan drug exclusivity for Rebetol® for the treatment of chronic hepatitis C in pediatric patients, which expired on July 29, 2010. The six-month pediatric exclusivity extension for this orphan indication expired on Jan. 29, 2011.[11]

  - On April 6, 2004, FDA acknowledged that generic applicants were permitted to seek approval of the adult use of ribavirin even though the pediatric use is protected by orphan drug exclusivity. Ltr. from S. Galson to D. Fox at 8 n.21, Dkt. No. 2003P-0321/CP1 (Apr. 6, 2004) ("[C]ertain pediatric information is currently protected by orphan exclusivity, but ANDA applicants for generic ribavirin capsule drug products may still receive approval for the adult use of ribavirin capsules in combination with Intron A") ("Rebetol CP Ruling").

---

[7] *See* Orange Book Searchable Database, at Patent and Exclusivity Search Results for NDA No. 21356.

[8] *See* Approval Letter for Teva Pharmaceuticals USA, ANDA No. 91-612 *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/091612Orig1s000ltr.pdf (last visited Apr. 18, 2015).

[9] *See* Orphan Drug Designations and Approval Database, at Orphan Drug Approval for Colazal, *available at* http://www.accessdata.fda.gov/scripts/opdlisting/oopd/ (last visited Apr. 18, 2015) (searchable by proprietary name) ("Orphan Drug Database").

[10] *See* Drugs@FDA, Approval Histories related to ANDA Nos. 77-806 (Roxane); 77-807 (Mylan) and 77-883 (Apotex Inc.), *available at* http://www.accessdata.fda.gov/scripts/cder/drugsatfda/ (last visited Apr. 18, 2015).

[11] *See* Orphan Drug Database, at Orphan Drug Approval for Rebetol.

Otsuka has not previously tried to distinguish this precedent or to suggest that FDA's regulations do not authorize carve-outs under the circumstances presented in this case.[12] Instead, Otsuka's sweeping contention is that FDA has acted lawlessly for more than a decade (from 2004 to 2015) when it granted ANDA approvals in just this situation—where an NDA holder has an orphan drug exclusivity with a pediatric component. But as discussed above, Otsuka's radically narrow construction of FDA's carve-out authority is not supported, much less compelled, by the text, structure, legislative history, or purpose of the FDCA. Under *Chevron*, Otsuka's effort to uproot settled agency precedent must be rejected.

Conclusion

For the foregoing reasons, Intervenor-Defendants respectfully request that the Court grant their Motion for Summary Judgment.

Respectfully submitted,

[12] To this point, Otsuka has argued only that FDA's regulations are unlawful under the statute. *See* Pls.' Mot. for TRO at 20-22. To the extent Otsuka changes course at the summary judgment stage and argues that FDA's action is inconsistent with its own regulations, Otsuka would have to overcome the "substantial deference" an agency receives when construing its own regulations. *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994); *see also* Mem. Op. at 17.

TEVA PHARMACEUTICALS USA, INC.

By: /s/ Brian T. Burgess

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

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

Attorneys for Intervenor-Defendant Teva Pharmaceuticals USA, Inc.

APOTEX INC. and
APOTEX CORPORATION

By: /s/ Jerrold A. Thrope

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

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

Attorneys for Intervenor-Defendants Apotex Inc. and Apotex Corporation

ALEMBIC PHARMACEUTICALS LIMITED, ALEMBIC LIMITED, ALEMBIC GLOBAL HOLDING SA, AND ALEMBIC PHARMACEUTICALS, INC.

By: /s/ Jonathan M. Weinrieb

Jonathan M. Weinrieb (Bar No. 19270)
Arthur Y. Tsien (*pro hac vice*)
OLSSON FRANK WEEDA TERMAN MATZ PC
600 New Hampshire Avenue, N.W. Suite 500
Washington, D.C. 20037
(202) 789-1212

Dennies Varughese (*pro hac vice*)
STERNE, KESSLER, GOLDSTEIN, & FOX P.L.L.C.
1100 New York Avenue, NW
Washington, D.C. 20005

ZYDUS PHARMACEUTICALS (USA) INC.

By: /s/ Chad A. Landmon

Chad A. Landmon (*pro hac vice*)
William C. Rose (*pro hac vice*)
AXINN, VELTROP & HARKRIDER LLP
950 F. Street, N.W.
Washington, DC 20004
(202) 912-4700
clandmon@axinn.com
wrose@axinn.com

Delphine Knight Brown (*pro hac vice*)
Suchira Ghosh (*pro hac vice*)
AXINN, VELTROP & HARKRIDER LLP
114 W. 47th St., 22nd Floor
New York, NY 10036

(202) 371-2600

Attorneys for Intervenor-Defendants Alembic Pharmaceuticals Limited, Alembic Limited, Alembic Global Holding SA, and Alembic Pharmaceuticals, Inc.

TORRENT PHARMA INC. AND TORRENT PHARMACEUTICALS LTD.

/s/ Kimberly A. Ashmore
Kimberly A. Ashmore (Bar No. 28079)
kashmore@wileyrein.com
Wiley Rein LLP
1776 K Street, NW
Washington, DC 20006
(202) 719-7000 (telephone)
(202) 719-7049 (fax)

Of Counsel:

A. Neal Seth (pro hac vice pending)
nseth@wileyrein.com
Wiley Rein LLP
1776 K Street, NW
Washington, DC 20006
(202) 719-7000 (telephone)
(202) 719-7049 (fax)

Attorneys for Intervenor-Defendants Torrent Pharma Inc. and Torrent Pharmaceuticals Ltd.

(212) 728-2201
dknightbrown@axinn.com
sghosh@axinn.com

Stephen Simms (Bar No. 4269)
Simms Showers LLP
201 International Circle
Baltimore, MD 21030
(443) 209-8704
jssimms@simmsshowers.com

Attorneys for Intervenor-Defendant Zydus Pharmaceuticals (USA) Inc.

Dated: May 11, 2015.

CERTIFICATE OF SERVICE

I certify that this document filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) on May 11, 2015.

/s/ *Brian T. Burgess*
Brian T. Burgess