DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

April 28, 2015

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Dear Mr. Tyler:

Elizabeth Dickinson, Chief Counsel, Food and Drug Administration (FDA) has referred your letter of January 21, 2015[1] to me for response. In the letter, you state that "Otsuka's position is that Abilify orphan drug exclusivity has implications for a generic version of Abilify and, specifically, that FDA cannot approve an ANDA for a generic version of Abilify pending the expiration of Otsuka's orphan exclusivity period."[2] More specifically, you argue that "because Abilify's approved indication for the treatment of Tourette's disorder in pediatric patients is protected by orphan drug exclusivity, and FDA cannot omit pediatric information protected by orphan drug exclusivity, FDA is precluded from approving an ANDA for a generic version of Abilify until Abilify's orphan drug exclusivity period expires."[3]

For the reasons described below, we reject Otsuka's arguments and conclude that generic versions of Abilify that otherwise meet the standards for approval, may be approved during the orphan drug exclusivity (ODE) period for Abilify because a generic version of Abilify with the labeling related to use of aripiprazole in pediatric patients with Tourette's Disorder carved out will remain safe and effective for the remaining non-protected conditions of use. We further conclude that section 505A(o) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), entitled "Prompt Approval of Drugs under Section 505(j) When Pediatric Information Is Added to Labeling," does not dictate a contrary result. Accordingly, today FDA has issued approvals for multiple Abbreviated New Drug Applications (ANDAs) referencing Abilify with the protected labeling relating to Tourette's Disorder in pediatric patients carved out.

I. Background

Abilify is the proprietary name for the Otsuka Pharmaceutical's (Otsuka's) products approved under the following new drug applications (NDAs):

- 021436-Aripiprazole Tablets, 2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg
- 021713-Aripiprazole Oral Solution, 1 mg/mL
- 021729-Aripiprazole Orally Disintegrating Tablets, 10 mg and 15 mg[4]
- 021866-Aripiprazole Injection, 7.5 mg/mL

[1] Letter to Elizabeth H. Dickinson, Chief Counsel, FDA, from Ralph S. Tyler, Venable LLP (January 21, 2015).

[2] Id. at 1.

[3] Id. at 2.

[4] 20 mg and 30 mg strengths are in the Discontinued section of the Orange Book.

Abilify is approved for the following indications – 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, and Agitation Associated with Schizophrenia or Bipolar Mania.[5]

FDA first approved Abilify tablets on November 15, 2002 and no ANDAs have been approved for any of the Abilify products since that initial approval. Otsuka's Abilify NDAs 021436, 021713, 021729 and 021866 are currently designated as reference listed drugs (RLDs) for the Tablet, Oral Solution, Orally Disintegrating Tablet and Injection dosage forms of aripiprazole, respectively.[6]

On December 12, 2014, the Center for Drug Evaluation and Research's (CDER's) Division of Psychiatry Products (DPP) approved Supplement No. 038 to NDA 021436, Supplement No. 030 to NDA 021713, Supplement No. 022 to NDA 021729 and Supplement No. 023 to NDA 021866. The December 12, 2014 approvals were for the addition of a new indication for treatment of Tourette's Disorder with labeling that describes pediatric clinical trials in patients with Tourette's Disorder, provides instructions only for pediatric dosing in Tourette's Disorder, and describes warnings and adverse reactions for pediatric patients with Tourette's Disorder.

Upon approval of the supplements, these NDAs received three years of Hatch-Waxman (HW) exclusivity and were assigned the Orange Book code I-700, "treatment of pediatric patients with Tourette's Disorder (6-18 years)."[7] Upon approval of the supplements, these products also received seven years of Orphan Drug Exclusivity (ODE) for the "Treatment of Tourette's Disorder."[8] In addition to the two exclusivities for Tourette's Disorder, the only remaining exclusivity for Abilify is three-year HW exclusivity for "Labeling Revisions Resulting from a Maintenance Trial in Pediatric Patients with Irritability Associated with Autistic Disorder" (Orange Book code M-137).[9]

This letter responds to issues raised in your letter of January 21, 2015 and therefore only addresses the labeling carve-out for Tourette's Disorder (protected both by three-year HW

[5] The latter indication is approved only for Abilify Injection.

[6] See *Approved Drug Products with Therapeutic Equivalence Evaluations*, 35th Ed. 2015 (commonly referred to as the "Orange Book"), http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm.

[7] See Orange Book at http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=021436&Product_No=001&table1=OB_Rx (accessed April 25, 2015).

[8] See id.; Letter from Gayatri R. Rao, M.D. to Otsuka Pharmaceutical Development & Commercialization, Inc, re: Orphan-drug designation 05-2079 (February 24, 2015). As noted in FDA's General Advice letters to Otsuka dated March 27, 2015 and April 10, 2015, the scope of approval is reflected by the approved labeling, not the HW exclusivity or ODE codes or approval letters.

[9] See Orange Book at http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=021436&Product_No=001&table1=OB_Rx (accessed April 25, 2015). Abilify is also protected by a number of listed patents which will not be addressed herein.

exclusivity expiring December 12, 2017 and seven-year ODE expiring December 12, 2021) for ANDAs referencing NDAs 021436, 021713, 021729 and 21866.[10] As noted above, today FDA has issued approvals for multiple ANDAs referencing NDAs 021436 and 021729 with labeling relating to the ODE and the 1-700 HW exclusivity carved out.

II. Legal Background

a. Hatch-Waxman Amendments, Patent Listing, and Three-Year Exclusivity

The FD&C Act and FDA regulations require that a sponsor seeking to market a brand-name or innovator drug submit an NDA. NDAs contain, among other things, extensive scientific data demonstrating the safety and effectiveness of the drug for the indication(s) for which approval is sought.[11] In addition, an NDA sponsor must submit with its application a list of patents that claim the approved drug product, drug substance, or approved method of use and for which a claim of infringement can reasonably be asserted against a person engaged in the manufacture, use or sale of the drug product. For method-of-use patents, the sponsor must supply a brief description of the approved method(s) of use claimed by the listed patent. Section 505(b)(1)(G) of FD&C Act; 21 C.F.R. 314.53(b).

The *Drug Price Competition and Patent Term Restoration Act of 1984* (Public Law 98-417) (the Hatch-Waxman Amendments or HW Amendments) was added to the FD&C Act in 1984 as a compromise piece of legislation to create an abbreviated pathway for companies seeking to market a generic version of a previously approved drug. The goals of Congress in enacting the HW Amendments were to provide an abbreviated pathway to speed up approval of generic drug applications while preserving the incentives for brand name companies to innovate. Congress wanted to ensure that on the one hand brand-name drug manufacturers would have meaningful patent protection and a period of marketing exclusivity to enable them to recover their investments in the development of new drugs, while on the other hand ensuring that once the applicable patent protection and exclusivity for these new drugs has expired, consumers would benefit from the rapid availability of lower priced generic versions of innovator drugs.

Among other provisions, the HW Amendments added section 505(j) to the FD&C Act. Under this section, an applicant may submit an ANDA for approval of a generic version of a listed drug approved under section 505(c) of the FD&C Act.[12] The ANDA approval process shortens the time and effort needed for approval by, among other things, allowing an ANDA applicant to rely on FDA's previous finding of safety and effectiveness for a listed drug rather than requiring the ANDA applicant to repeat the clinical trials conducted for the listed drug it references and independently demonstrate the safety and effectiveness of its proposed drug. To rely on such a finding, the ANDA applicant must show that its proposed drug product is the same as the listed drug in many respects (including active ingredient, dosage form, strength, route of

[10] This letter does not address the Abilify Maintena Kit, Aripiprazole Extended-Release Injection, 300 mg and 400 mg (NDA 202971) because the Tourette's Disorder information was not added to the labeling for these products.

[11] Section 505(b)(1) of the FD&C Act.

[12] *Drug Price Competition and Patent Term Restoration Act of 1984,* Pub. L. No. 98-417, 98 Stat. 1585.

administration, and, with certain exceptions, labeling), and that its product is bioequivalent to the listed drug.

The ANDA applicant must identify the listed drug on which it seeks to rely for approval. As described in more detail below, the timing of ANDA approval depends on, among other things, any patent and exclusivity protection for the listed drug that the ANDA references and on whether the ANDA applicant challenges those patents or seeks approval for uses covered by that exclusivity.[13]

Specifically, with respect to each patent submitted by the sponsor for the listed drug and listed in the Orange Book, the ANDA applicant generally must submit to FDA one of four specified certifications under section 505(j)(2)(A)(vii) of the FD&C Act. The certification must state one of the following:

> (I) that such patent information has not been filed (a paragraph I certification),
> (II) that such patent has expired (a paragraph II certification),
> (III) the date on which such patent will expire (a paragraph III certification), or
> (IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted (a paragraph IV certification).[14]

If an applicant files a paragraph I or II certification, the patent in question will not delay ANDA approval. If an applicant files a paragraph III certification, the applicant agrees to wait until the relevant patent has expired before seeking final approval of its ANDA. If, however, an applicant wishes to seek approval of its ANDA before a listed patent has expired by challenging the validity of a patent or claiming that a patent would not be infringed by the product proposed in the ANDA or is unenforceable, the applicant must submit a paragraph IV certification to FDA. An applicant submitting a paragraph IV certification to a listed patent must provide the NDA holder and each patent owner with notice of its patent certification, including a description of the legal and factual basis for the ANDA holder's assertion that the patent is invalid or not infringed.[15]

If a patent is listed at the time an ANDA is submitted and, in response to a paragraph IV certification, the NDA holder or patent owner initiates a patent infringement action against the ANDA applicant within 45 days of receiving the required notice, approval of the ANDA generally will be stayed for 30 months from the date of the notice or such shorter or longer time as the court might order.[16] When the 30-month period has expired, the patent ceases to be a barrier to final ANDA approval, even if the patent litigation is ongoing. Similarly, if the NDA holder and patent owner receive notice of paragraph IV certification and decline to sue within 45 days of receipt of notice, the patent will not be a barrier to approval. FDA plays a ministerial

[13] See, e.g., sections 505(b), (c), (j)(2)(A)(vii), and (j)(5)(B) of the FD&C Act.

[14] Section 505(j)(2)(A)(vii) of the FD&C Act; see also 21 CFR 314.94(a)(12)(i)(A).

[15] Section 505(j)(2)(B) of the FD&C Act.

[16] Section 505(j)(5)(B)(iii) of the FD&C Act.

role in the patent listing process and does not evaluate patent listings or any method-of-use descriptions submitted by the NDA sponsor to confirm or deny the appropriateness of the listing or the accuracy of the descriptions.[17]

The four patent certifications described above are not the only way in which an ANDA applicant may address all relevant patents. When a patent is listed only for a method of use, an ANDA applicant seeking to omit that approved method of use covered by the listed patent need not file a paragraph III or IV certification for that patent. Instead, the applicant may submit a "section viii statement" acknowledging that a given method-of-use patent has been listed, but stating that the patent at issue does not claim a use for which the applicant seeks approval. Specifically, section 505(j)(2)(A)(viii) of the FD&C Act provides that "if with respect to the listed drug referred to in [section 505(j)(2)(A)(i)] information was filed under subsection (b) or (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, [the ANDA must contain] a statement that the method of use patent does not claim such a use."

Such a statement requires the ANDA applicant to omit from its labeling information pertaining to the protected use.[18] If an ANDA applicant files a section viii statement (and makes the requisite labeling carve out), the patent claiming the protected method of use will not serve as a barrier to ANDA approval.[19] Under the FD&C Act, an ANDA applicant must generally submit either a patent certification or a section viii statement for each listed patent.[20] FDA implementing regulations at 21 CFR 314.94(a)(12)(iii) describe when a section viii statement is required:

> If patent information is submitted under section 505(b) or (c) of the [FD&C Act] and § 314.53 for a patent claiming a method of using the listed drug, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, [the ANDA applicant must submit] a statement explaining that the method of use patent does not claim any of the proposed indications.

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[17] See, e.g., *Apotex, Inc. v. Thompson*, 347 F.3d 1335, 1349 (Fed. Cir. 2003); *aaiPharma v. Thompson*, 296 F.3d 227, 242–243 (4th Cir. 2002).

[18] 21 CFR 314.92(a)(1) and 314.94(a)(12)(iii).

[19] See also H.R. REP. NO. 98-857 (Part I) at 21.

> ...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.

[20] A split certification with a paragraph IV certification to some patent claims and a section viii statement to others may be permitted when an ANDA applicant seeks to challenge one or more claims of a patent as invalid, unenforceable or not infringed but also seeks to carve out from its labeling an indication or method of use covered by the same patent.

FDA regulations also expressly recognize that by submitting a section viii statement, an ANDA applicant may omit from the proposed labeling a method of use protected by a listed patent, and therefore need not seek approval for that use.[21]

In addition to provisions tying timing of ANDA approval to relevant patents for the listed drugs, the HW Amendments also included provisions for periods of exclusivity for certain innovations and for changes to approved NDAs. For example, upon its initial approval, Abilify received five years of new chemical entity exclusivity, which prevented submission of ANDAs referencing Abilify for a period of at least four years.[22] See section 505(j)(5)(F)(ii) of the FD&C Act. That exclusivity has since expired and no longer bars ANDA submission or approval.

Most relevant to the issues raised in your letter, the HW Amendments provide that three-year exclusivity attaches to certain changes to an approved NDA.[23] Specifically, under section 505(j)(5)(F)(iv) of the FD&C Act, if a supplemental application is approved and "contains reports of new clinical investigations (other than bioavailability studies), essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement," FDA may not approve an ANDA "*for a change approved in the supplement* before the expiration of three years from the date of approval of the supplement. . . ." (emphasis added). In contrast to the HW provisions regarding five-year new chemical entity exclusivity which provide that if the criteria for five-year exclusivity are met for a listed drug, "no application may be submitted [under section 505(j)] which refers to the application [that has obtained five year exclusivity]" for a period of five years (or four years if it challenges a listed patent with a paragraph IV certification), three-year exclusivity for a supplement does not prevent the submission or approval of every application that references the product with the exclusivity protection. Instead, it protects against the approval of an ANDA that includes the "change approved in the

[21] See also *Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed; Final Rule*, 68 FR 36676 (June 18, 2003) (Patent Submission and Listing Rule). In the preamble to this final rule, we stated that the section viii statement permits an ANDA applicant to "avoid certifying to a patent by stating that it is not seeking approval for the use claimed in the listed patent." Id. at 36682. We stated, "[o]ur position has been that, for an ANDA applicant to file a section viii statement, it must 'carve-out' from the proposed ANDA labeling, the labeling protected by the listed patent." Id.

[22] Orange Book at ADA 5 (23rd ed. 2003).

[23] In addition to the current three-year HW exclusivities for "Treatment of pediatric patients with Tourette's Disorder (6-18 years)," and "Labeling Revisions Resulting from a Maintenance Trial in Pediatric Patients with Irritability Associated with Autistic Disorder," Abilify has already received three-year exclusivity for each of the following indications: "Longer-Term Efficacy of Aripiprazole in the Treatment of Schizophrenia" (Orange Book at ADA 6 (24th ed. 2004)); "Treatment of Acute Manic and Mixed Episodes Associated with Bipolar Disorder" (Orange Book at ADA 11 (25th ed. 2005)); "Maintenance Therapy in Bipolar I Disorder" (Orange Book at ADA 11 (27th ed. 2007)); "Adjunctive Treatment to Treat Patients with Major Depressive Disorder" (Orange Book at ADA 13 (28th ed. 2008)); "Treatment of Acute Manic or Mixed Episodes Associated with Bipolar I Disorder in Pediatric Patients Aged 10-17 Years" (Orange Book at ADA 13 (29th ed. 2009)); "Adjunctive Therapy Added to Lithium or Valproate in Short Term Treatment Bipolar Disorder Manic or Mixed" (Orange Book at ADA 13 (29th ed. 2009); "Treatment of Irritability Associated with Autistic Disorder in Pediatric Patients Ages 6-17 Years of Age" (Orange Book at ADA 15 (30th ed. 2010); and "Maintenance Treatment of Bipolar I Disorder as an Adjunct to Lithium or Valproate" (Orange Book at ADA 14 (32d ed. 2012)), all of which have since expired.

supplement." An ANDA that carves out from its proposed labeling the exclusivity-protected change and therefore does not include the "change approved in the supplement" is not barred by three-year exclusivity from approval during the three-year HW exclusivity term.

b. Orphan Drug Exclusivity

The Orphan Drug Act (Public Law 97-414) was enacted in 1983 and amended the FD&C Act, the Public Health Service Act, and the Internal Revenue Code. In enacting the Orphan Drug Act, Congress sought to promote the development of promising drugs for rare diseases and conditions that would not otherwise be developed and approved, including drugs that are potentially safer or more effective than already approved drugs. Congress recognized that the market for drugs intended to treat people with rare diseases or conditions is generally so limited that the cost of developing such drugs makes a profit by the developer unlikely. Accordingly, as amended, the Orphan Drug Act provides various incentives, including tax credits for clinical research undertaken by a sponsor to generate required data for marketing approval, formal protocol assistance to sponsors of drugs for rare diseases, and a seven-year exclusivity period during which FDA may not approve another sponsor's application "for such drug for such disease or condition," subject to certain conditions. See sections 525-28 of the FD&C Act and section 236 of the Public Health Service Act; see also 21 CFR Part 316.

To receive seven-year ODE, a sponsor must participate in a two-step process that includes designation and approval. A sponsor must first submit a request for designation of its drug for a rare disease or condition which must include, among other things, a scientific rationale to establish a medically plausible basis for the use of the drug for the rare disease or condition identified. See section 526 of the FD&C Act; see also 21 CFR 316.20. To obtain ODE the sponsor must then obtain approval of the drug for the rare disease or condition for which orphan designation was granted. ODE begins on the date that the marketing application is approved and applies to preclude approval for seven years of the same drug (same active moiety) for the same orphan indication for which the drug has been designated and approved. See section 527(a) of the FD&C Act (providing that FDA "may not approve another application . . . for such drug *for such disease or condition* . . . until the expiration of seven years") (emphasis added); 21 CFR 316.31(b)("Orphan-drug exclusive approval protects only the approved indication or use of a designated drug."). ODE, like three-year HW exclusivity, is limited in its scope and does not preclude approval of the same drug for which ODE was granted for a different, unprotected indication.

c. Same Labeling Requirements for Products Approved in ANDAs

Section 505(j)(2)(A)(i) of the FD&C Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]." Section 505(j)(2)(A)(v) also requires that an ANDA contain "information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug . . . except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the FD&C Act] or because the new [generic] drug and the listed drug are produced or distributed by

different manufacturers." See also 21 CFR 314.92(a)(1), 314.94(a)(8)(iv) and 314.127(a)(7)). A parallel provision appears in section 505(j)(4)(G) of the FD&C Act.[24]

Although these provisions are known as the "same labeling" requirement, they do not require that a generic drug's labeling be identical to that of the listed drug it references in every respect. Instead, these provisions reflect Congress' intent that the generic drug be safe and effective for each condition of use prescribed, recommended, or suggested in the generic drug labeling but do not require that an ANDA be approved for each condition of use for which the listed drug is approved. In describing the HW amendments, Congress explicitly acknowledged that, "the bill permits an ANDA to be approved for less than all of the indications for which the listed drug has been approved." H.R. Rep. No. 98-857, pt.1, at 2. See also id. at 21 ("The [ANDA] applicant need not seek approval for all of the indications for which the listed drug has been approved.").

In interpreting the statutory exception to the same labeling requirement, which allows certain labeling differences due to the fact that the proposed ANDA and the listed drug are "produced or distributed by different manufacturers," the regulations at 21 CFR 314.92(a)(1) explicitly state that a proposed generic drug product must have the same conditions of use as the listed drug, except that "conditions of use for which approval cannot be granted *because of exclusivity* or an existing patent may be omitted" (emphasis added). These provisions thus specifically affirm that ANDA applicants may carve out from proposed labeling patent or exclusivity-protected conditions of use and obtain approval for the remaining non-protected conditions of use. Section 314.94(a)(8)(iv) more explicitly sets forth examples of permissible differences in labeling that may result because the generic drug product and listed drug are produced or distributed by different manufacturers. Permissible differences include, but are not limited to, the following:

> . . .differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or *omission of an indication or other aspect of labeling protected by patent or accorded exclusivity* under section 505(j)(5)(F) of the act[25] (emphasis added).

The regulations at 21 CFR 314.127(a)(7) further provide that to approve an ANDA containing proposed labeling that omits "aspects of the listed drug's labeling [because those aspects] are *protected by patent, or by exclusivity*," we must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use" (emphasis added).

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[24] Section 505(j)(4)(G) of the FD&C Act provides that FDA must approve an ANDA unless, among other things, "the 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] except for changes required because of differences approved under [an ANDA suitability petition] or because the drug and the listed drug are produced or distributed by different manufacturers."

[25] We note that although the regulation provides removal of an aspect of labeling protected by exclusivity under section 505(j)(5)(F) as an example of a permissible difference due to difference in manufacturer, FDA has never interpreted this example as the only permissible exclusivity-based carve-out. On the contrary, FDA has consistently permitted labeling carve-outs based on ODE protection as well. See, e.g., ANDA labeling approvals for levoleucovorin (carving out labeling protected by both HW exclusivity and ODE), temozolomide (carving out labeling protected by both HW exclusivity and ODE), and tacrolimus (carving out labeling protected by ODE).

Relevant case law affirms an ANDA applicant's ability to carve out protected labeling without violating the "same labeling" requirement. For example, in *Bristol Myers Squibb v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996), the D.C. Circuit ruled that "the statute expresses the legislature's concern that the new generic be safe and effective for each indication that will appear on its label; whether the label for the new generic lists every indication approved for use of the pioneer is a matter of indifference." Similarly, in *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141, 148, n. 3 (4th Cir. 2002), the Fourth Circuit upheld the right of an ANDA applicant to carve out an indication protected by ODE as a permissible difference due to a difference in manufacturer. The Court observed that orphan exclusivity was "disease-specific, not drug-specific," and noted that if it adopted Sigma Tau's argument this could mean that once we approve an orphan drug for a protected indication, "generic competitors might be prohibited from entering the market for almost any use." Id. at 147. The court further stated that Sigma-Tau's argument might extend exclusivity beyond what Congress intended and "frustrate the longstanding practice of Congress, the FDA, and the courts not to interfere with physicians' judgments and their prescription of drugs for off-label uses." Id. (citations omitted). The court asserted that "[Sigma Tau's theory] to bar the approval of generic drugs, even for unprotected indications. . . [would add] a huge evidentiary hurdle to the generic drug approval process [and] would be profoundly anti-competitive." Id.. Accordingly, the court rejected Sigma Tau's argument and concluded that the statutory scheme permitted an ANDA applicant to carve out the orphan-protected indication at issue.

Thus, the statute, regulations, and applicable case law permit the omission of an indication or other aspect of labeling protected by a listed patent or applicable exclusivity as an acceptable difference between the proposed generic drug and the listed drug that are produced or distributed by different manufacturers if the omission does not render the proposed generic drug less safe or effective than the listed drug for the remaining non-protected conditions of use that remain in the labeling.

d. Pediatric Labeling, Carve-outs and Disclaimers

When a product is approved for use in adults for an indication that also occurs in pediatric populations, FDA generally presumes, based on experience, that the product will be used in the pediatric population for that adult-approved indication regardless of whether it is labeled for that use. It is this experience (of drugs that were approved for adults for an indication that occurs in pediatric patients being used in pediatric patients without proper dosing or safety information) that led to FDA's promulgation of the Pediatric Rule and its later codification in the Pediatric Research Equity Act (PREA) (which requires studies of drugs in pediatric populations for indications which have been approved in adults). See section 505B of the FD&C Act. See also 21 CFR 201.57(c)(9)(iv)(C) ("If there are specific statements on pediatric use of the drug *for an indication also approved for adults* that are based on adequate and well-controlled studies in the pediatric population, they must be summarized in the 'Pediatric use' subsection".) (emphasis added).

Because pediatric patients and adults metabolize drugs differently, are susceptible to different safety risks, and often require different dosing instructions, Congress gave FDA explicit authority to find a drug misbranded when it is approved for adults for an indication that occurs in

pediatric patients but does not include adequate information regarding the use of the drug in pediatric populations for that approved indication. See section 505B(a)(2)(A)(i) (requiring submission of pediatric studies "*for the claimed indications* in all relevant pediatric subpopulations.") (emphasis added), and section 505B(d)(2) (noting that if a drug fails to comply with provisions of PREA for submission of pediatric studies for the claimed indications, it "may be considered misbranded solely because of that failure").[26]

When FDA's concern that drugs approved for adult indications that also occur in pediatric patients be labeled for use in pediatric patients is implicated by the labeling carve-out scheme in place for patents and exclusivities under section 505(j), additional considerations regarding potential labeling carve-outs may apply. In some such cases, where a drug is approved in adults and pediatric patients for the same indication but the pediatric information is protected by exclusivity and is significantly different from the information regarding use in adults for the same indication, a carve-out of pediatric information while adult information is retained in the ANDA labeling may result in a potential safety risk to pediatric patients. The risk arises because pediatric patients may be given the drug without adequate safety or dosing information and with the unsubstantiated expectation that it will behave in the same way it does in adults. In such cases, even though a drug is otherwise subject to a carve out under section 505(j)(2)(A)(v) of the FD&C Act, and 21 CFR 314.92(a)(1), 314.94(a)(8)(iv) and 314.127(a)(7), the drug with the labeling carved out might not be considered safe and effective for the remaining non-protected conditions of use. In such a case, FDA might consider a generic drug misbranded for failing to include the pediatric information that corresponds to the approved adult indication and will not approve it for the adult indication with the corresponding pediatric information omitted. [27]

To ensure that ANDA approval is not delayed in such cases (i.e., 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), Congress added section 505A(o) to the FD&C Act in the Best Pharmaceuticals for Children Act. See 147 Cong. Rec. H8105 (Nov. 13, 2001) (noting that section 505A(o) was intended to close the potential Glucophage exclusivity "loophole"). Section 505A(o), entitled "Prompt Approval of Drugs under Section 505(j) When Pediatric Information Is Added To Labeling," 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

[26] The requirement for pediatric information and the possibility of being found misbranded for failure to include that information only arises for indications for which a drug is approved in adults. See Section 505B(a) and section 505(B)(b) (limiting pediatric study requirement for marketed drugs to the "labeled indications."). PREA does not require that sponsors provide pediatric information for indications for which they do not have (or seek) adult approval.

[27] The Glucophage precedent is an example of such a case. Bristol Myers Squibb, Glucophage's sponsor, undertook pediatric studies of the drug for an indication for which it had previously been approved in adults and earned three years of HW exclusivity after pediatric-use information was added to the labeling. FDA would not approve an ANDA for Glucophage even for the adult indication until the expiry of the three-year exclusivity resulting from the pediatric studies because the agency concluded that, given that the drug was approved for the same indication in adults, the protected pediatric information was necessary for the safe use of the drug and therefore could not be carved out. As a result, the exclusivity awarded for the pediatric information provided a de facto exclusivity for use of the drug in all populations. See 147 Cong. Rec. H10209 (Dec. 18, 2001) (discussing the Glucophage exclusivity).

misbrand the product. 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).[28]

Specifically, for pediatric labeling protected by three-year HW exclusivity, section 505A(o)(1) provides that an ANDA "shall *not be considered ineligible for approval* under [section 505(j)] *or misbranded*[29] under section 502 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 . . . exclusivity under clause (iii) or (iv) of section 505(j)(5)(F)." (emphasis added).

Section 505A(o)(2) further provides that notwithstanding any HW exclusivity, the Secretary may require a drug that omits pediatric labeling protected by HW exclusivity to include (A) a statement that, because of marketing exclusivity for a manufacturer – (i) the drug is not labeled for pediatric use; or (ii) [in the case of a drug not labeled due to patent or HW exclusivity] the drug is not labeled for pediatric use [due to patent or HW exclusivity]; and (B) a statement of any appropriate pediatric contraindications, warnings, precautions, or other information that the Secretary considers necessary to assure safe use."

These provisions evidence Congress' intent that approval should not be withheld from ANDAs for unprotected indications based on the inability to safely carve out pediatric information protected by three-year HW exclusivity. See Best Pharmaceuticals for Children Act House Report 107-277 (November 9, 2001) at 30 ("[505A(o)]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 provisions"); id. at 38 ("[505A(o)] 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*.") (emphasis added). See also Letter from Janet Woodcock to Terry G. Mahn (May 21, 2003), Docket No. 02P-0469/CP1 at 12 (noting that section 11 of BPCA codified at 505A(o) was entitled "Prompt Approval of Drugs under Section 505(j) When Pediatric Information is Added to Labeling" and was designed to ensure that protection of pediatric labeling for a reference listed drug will not block generics from entering the marketing).

[28] See section 505A(o)(2)(B)(permitting FDA to require that ANDA labeling that omits a pediatric indication or other aspect of labeling protected by HW exclusivity include "a statement of any appropriate pediatric contraindications, warnings, precautions, or other information that the Secretary considers necessary to assure safe use.").

[29] Note that the misbranding that is referred to in this context is the misbranding that occurs when a drug product is approved in adults for an indication that also occurs in pediatric patients but is not fully labeled for the relevant pediatric populations in which it occurs. FDA generally does not consider a drug misbranded solely because a drug product is labeled for neither adults nor pediatric patients for an indication for which the FDA believes it might be safe and effective in one or both populations.

The language in section 505A(o) applies on its face to allow certain information to remain in ANDA labeling when the information is protected by three-year HW exclusivity if removing that information would otherwise misbrand the drug by rendering it unsafe or ineffective for the remaining non-protected conditions of use. Section 505A(o) was not intended to speak directly to, and leaves unchanged other situations where carve-outs are permissible and would not misbrand the drug.[30] Accordingly, it does not limit but, in fact, is complementary to FDA's longstanding approach to labeling carve-outs under section 505(j). As noted above, under that longstanding approach, "conditions of use for which approval cannot be granted because of exclusivity or an existing patent may be omitted." 21 CFR 314.92(a)(1). Under section 505(j) and FDA regulations, FDA has long carved out from ANDA labeling information protected by ODE, consistent with the Orphan Drug Act and FDA's implementing regulations which, as described above, provide that ODE only protects against approval of the same drug for the same indication or use. As the *Sigma Tau* court made clear, carve-out of an orphan-protected indication is permissible provided that the drug without the protected indication will remain safe and effective for the remaining, non-protected conditions of use.

III. Precedent – Meloxicam Tablets

As noted in section II of this letter, the statute, case law, and FDA's regulations support the removal of an indication or other information from ANDA labeling when that indication or information is protected by three-year HW exclusivity and/or ODE as long as the ANDA with that labeling carved out remains safe and effective for the remaining non-protected conditions of use. See section 505(j)(2)(A)(v) and 21 CFR 314.92(a)(1). As further noted, for carve outs of pediatric information protected by three-year HW exclusivity, section 505A(o) specifically describes, among other things, inclusion of any necessary warnings, precautions, contraindications or other information necessary for safe use of the product when pediatric information protected by HW exclusivity would otherwise be subject to a labeling carve out. OGD precedent has established how these provisions are interpreted when labeling is covered both by HW exclusivity and ODE. For example, OGD previously considered a labeling carve out of pediatric information protected both by three-year HW exclusivity and ODE for ANDAs referencing Mobic (meloxicam tablets) NDA 20938. Supplement Nos. 013 and 015 to the Mobic NDA were approved under NDA 20938 on August 11, 2005.[31] Upon approval, Supplement No. 013 was determined to satisfy the criteria for three-year HW exclusivity which was listed in the Orange Book with exclusivity code I-469, "Relief of the Signs and Symptoms of Pauciarticular or Polyarticular Course Juvenile Rheumatoid Arthritis in Patients 2 years of Age and Older." This exclusivity expired on August 11, 2008, but a six-month period of pediatric exclusivity attached to that exclusivity, which period expired February 11, 2009.[32]

ODE was also awarded to Mobic upon approval of Supplement No. 013 for "Treatment of Juvenile Rheumatoid Arthritis." ODE associated with NDA 20938 expired on August 11, 2012

[30] See section 505A(o)(3)(D) stating that "except as expressly provided in [section 505A(o)(1) and (2)]" section 505A(o) does not affect "the operation of section 505."

[31] S-013 to NDA 20938 was the efficacy supplement which upon approval resulted in the three-year HW and seven-year ODE while S-015 was a labeling supplement.

[32] See Orange Book at ADA 87 (27th ed. 2007).

with an additional six months of pediatric exclusivity that attached, expiring February 11, 2013.[33]

FDA approved multiple ANDAs referencing Mobic between July 19, 2006 and July 31, 2006, with each of these ANDAs employing a carve-out of labeling associated with the ODE and the I-469 HW exclusivity awarded to NDA 20938. The labeling of these ANDAs omitted certain information related to Treatment of Juvenile Rheumatoid Arthritis.

IV. Otsuka's Arguments and FDA's Response

As noted above, your January 21, 2015 letter argues that FDA cannot approve an ANDA for a generic version of Abilify pending the expiration of Otsuka's ODE period.[34] You contend that section 505A(o) permits a carve out only of pediatric information protected by HW exclusivity, not of information protected by ODE. Accordingly, you argue, because ODE is not expressly enumerated as a basis for a labeling carve-out under section 505A(o), ANDAs referencing Abilify must await the expiration of ODE before they will be eligible for approval. Subsequently, Otsuka sued FDA and submitted briefs and other pleadings arguing that FDA must await expiration of the ODE for Treatment of Tourette's Disorder before it can approve ANDAs for any indication, including indications for which patents and exclusivities have expired.

Otsuka's arguments fail on multiple counts. First, the relevant information regarding Tourette's Disorder in pediatric patients is protected by HW exclusivity so it expressly falls within the contours of section 505A(o).[35] Thus, if FDA had concluded that certain information relating to Tourette's Disorder (e.g. certain warnings or adverse event information) in pediatric patients was essential to assure the safe use of the product, FDA would have been permitted to allow that information to remain in the labeling under section 505A(o). (In this case, FDA determined that such information was not necessary to assure safe use of the product).

In addition, even if the relevant data and information were not protected by HW exclusivity and were protected by ODE only and we were to assume, *arguendo*, that section 505A(o) did not apply, this would not preclude an appropriate labeling carve-out and ANDA approval in this case. FDA has long interpreted the differences due to differences in manufacturer exception to the "same labeling" requirement in section 505(j)(2)(A)(v) and 21 CFR 314.92(a)(1), 21 CFR 314.94(a)(8)(iv) and 21 CFR 314.127(a)(7) to allow carve-outs of labeling protected by ODE as

[33] See id.

[34] Although your letter asked that FDA not approve ANDAs that seek to rely on Abilify until the ODE expires, you did not submit this correspondence as a petition, thereby choosing to circumvent the clear and explicit statutory procedure for bringing such challenges described in section 505(q). *See* FDA Guidance for Industry—Citizen Petitions and Petitions for Stays of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act 6 (Nov. 2014) ("Communications with the Agency regarding any issues intended to delay the approval of an ANDA . . . are appropriately submitted through the petition process pursuant to § 10.30 or 10.35 rather than as correspondence to the NDA, ANDA . . . or another process").

[35] See Orange Book at ADA 18 (35th ed. 2015) (listing I-700, "Treatment of Pediatric Patients with Tourette's Disorder (6-18 years)" as covered by three-year HW exclusivity).

well as by HW exclusivity, as long as FDA determines that the drug with the information carved out remains safe and effective for the remaining non-protected conditions of use.

To determine if the carve out of the Tourette's Disorder information would leave the ANDAs safe and effective for the remaining non-protected conditions of use, we must consider both the information that will be carved out and the information that will remain in the labeling once the carve out is implemented. As described above, FDA has determined in certain instances that ANDA applicants needed to retain pediatric information related to an indication protected by exclusivity where carving it out would present a safety risk to pediatric patients using the drug for its approved (non-protected adult) indication.[36] As further described in section II.d, under PREA, pediatric information is only required (and lack of pediatric information will only misbrand the drug) when the indication for which pediatric information is being omitted is one that is approved for use in adults.

In this case, 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 to assure safe use. FDA has also determined that aripiprazole with the protected Tourette's Disorder information carved out remains safe and effective for all of the remaining non-protected conditions of use. In addition, there will be no information remaining in the aripiprazole labeling describing the use of generic aripiprazole in adults that would lead to an unsupported use of generic aripiprazole in pediatric patients with Tourette's Disorder.

This conclusion would remain the same even if the Tourette's Disorder indication were protected by ODE only. As Otsuka has so strenuously argued,[37] and as FDA has confirmed,[38] Abilify's labeling includes no dosing or administration information for Tourette's Disorder in adults. Thus, if pediatric information related to Tourette's Disorder is carved out for generic aripiprazole labeling, the remaining labeling would not include any information on use of the drug for adults with Tourette's Disorder because no such information exists in Abilify's labeling. Thus, the carved out generic labeling is safe and effective for the remaining, non-protected conditions of use and the above-described basis for finding a carve-out of pediatric information to be unsafe does not apply. In this case, the harm that section 505A(o) sought to address, use for an adult

[36] See e.g., ANDA labeling approvals for sildenafil tablets and zolpidem tartrate tablets.

[37] *See e.g.*,, Correspondence to William Bender, FDA, from Patrick Guinn, (Mar. 18, 2015) (noting that Otsuka submitted no data demonstrating the safety or effectiveness of Abilify in the non-pediatric adult population of patients with Tourette's Disorder and providing FDA with a declaration from Dr. Floyd Sallee, which stated that Tourette's Disorder "presents in fundamentally different ways" in adults and pediatric patients and the dosing for the two populations is different); Compl. ¶¶ 40-42 ("[W]ithout specialized knowledge, a clinician could not treat an adult with Tourette's Disorder with Abilify in reliance on a label containing dosing instructions for the pediatric population."); Otsuka Mot. for TRO and/or PI at 4 ("The narrow pediatric indication is made clear by Otsuka's label").

[38] General Advice Letter to NDA 21436/S-038, 21713/S-030, 21279/S-022, 21866/S-23 dated April 10, 2013 ("The labeling describes only pediatric clinical trials, provides instructions only for pediatric dosing in Tourette's Disorder, and describes warnings and adverse reactions only for pediatric patients with Tourette's Disorder. Thus, the approval of Abilify for Tourette's Disorder is only for the pediatric population.").

indication in pediatric patients without adequate pediatric safety or dosing information, will not be implicated.

Accordingly, a carve out is permissible in this case and an ANDA with labeling related to use of Abilify in pediatric patients with Tourette's Disorder carved out is safe and effective for the remaining non-protected conditions of use, and is not misbranded, regardless of the applicability or inapplicability of 505A(o).

It should be noted as a more general matter that Otsuka's arguments regarding the meaning of section 505A(o) turn section 505A(o) on its head. Otsuka seeks to use a provision designed to ensure that ANDA approval would not be delayed in certain circumstances to support its arguments to delay approval for any ANDA referencing Abilify, including those ANDAs seeking approval only for the non-protected indications. Otsuka contends that because section 505A(o) mentions only HW-protected information, Congress intended to negate FDA's pre-existing authority to carve out pediatric information protected by ODE in any circumstance, even where an ANDA with that labeling carved out remains safe and effective for the remaining, non-protected conditions of use. Section 505A(o) did not purport to describe what can be omitted from ANDA labeling; it described information that can be retained. Contrary to Otsuka's position, Congress explicitly stated in section 505A(o) that the addition of that provision was not intended to have any effect on FDA's preexisting interpretation of other provisions of section 505, including the provisions under section 505(j) that otherwise allow for labeling carve outs where the labeling retained would result in a drug product that is safe and effective for the remaining non-protected conditions of use.[39] Thus, FDA's interpretations of the same labeling requirement and of the scope of the difference due to difference in manufacturer exception remain unchanged. The words of section 505A(o), when viewed in the context of the statute as a whole, do not bear the weight that Otsuka ascribes to them.

V. Conclusion

Today, we approved ANDAs that carve out of both the ODE and I-700 HW exclusivity. These approvals are supported by the statute, the regulations and past precedents. Consistent with the conclusion that omission of the protected Tourette's Disorder indication and related information does not render the generic drug less safe or effective than Abilify for the remaining non-protected conditions of use, we have permitted these ANDAs to omit from their labeling all information related to treatment of Tourette's Disorder.

Sincerely,

John R. Peters -S

Digitally signed by John R. Peters -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=John R. Peters -S, 0.9.2342.19200300.100.1.1=1300383953
Date: 2015.04.28 12:44:28 -04'00'

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[39] See section 505A(o)(3)(D) stating that "except as expressly provided in [section 505A(o)(1) and (2)]" section 505A(o) does not affect "the operation of section 505."