JOINT APPENDIX OF ADMINISTRATIVE RECORD:

TAB 54

Civil Action No. 14-cv-2126 (RBW)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 08, 2015

FROM: The Exclusivity Board, Center for Drug Evaluation and Research

SUBJECT: Astagraf XL (tacrolimus extended-release capsules) 3-year exclusivity

TO: NDA 204096 Envarsus XR (tacrolimus extended-release tablets)

OVERVIEW

On October 30, 2014, the Food and Drug Administration (FDA or the Agency) tentatively approved new drug application (NDA) 206406 for Envarsus XR (tacrolimus extended-release tablets) (Envarsus XR), sponsored by Veloxis. The tentative approval decision rested on the Agency's conclusion that the 3-year exclusivity listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book) for Astellas Pharma US, Inc's (Astellas') tacrolimus extended-release capsules, Astagraf XL (NDA 204096), prevented the final approval of Envarsus XR. At the same time, the Center for Drug Evaluation and Research's Exclusivity Board (Exclusivity Board) noted that it had become aware that an analysis under section 505(v) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which applies to Old Antibiotics,[1] such as tacrolimus, was not conducted.[2] The Exclusivity Board indicated that it was in the process of

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[1] Old Antibiotics are those for which a first application was received by the Agency prior to November 21, 1997, the date of enactment of the Food and Drug Administration Modernization Act of 1997 (FDAMA). FDAMA repealed section 507 of the FD&C Act under which antibiotics were approved, and provided that drugs approved under section 507 would thereafter be considered to have been reviewed and approved under section 505. Antibiotics for which applications were received after FDAMA was enacted could avail of 3-year exclusivity (among other Hatch-Waxman provisions), but Old Antibiotics were excluded from such incentives until the enactment of the QI Program Supplemental Funding Act of 2008, Pub. L. No. 110–379, 122 Stat. 4075 (the "QI Act"), which amended the FD&C Act to create section 505(v).

[2] In the October 30, 2014 Exclusivity Board memorandum, the reference to a lack of analysis under section 505(v) was intended to underscore the lack of documentation regarding whether Astagraf XL met FDA's interpretation of the meaning of "conditions of use" in section 505(v)(3) of the FD&C Act as described more fully in the Agency's response to Viropharma's citizen petition regarding its antibiotic drug, Vancocin. See Letter from Janet Woodcock, M.D., Director, CDER, FDA, to Thomas F. Doyle, ViroPharma, Inc., Docket No. FDA-2006-P-0007 (Apr. 9, 2012) ("Vancocin CP Response"). As discussed in more detail below, FDA interprets this statutory provision to permit exclusivity for an Old Antibiotic only for a significant new use and not to provide exclusivity for refinements in labeling related to previously approved conditions of use. Astellas referred to section 505(v) in its Request for Exclusivity for Astagraf XL (attached to the Exclusivity Summary for Astagraf XL), but that discussion and FDA's exclusivity summary did not explicitly address whether the change in dosing regimen was a "significant new use" within the meaning of section 505(v)(3) as FDA has interpreted it.

assessing the issue to confirm whether 3-year exclusivity was properly granted, and would address whether the clinical studies which were essential for the approval of Astragraf XL involved any "significant new uses" for tacrolimus under section 505(v)(3)(B) of the FD&C Act, as interpreted by FDA.

The Exclusivity Board has reviewed the exclusivity question. The Board recommends that CDER continue to recognize Astagraf XL's 3-year exclusivity and that Astagraf XL's 3-year exclusivity remain in the Orange Book.

BACKGROUND

Tacrolimus, a calcineurin inhibitor, indicated for prophylaxis of organ rejection in liver, kidney and heart transplant recipients was first approved by FDA in 1994 under the trade name Prograf. Developed by Astellas, Prograf is an immediate-release (IR) tacrolimus product that is dosed twice daily (BID) in capsule form. On July 19, 2013, FDA approved Astagraf XL, an extended-release (ER) tacrolimus capsule that is intended to be dosed once daily (QD). The Agency recognized 3-year exclusivity for Astagraf XL under sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the FD&C Act, notated in the Orange Book as new dosage form (NDF) exclusivity. These statutory provisions bar FDA from approving a drug with the same "conditions of approval" as a drug product that has 3-year exclusivity until that exclusivity expires. The Agency found that the Astagraf XL NDA met the statutory and regulatory conditions for 3-year exclusivity because it was supported by new clinical investigations conducted or sponsored by Astellas that were essential to approval of the NDA and that were not bioavailability studies. The exclusivity-supporting clinical investigations were two Phase 3 controlled clinical trials of 12-month duration, both of which demonstrated that Astagraf XL was non-inferior to Prograf on the endpoint of biopsy-proven acute rejection, when used with mycophenolate mofetil and corticosteroids, in a regimen with or without basiliximab induction.

On September 12, 2014, Astellas submitted a letter to the Division of Transplant and Ophthalmology Products (DTOP) requesting that the Agency clarify the types of products that could/could not be granted approval during Astagraf XL's 3-year exclusivity period. DTOP referred the letter to the Exclusivity Board. Upon review of the letter and the administrative record for Astagraf XL, the Exclusivity Board determined that that the exclusivity analysis for Astagraf XL had not included an explicit inquiry regarding whether Astagraf XL was eligible for 3-year exclusivity in light of section 505(v)(3)(B) of the FD&C Act (as the Agency had interpreted it in its exclusivity

determination for Vancocin). On October 17, 2014, the Exclusivity Board requested that Astellas address the applicability of section 505(v)(3)(B) and the Agency's interpretation of that section (as set forth in its exclusivity determination for Vancocin) to Astagraf XL.[3] Astellas responded on October 27, 2014, asserting, essentially, that Astagraf XL satisfied the requirements for exclusivity under section 505(v) of the FD&C Act because the clinical studies essential to its approval established the safety and effectiveness of Astagraf XL's QD dosing regimen, which Astellas asserted was a new "condition of use," compared to Prograf's BID dosing regimen.

ANALYSIS

The QI Act amended the FD&C Act to add section 505(v), a new provision that provided Old Antibiotics an opportunity for 3-year exclusivity under certain circumstances. This exclusivity is subject, however, to the limitation in section 505(v)(3)(B), which provides that 3–year exclusivity is not available for "any condition of use for which the [Old Antibiotic] ... was approved before the date of the enactment [of the QI Act]." The original exclusivity decision for Astagraf XL did not contain an express discussion of the Agency's interpretation of section 505(v)(3)(B). This memorandum addresses whether exclusivity for Astagraf XL should continue to be recognized in light of this interpretation.

FDA has publicly applied its interpretation of section 505(v)(3)(B) on only one occasion. In 2012, FDA rejected Viropharma's assertion that its labeling changes for Vancocin were eligible for 3-year exclusivity.[4] In its response, the Agency considered the plain text of the statute and concluded that Old Antibiotics faced a higher hurdle for 3-year exclusivity than other drugs.

> [The] availability of 3-year exclusivity for Old Antibiotics was not without limitation. Rather than simply placing new applications and supplements for Old Antibiotics under the pre-existing Hatch-Waxman regulatory scheme, Congress prescribed specific limits to this eligibility under section 505(v)(3)(B) of the FD&C Act. The QI Act provides that 3-year exclusivity period is not available for "any condition of use for which the [Old Antibiotic] ... was approved before the date of the enactment [of the QI Act].
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> The QI Act does not expressly define what constitutes a "condition of use ... approved before the date of enactment." As an initial matter, FDA concludes that this limitation must exclude from exclusivity some applications and supplements containing new clinical studies that otherwise would qualify a non-Old Antibiotic product for 3-year Hatch-Waxman exclusivity . . . . Thus, to give content to this

[3] See Letter from Janet Woodcock, M.D., Director, CDER, FDA, to Thomas F. Doyle, ViroPharma, Inc., Docket No. FDA-2006-P-0007 (Apr. 9, 2012) ("Vancocin CP Response").
[4] Id.

> limitation, FDA must find that *there is a higher hurdle for exclusivity* for an Old Antibiotic than there is for another kind of product seeking 3-year exclusivity.[5]

After reviewing the legislative history of the QI Act, the Agency concluded that it interpreted "section 505(v)(3)(B) to permit 3-year Hatch-Waxman exclusivity for Old Antibiotics *only for a significant new use* for an Old Antibiotic (such as a new indication for a previously approved antibiotic, or a new approval for a submitted but never previously approved antibiotic), not for refinements in labeling related to previously approved uses for Old Antibiotics."[6] FDA noted that "the legislation created incentives for sponsors to find new uses for Old Antibiotics, and *bring 'old but never approved' antibiotics to the market,*" and cited, among other things, to Senator Kennedy's statements in the Congressional Record.[7]

In the ensuing litigation, the District Court first determined that the relevant statutory provision is "likely ... ambiguous"[8] because it does not address what constitutes "a condition of use approved before the date of the QI Act's enactment." In doing so, the Court rejected Viropharma's assertion that the regulatory definition of "conditions of use" should govern, concluding that the regulatory definition is "unrelated."[9] The Court held that under Chevron's step two, FDA's interpretation in its Citizen Petition response was reasonable and furthered Congress's express purpose "to balance the need to encourage development of new antibiotic drugs . . . and the desire to ensure access to previously approved antibiotics through approval of generic versions of such antibiotics."[10]

Crucially, Viropharma asserted that the Agency interpreted the relevant provisions such that it "will only allow exclusivity where an sNDA specifies a new indication for an Old Antibiotic." The Court rejected that assertion.[11] The Court noted that FDA had concluded, among other things, that Vancocin's labeling changes "did not prescribe a new dosing regimen," which, in the Court's opinion, confirmed that FDA's interpretation of "significant new use" was broader than just a new

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[5] Id. at 69-70 (emphasis added).
[6] Id. at 70 (emphasis added).
[7] Id. at 70 n. 334 (emphasis added) ("The amendment strikes the right balance between innovation and access, and closes a loophole that eliminated the incentives to bring old but never approved antibiotics to market.").
[8] ViroPharma, Inc. v. Hamburg, 898 F. Supp. 2d 1, 18 (D.D.C. 2012). See Appendix B.
[9] Id. Specifically, the court rejected Viropharma's argument that "conditions of use" is used throughout the FD&C Act and in the Agency's regulations to "unambiguously include a variety of aspects of a drug and its administration that go beyond the 'significant new uses' contemplated by the FDA's interpretation of … [section 505(v)(3)(B)]."
[10] Id. at 20. (citing Senator Kennedy's statements in the Congressional Record that the QI Act "includes limits that would prevent pharmaceutical manufacturers from abusing the process to extend the life of old active ingredient drugs.").
[11] Id. at 21. ("The crux of the agency's interpretation is 'significant new use,' and by its terms it clearly includes more than just new indications.").

indication.[12] FDA's litigation briefs also stated that "for a change approved in a supplement to constitute a departure from a previously approved condition of use – and hence be eligible for three-year exclusivity – it would have to change how, to whom, or for which purposes a drug is administered."[13] FDA noted that, "'[c]onditions of use' thus include a drug product's indication and dosing regimen, for instance, but do not include all contents of a drug product's labeling."[14]

Astellas has asserted that the clinical studies that were essential for Astagraf XL's approval established the safety and effectiveness of its QD dosing regimen, which is different from the previously approved tacrolimus product's BID dosing regimen. According to Astellas, Astagraf XL's new dosing regimen meets the requirement under section 505(v)(3)(B) such that its exclusivity is for a condition of use not approved before the enactment of the QI Act. The Exclusivity Board agrees that Astagraf XL's clinical studies supported a change in "how, to whom or for which purposes" tacrolimus is administered[15] and therefore meet the standard for exclusivity for an Old Antibiotic under section 505(v)(3)(B) of the FD&C Act.[16]

Under the specific circumstances before us, the Exclusivity Board recommends that Astagraf XL's exclusivity continue to be recognized and listed in the Orange Book.

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[12] Id. at 22.
[13] ViroPharma, Inc. v. Hamburg, Federal Defendant's Memorandum in Opposition to Plaintiff's Motion for TRO and/or PI at 22 (Apr. 17, 2012).
[14] Id.
[15] The Exclusivity Board acknowledges that the reviews for Astagraf XL state that there is no substantial evidence of a clinical benefit with respect to potential improved patient adherence with once-daily dosing of Astagraf XL compared to Prograf (see, e.g., Astagraf XL Clinical Review (June 19, 2013) at 6; Astagraf XL Cross-Discipline Team Leander Review at 18, 37). As stated in the text, the once-daily dosing for Astagraf XL is a new dosing regimen. At this time, FDA does not consider a demonstration of a clinical benefit of a new dosing regimen compared to a past dosing regimen to be a prerequisite to establishing a significant new condition of use for exclusivity purposes.
[16] We note that this determination is based on the particular facts and circumstances relating to the Astagraf XL approval. In other cases, it may be legally supportable to question whether a particular change in dosing regimen constitutes a significant new condition of use within the meaning of the statute. The Agency intends to further consider this issue as well as any relevant policy considerations prospectively and may issue clarifying guidance as appropriate.

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/s/

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