CONFIDENTIAL INFORMATION – FILED UNDER SEAL

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

VELOXIS PHARMACEUTICALS, INC., Plaintiff, v. UNITED STATES FOOD AND DRUG ADMINISTRATION, *et al.*, Defendants.	Civil Action No. 14-cv-2126 **FILED UNDER SEAL**

DEFENDANTS' MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF THEIR MOTION TO DISMISS, OR IN THE ALTERNATIVE, FOR SUMMARY JUDGMENT AND OPPOSITION TO PLAINTIFF'S SUMMARY JUDGMENT MOTION

CONFIDENTIAL INFORMATION – FILED UNDER SEAL

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

CONFIDENTIAL INFORMATION – FILED UNDER SEAL

Statutes

Rules

Regulations

CONFIDENTIAL INFORMATION – FILED UNDER SEAL

INTRODUCTION

Veloxis Pharmaceuticals, Inc. ("Veloxis") is asking this Court to second-guess FDA's decision, contained in the agency's January 12, 2015 letter to Veloxis, that approval of Veloxis' once-daily extended-release tacrolimus product, Envarsus XR ("Envarsus"), is blocked by three-year marketing exclusivity granted to a previously-approved product, Astagraf XL ("Astagraf"). FDA's well-reasoned and thorough 53-page letter decision explains in detail that because Astagraf was previously approved by FDA as a once-daily extended-release tacrolimus product for the prophylaxis of organ rejection for use in *de novo* kidney transplant patients, the agency is prohibited by the Federal Food, Drug, and Cosmetic Act ("FDCA") from issuing final approval to Envarsus for a shared "condition of approval" until Astagraf's exclusivity expires in July 2016.[1] The agency's letter invited Veloxis to submit revised labeling for a condition of approval of Envarsus that is not blocked by Astagraf, which would enable FDA to approve Veloxis' application for Envarsus and allow Veloxis to immediately introduce Envarsus into the U.S. market. To date, Veloxis has failed to supply the agency with revised labeling, opting instead to proceed with this expedited litigation.

Veloxis claims that Astagraf's exclusivity should not block Envarsus' entry into the U.S. market because Veloxis did not rely on FDA's prior findings that Astagraf is safe and effective in its application; because it questions the clinical studies Astagraf's sponsor (Astella Pharma US, Inc. ("Astellas") relied on to support approval; because the two drugs are different; and because it claims that Astagraf was ineligible for exclusivity in the first place. Veloxis' arguments miss the mark for at least four reasons.

First, Veloxis' request that this Court second-guess the agency's interpretation of its own

[1] *See* Administrative Record ("AR") at FDA 00001-00057 (attached here as Exhibit A, for the Court's convenience).

statute and regulations as well as its scientific judgment must fail under well-settled principles of deference. These types of determinations fall squarely within the expert discretion of FDA, which Congress has determined is in the best position to make such highly-technical decisions. *Second*, Veloxis' challenge to Astagraf's exclusivity based on the submission date of Astagraf's new drug application ("NDA") is mistaken. The relevant statutory provision, 21 U.S.C. § 355(v)(1)(B)(i), unequivocally states that eligibility for three-year exclusivity applies to an application submitted *after* the date of the enactment of the QI Program Supplemental Funding Act of 2008 ("QI Act"), and it is undisputed that Astellas submitted the Astagraf application after enactment of the QI Act. *Third*, although it is undisputed that Envarsus and Astagraf are both once-daily, extended-release dosage forms of tacrolimus for the prophylaxis of organ rejection for use in *de novo* kidney transplant patients, Veloxis turns the statutory provision governing exclusivity here on its head by focusing on the differences between the two drugs. Under 21 U.S.C. § 355(c)(3)(E)(iii), and FDA's well-established interpretation of that provision, to determine if a subsequent application is blocked by another application's three-year exclusivity, the question is whether the two drugs share exclusivity-protected "conditions of approval," meaning those "conditions of approval" for which new clinical investigations were essential. Envarsus and Astagraf clearly do. *Fourth*, that Veloxis chose to rely on findings of safety and effectiveness for another drug instead of Astagraf in its application does not change this analysis, as the statute bars FDA from approving certain later-in-time drug applications that share exclusivity-protected "conditions of approval" with a previously-approved drug, regardless of the drug an applicant may rely on in its application.

Because FDA has carefully interpreted and applied the controlling FDCA provisions and FDA regulations to the facts of this case, after reviewing all relevant documents, and reasonably

CONFIDENTIAL INFORMATION – FILED UNDER SEAL

determined that Astagraf blocks Envarsus for the exclusivity-protected conditions of approval shared by these two drugs, plaintiff's motion for summary judgment should be denied, and Veloxis' complaint should be dismissed or summary judgment entered in favor of FDA, FDA Commissioner Dr. Margaret Hamburg, the United States Department of Health and Human Services ("HHS"), and HHS Secretary Sylvia Burwell ("the Federal Defendants").

STATUTORY AND REGULATORY BACKGROUND

A. New Drug and Abbreviated Applications

Under the FDCA, 21 U.S.C. § 301 *et seq.*, pharmaceutical companies seeking to market "pioneer" or "innovator" drugs must first obtain FDA approval by filing an NDA containing scientific data demonstrating the safety and effectiveness of the drug. 21 U.S.C. § 355(a), (b)(1). These "stand-alone" or "505(b)(1)" NDAs must contain clinical and scientific data and other information, including, among other things, investigative reports demonstrating the drug's safety and effectiveness, a statement of the drug's components, and specimens of proposed labeling for the drug. 21 U.S.C. § 355(b)(1). Astagraf is an approved "stand-alone" 505(b)(1) NDA.

To encourage innovation in the development of new drugs while also accelerating the availability to consumers of lower cost alternatives to such drugs, the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98–417) (the "Hatch-Waxman Amendments") created two abbreviated pathways for drug approvals: abbreviated new drug applications ("ANDAs") under 21 U.S.C. § 355(j), which is the pathway appropriate for duplicate or generic versions of a previously-approved drug, and 21 U.S.C. § 355(b)(2), an NDA (known as a "505(b)(2) application") for which some or all of the safety and/or effectiveness information relied upon for approval comes from investigations not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use. A 505(b)(2)

applicant may rely on FDA's finding of safety and effectiveness for a previously-approved drug (known as the "listed drug") of its choosing as long as the 505(b)(2) application provides an adequate scientific justification for the differences between the listed and proposed drug; a listed drug may share characteristics such as active ingredient, dosage form, route of administration, strength, indication, or conditions of use with the 505(b)(2) product. 21 U.S.C. § 355(b)(2); *see also* AR at FDA 00023. The 505(b)(2) application must also demonstrate that the proposed drug meets the statutory approval standard for safety and effectiveness. *Id.*

In this case, Veloxis chose to take advantage of the latter abbreviated process and filed the Envarsus NDA as a 505(b)(2) application, relying on FDA's safety and effectiveness findings for Prograf, an immediate-release tacrolimus drug approved in 1994, to support its application.

B. Three-Year Exclusivity

The Hatch-Waxman Amendments provide certain NDA holders (including 505(b)(2) holders) with periods of limited protection from competition for the innovation represented by their approved products. These periods are referred to generally as "exclusivity."

At issue here is three-year exclusivity, which operates by delaying the date on which FDA can give final approval to certain 505(b)(2) applications or ANDAs. Specifically, the statute states:

> If an application submitted under subsection (b) [of this section] for a drug, which includes an active ingredient . . . that has been approved in another application approved under subsection (b), is approved after the [date of the Hatch-Waxman Amendments] and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) if the investigations described in clause (A) of subsection (b)(1) and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a

> right of reference or use from the person by or for whom the investigations were conducted.

21 U.S.C. § 355(c)(3)(E)(iii).

Under the statute, the agency may not approve a 505(b)(2) application for the "conditions of approval" of an exclusivity-protected drug for a period of three years. *Id.* Although "conditions of approval" is not defined in the statute or regulations, the preamble to FDA's proposed regulations explains the agency's interpretation that the scope of three-year exclusivity covers "the innovative change" that is supported by the new clinical investigations:

> Exclusivity provides the holder of an approved new drug application limited protection from new competition in the marketplace for the innovation represented by its approved drug product. Thus, if the innovation relates to a new active moiety or ingredient, then exclusivity protects the pioneer drug product from other competition from products containing that moiety or ingredient. If the innovation is a new dosage form or route of administration, then exclusivity protects only that aspect of the drug product, but not the active ingredients. If the innovation is a new use, then exclusivity protects only that labeling claim and not the active ingredients, dosage form, or route of administration.

Proposed Rule "Abbreviated New Drug Application Regulations," 54 Fed Reg. 28872, 28896–97 (July 10, 1989) ("1989 Proposed Rule").

FDA thus interprets the scope of exclusivity to be related to the scope of the underlying "new clinical investigations" that were essential to the approval. Exclusivity *does not* extend beyond the scope of the approval and *does not* cover aspects of the drug product for which new clinical investigations were not essential. *Zeneca Inc. v. Shalala*, No. CIV.A. WMN–99–307, 1999 WL 728104, at *12 (D. Md. Aug. 11, 1999) *aff'd*, 213 F.3d 161 (4th Cir. 2000) ("The exclusivity extends only to the 'change approved in the supplement.'"); *AstraZeneca Pharm. LP v. FDA.*, 872 F. Supp. 2d 60, 79 (D.D.C. 2012) *aff'd*, 713 F.3d 1134 (D.C. Cir. 2013) (upholding as reasonable FDA's interpretation of parallel statutory language involving three-year exclusivity

in the ANDA context).[2] Because the only relevant conditions of approval for three-year exclusivity purposes are those for which the new clinical investigations were essential, a 505(b)(2) application can differ in certain respects from the previously-approved product protected by exclusivity and nonetheless be blocked if it shares the conditions of approval for which exclusivity was granted.

C. Exclusivity for "Old Antibiotics"

Until 1997, FDA approved applications for antibiotics, like tacrolimus, under a separate provision of the Act, 21 U.S.C. § 357. *See, e.g.*, Proposed Rule on Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs, 65 Fed. Reg. 3623 (Jan. 24, 2000) (listing tacrolimus as an Old Antibiotic). That provision was repealed by the Food and Drug Administration Modernization Act of 1997 ("FDAMA"), Pub. L. No. 105–115, Section 125, and all applications previously approved under 21 U.S.C. § 357 were deemed to have been filed under 21 U.S.C. § 355(b) and approved for safety and effectiveness under 21 U.S.C. § 355(c). Pub. L. No. 105–115, Title I, § 125(d)(1); *see also, ViroPharma, Inc. v. Hamburg*, 898 F. Supp. 2d 1, 6 (D.D.C. 2012).

In addressing the eligibility of antibiotics for exclusivity under the FDCA when it incorporated antibiotics into 21 U.S.C. § 355, Congress created a distinction between antibiotic drugs for which the first application was received after FDAMA's effective date (November 21, 1997), and those antibiotic drugs for which the first application was received before that date (commonly known as "Old Antibiotics"). *ViroPharma*, 898 F. Supp. 2d at 8. In FDAMA,

[2] Although these cases involved the parallel statutory provision for ANDAs, rather than the provision at issue here (*i.e.*, section 505(c)(3)(E)(iii)), the provision pertaining to ANDAs interpreted by the courts includes the same language regarding the scope of three-year exclusivity. The courts upheld as reasonable FDA's interpretation of the relationship between the scope of clinical studies that earned exclusivity, the change in the product that resulted, and the scope of the exclusivity earned. *Id.*

Congress expressly exempted Old Antibiotics from specified Hatch-Waxman provisions, including those relating to patent listing, patent certification, and exclusivity. *Id.* On October 8, 2008, the FDCA was again amended through Section 4 of the QI Act.[3] The QI Act incorporated Old Antibiotics into the Hatch-Waxman regulatory scheme for the first time by, among other things, removing FDAMA's exemptions for Old Antibiotics and creating a limited opportunity for an Old Antibiotic application to obtain Hatch-Waxman exclusivity if that application (or supplement thereto) was submitted after the QI Act's enactment. 21 U.S.C. § 355(v)(1)(B) ("an application . . . submitted . . . *after* the date of the enactment of [the QI Act] in which the drug that is the subject of the application contains [an Old Antibiotic]"). Old Antibiotic applications submitted after the date of the QI Act are eligible for three-year exclusivity under 21 U.S.C. § 355(c)(3)(E)(iii), as long as they also meet other requirements not disputed in this case (*e.g.*, the 21 U.S.C. § 355(v)(3)(B) "conditions of use" provision). *See ViroPharma*, 898 F. Supp. 2d at 22.

FACTUAL BACKGROUND

I. KIDNEY TRANSPLANT PATIENTS

When a kidney is transplanted from one person into another person, the immune system recognizes the transplanted organ as "non-self" and will try to attack and reject the transplanted organ. AR at FDA 00006; *see also* FDA 00117–78. Drugs that suppress the immune system (immunosuppressants) are administered to kidney transplant patients to prevent organ rejection. *Id.* These drugs must be started at the time the organ is transplanted, and must continue for as long as the transplanted organ is viable. *Id.* Multiple drugs are now included in the patient's

[3] *QI Program Supplemental Funding Act of 2008*, Pub. L. No. 110–379, 122 Stat. 4075, § 4, entitled "Incentives for the Development of, and Access to, Certain Antibiotics."

immunosuppressive regimen because relying solely on one immunosuppressant drug is not sufficient to provide adequate immunosuppression to these patients. *Id.*

A. The *De Novo* Patient Population

Kidney transplant patients are referred to as *de novo* patients at the time of transplant surgery. *Id.* Induction generally refers to the intensive level of immunosuppression administered to *de novo* kidney transplant patients from the start of the transplant surgery until soon after the surgery. *Id.* In all kidney transplant patients, induction involves, at a minimum, the use of a triple combination of drugs. AR at FDA 0007; *see also* FDA 00117–78. Approximately 85% of *de novo* kidney transplant patients use a four-drug (quadruple) immunosuppressive regimen. AR at FDA 00007; *see also* FDA 00179–81. After surgery, this regimen is carefully and frequently monitored, by, for example, measuring drug concentrations in the blood. AR at FDA 00008, 00179–81; *see generally* FDA 000182–87. A patient's immunosuppressive regimen is adjusted and customized to minimize the development of adverse reactions while also preventing the immune system from rejecting the kidney. *Id.* The goal is to find the optimum balance between efficacy (in preventing organ rejection) and toxicity (demonstrated by adverse reactions, such as hand tremors, that can result when a patient's immunosuppressive drug levels are too high for the patient to tolerate). AR at FDA 00008; *see also* FDA 00117–78. Kidney transplant recipients reach this optimum balance roughly three- to six-months post-surgery, although sometimes it can take years to achieve. *Id.*

B. Conversion

Once patients reach this optimum balance, they are no longer considered *de novo* patients and are considered maintenance patients. *Id.* These maintenance patients differ in certain respects from the *de novo* patients; for example, they no longer receive induction-level

immunosuppression. FDA 00008; *see also* FDA 00117–78. The term "conversion" refers to circumstances when a kidney transplant patient who has been treated with a regimen of three or four immunosuppressive drugs has one of those drugs discontinued and replaced with another drug. AR at FDA 00008; *see also* FDA 00117–78. The conversion may be initiated due to toxicity or inadequate efficacy. *Id.* Alternatively, the conversion can be for other reasons, such as a preference for once-daily or twice-daily dosing regimens based on personal convenience or other considerations in the practice of medicine. *Id.*

When a patient is converted to another drug, clinical practice requires additional and/or more frequent monitoring, clinical visits, and laboratory tests, which would not be needed in maintenance patients who continue on their same regimen. *Id.* Because immunosuppression in kidney transplant patients is highly individualized and requires a delicate balance, the clinical study design needed to demonstrate the safety and efficacy of immunosuppressants in certain populations is specialized. Separate clinical studies are needed to support approval in each of these populations. *Id.*

II. TACROLIMUS

Tacrolimus is produced by the microorganism *Streptomyces tsukubaensis* and thus meets the statutory definition of an antibiotic drug[4] even though it is approved as an immunosuppressant to prevent organ rejection rather than for antimicrobial use. AR at FDA 00009; FDA 00213. Tacrolimus was first approved by FDA as a 505(b)(1) NDA on April 8, 1994, under the trade name Prograf. AR at FDA 00009; FDA 00188–230.

[4] 21 U.S.C. § 321(jj) defines "antibiotic drug" as "any drug . . . composed wholly or partly of any kind of penicillin, streptomycin . . . or any other drug intended for human use containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution . . . or any derivative thereof."

The Prograf NDA is currently held by Astellas. *Id.* Prograf is an immediate-release capsule available in 0.5, 1, or 5-mg dosage strengths, and is indicated for the prophylaxis of organ rejection in patients receiving liver, kidney, or heart transplants. *Id.* The recommended dosing frequency of Prograf is twice-daily. *Id.*

As noted above, tacrolimus is commonly referred to as an "Old Antibiotic." There are no patents or exclusivities remaining for the Prograf NDA, and FDA has approved several ANDAs referencing the Prograf NDA (*i.e.*, generic versions of immediate-release tacrolimus). AR at FDA 00009; FDA 00311–20.

III. ASTAGRAF

Astagraf is a tacrolimus capsule developed as an extended-release formulation and intended for once-daily administration and indicated for the prophylaxis of organ rejection in patients receiving a kidney transplant. AR at FDA 00010, 00321–57. It is also available in 0.5, 1 or 5-mg dosage strengths. *Id.* Astellas first submitted an NDA for Astagraf proposing this use on December 19, 2005 (NDA 50-811).[5] After some back-and-forth with FDA regarding deficiencies with its application, Astellas asked for withdrawal of NDA 50-811 on January 29, 2009, and FDA acknowledged the withdrawal on February 10, 2009. AR at FDA 00011–12; FDA 00873-75. On September 29, 2009, FDA met with Astellas to discuss the proposed data to support submission of a new NDA for its once-daily extended release tacrolimus product for use in kidney transplant patients. AR at FDA 00012; FDA 00882–98. Astellas submitted a new application (NDA 204096) for Astagraf on September 21, 2012, and FDA approved it on July 19, 2013, based on two clinical trials conducted in *de novo* kidney transplant patients (Studies 158 and 12-03). AR at FDA 00015; FDA 00911–26. When Astagraf was approved, FDA

[5] Initially, the proposed name for the drug product was Prograf XL and then Advagraf; the drug was named Astagraf during the review of NDA 204096. AR at FDA 00064; FDA 00903.

determined that the NDA should receive three-year exclusivity because Astellas conducted new clinical investigations essential to approval. AR at FDA 00016; AR at FDA 01082–101.

IV. TENTATIVE APPROVAL OF ENVARSUS

Envarsus is a tacrolimus tablet developed as an extended-release formulation and is intended for once-daily administration and indicated for the prophylaxis of organ rejection in patients receiving a kidney transplant. AR at FDA 00016; FDA 01302; *see also* AR at FDA 01547–84. It is available in 0.75, 1 or 4-mg dosage strengths.[6] Veloxis filed the Envarsus NDA on December 28, 2013. In support of its NDA, Veloxis submitted two main clinical studies: one study in *de novo* kidney transplant recipients, and a second study in stable kidney transplant recipients converted from Prograf to Envarsus. AR at FDA 00016; FDA 01130. Envarsus' current labeling encompasses use in both *de novo* and conversion kidney transplant patient populations. AR at FDA 001547–84.

On October 30, 2014, FDA concluded that Envarsus was safe and effective for the prophylaxis of organ rejection in kidney transplant patients in both *de novo* and conversion kidney transplant patients, and issued a tentative approval to that effect. AR at FDA 00018; FDA 01544–84. The Envarsus NDA would have been fully approved at that time, but for Astagraf's exclusivity. AR at FDA 01544–45.

V. PROCEDURAL HISTORY

On September 12, 2014, Astellas submitted a letter to FDA requesting that the agency clarify the scope of Astagraf's exclusivity. AR at FDA 00018; FDA 01417–19. Astellas explained that it believed that Astagraf's "conditions of approval protected by [section

[6] Veloxis revised Envarsus' dosage strengths after FDA requested that Veloxis develop different strengths from Prograf due to concerns about the potential for medication errors. AR at FDA 00071; FDA 01132–34.

505(c)(3)(E)(iii) of the FD&C Act] encompass the once[-]daily formulation of tacrolimus indicated for the prophylaxis of organ rejection in transplant recipients regardless of patient setting, and no application for those conditions can be approved until expiration of the exclusivity period on July 19, 2016." *Id.* The letter also conveyed Astellas' belief, based on public information, that the Envarsus NDA covered the same active ingredient and dosing frequency and asked whether another once-daily tacrolimus product (*e.g.*, Envarsus) could be approved by FDA during the period of Astagraf's exclusivity. *Id.* While it sought clarification of the agency's views of Astagraf's exclusivity, this letter did *not* ask the agency to take any action with respect to Envarsus. *Id.*[7]

On October 17, 2014, FDA's Center for Drug Evaluation and Research ("CDER") issued a letter to Astellas seeking additional information regarding Astagraf's exclusivity. AR at FDA 00019; FDA 01420. On October 27, 2014, Astellas' outside counsel submitted a letter asserting that the agency had properly determined that Astagraf was eligible for three-year exclusivity under 21 U.S.C. §§ 355(c) and 355(v). AR at FDA 00019; FDA 01508–33.

After receiving Astellas' letter, FDA sent an Information Request, dated October 27, 2014, to Veloxis, requesting Veloxis' position on whether approval of the Envarsus 505(b)(2) application would be affected by Astagraf's exclusivity. AR at FDA 00019; FDA 01534–36. On October 29, 2014, Veloxis responded with a letter stating that Astagraf's "exclusivity does not affect the type of action letter FDA can issue for Envarsus XR," because Envarsus has a "different dosage form and different proposed conditions of use" than Astagraf. AR at FDA 00019; FDA 01537. Further, Veloxis claimed that the "Envarsus XR development program did

[7] Because Astellas' September 12, 2014 letter did not ask the agency to take an action with respect to Envarsus, Astellas was not required to submit it as a Citizen Petition under 21 U.S.C. § 355(q).

not rely upon any of the studies Astellas performed which were essential to the approval of Astagraf XL." AR at FDA 00019; FDA 01537–38.

Based on Veloxis' reply, FDA further considered whether the Envarsus NDA was blocked by Astagraf's exclusivity. AR at FDA 00019; FDA 01540–43. FDA concluded that the exclusivity for Astagraf covers its extended-release dosage form and its once-daily dosing regimen, both of which were changes from the previously approved tacrolimus drug, Prograf, and were supported by new clinical investigations essential to the approval of Astagraf. AR at FDA 00019; FDA 00036; FDA 01542. Because Envarsus is also an extended-release dosage form of tacrolimus with a once-daily dosing regimen, FDA determined at that time that Envarsus shares Astagraf's exclusivity-protected conditions of approval. Accordingly, FDA issued a tentative approval letter to Veloxis on October 30, 2014, stating that Envarsus could not be approved until Astagraf's exclusivity expires in July 2016. AR at FDA 00019; FDA 01544–45.

Counsel for Veloxis contacted FDA's Office of the Chief Counsel ("OCC") on October 31, 2014, requesting a meeting with FDA and asking FDA to retract its tentative approval and to issue a letter approving the Envarsus NDA. AR at FDA 00019; FDA 01585–87. On November 6, 2014, representatives of Veloxis met with representatives of FDA. AR at FDA 00019; FDA 01588. On November 10, 2014, FDA issued a General Advice/Information Request letter to Veloxis, explaining that, at the November 6 meeting, Veloxis had presented new information for the agency to evaluate and had asked FDA to reconsider its decision to tentatively approve the Envarsus NDA. AR at FDA 00020; FDA 01623–24. Veloxis submitted a "Request For Final Approval" on November 14, 2014. AR at FDA 00020; FDA 01626–738. In this letter, Veloxis conceded that Astagraf is entitled to three-year exclusivity under 21 U.S.C. § 355(c)(3)(E)(iii). AR at FDA 00034 n.146; FDA 01636 ("Veloxis does not dispute that Astagraf XL is entitled to

three-year exclusivity under section 505(c)(3)(iii) of the Act . . .”). On December 2, 2014, Veloxis submitted an amendment to its “Request For Final Approval.” AR at FDA 00020; FDA 01739–42. In this letter, Veloxis asserted for the first time that Astagraf was ineligible to receive three-year exclusivity under 21 U.S.C. § 355(v) because Astagraf was the subject of a pending application prior to the date of the QI Act. AR at FDA 00020; FDA 01739.

While reviewing the issues raised by Veloxis and Astellas, FDA preliminarily determined that the new clinical investigations essential to Astagraf’s approval demonstrated only the safety and effectiveness of the drug in *de novo* patients but not in conversion patients and that, therefore, Envarsus’ approval for the conversion use would not be blocked by Astagraf ’s exclusivity. AR at FDA 00020. To that end, FDA held a teleconference with Veloxis on December 5, 2014, and suggested that Veloxis submit an amendment to their 505(b)(2) application with labeling seeking approval only for the unprotected conversion use. AR at FDA 001748–49.

On December 8, 2014, Veloxis sent a letter to FDA declining to pursue the proposed option discussed on December 5. AR at FDA 00021, 01751–58. In its letter, Veloxis reiterated its position that FDA should immediately approve Envarsus for all of the uses reflected in the labeling submitted in the Envarsus NDA. *Id*. With the December 8, 2014 submission, Veloxis also submitted a declaration from Dr. Anthony Langone regarding the Envarsus NDA. *Id.* Veloxis later submitted a letter on December 12, 2014, containing an additional exclusivity precedent for the agency’s consideration. AR at FDA 00021; FDA 01759–61.

On December 12, 2014, FDA sent a letter to Veloxis indicating that although Veloxis’ November 14, 2014, submission requested that FDA respond within 21 days, and that FDA had initially estimated that it could respond during the week of December 8, the agency had not had

adequate time to fully consider the entire record and all of Veloxis' submissions. AR at FDA 00021; FDA 01762–66. The agency's letter indicated that FDA intended to respond no later than January 12, 2015. *Id.*

On December 16, 2014, Veloxis sent a letter to the agency stating the company's intent to pursue "court intervention" to require FDA to "grant final approval to the Envarsus XR NDA." AR at FDA 00021; FDA 01768–70. Although Veloxis knew the agency had not yet reached a final decision, Veloxis filed a complaint in the U.S. District Court for the District of Columbia on the same day. Dkt. No. 1. On December 17, 2014, FDA moved to stay the proceedings pending final agency action. Dkt. No. 6. The Court granted FDA's motion to stay on December 18, 2014. Dkt. No. 9.

On January 12, 2015, FDA issued two letters to Veloxis in which the agency discussed in detail the agency's position. The 53-page General Advice letter the agency sent to Veloxis on January 12, 2015 closely maps the slightly longer decisional memorandum that FDA issued that same day. *Compare* AR at FDA00005–57 *with* AR FDA 00058–00116. FDA's January 12, 2015 decision was made with input from the agency's scientific experts and policymakers, and involved the intersection of complex legal, regulatory, policy, scientific, and technical issues. Specifically, FDA's January 12, 2015 decision encompassed:

> evaluation of the arguments raised by Astellas and Veloxis; reexamination of the studies conducted to support both the Astagraf XL and Envarsus XR NDAs; review of the documents from NDAs for products cited as precedent regarding FDA's past treatment of the scope of 3-year exclusivity; and reevaluation of the Agency's prior determinations that Astagraf XL is entitled to 3-year exclusivity, that such exclusivity is not circumscribed by the limitations described in section [21 U.S.C. § 355(v)], and that this exclusivity blocks approval of the Envarsus XR NDA.

AR at FDA 00005. After this extensive review of the issues raised by the parties, FDA concluded in its January 12, 2015 decision that:

> [Three]-year exclusivity for Astagraf XL is proper under section[s] [21 U.S.C. § 355(c)(3)(E)(iii) & § 355(v)]. This exclusivity is based on the new clinical investigations essential to the approval of the once-daily, [extended-release] dosage form of tacrolimus for prophylaxis of organ rejection for use in *de novo* kidney transplant patients. In addition, FDA concludes that the Envarsus XR NDA is a once-daily, [extended-release] dosage form of tacrolimus for prophylaxis of organ rejection that is blocked from approval for *de novo* kidney transplant patients by Astagraf XL's exclusivity until that exclusivity expires on July 19, 2016.
>
> FDA also concludes, however, that the Envarsus XR NDA can be approved now for conversion of stable kidney transplant patients from tacrolimus immediate-release (IR) products to Envarsus XR (the conversion use), pending Veloxis' submission and FDA approval of an appropriate labeling amendment deleting reference to the *de novo* population and seeking approval for the conversion use only.

AR at FDA 00005–6. To date, Veloxis has not submitted revised labeling.[8]

The Court held a status conference with the parties on January 14, 2015, and entered the proposed expedited scheduling order on January 15, 2015. Dkt. No. 14. In accordance with that order, FDA produced the more than 6,000-page administrative record for this case on January 27, 2015. Veloxis moved for summary judgment on February 6, 2015.[9]

---

[8] In a letter dated January 20, 2015, Veloxis asked FDA to use its discretion to administratively split the Envarsus NDA into separate applications to enable this litigation to proceed untouched, yet allow FDA to proceed with approving Envarsus for the conversion use only. Although Veloxis refers to the January 20, 2015 letter in its brief, *see* Pl. Br. at 14–15, the letter post-dates the agency's January 12, 2015 decision and is therefore not properly part of the administrative record in this case. *Camp v. Pitts*, 411 U.S. 138, 142 (1973) ("[T]he focal point for judicial review should be the administrative record already in existence, not some new record made initially in the reviewing court."). Because Veloxis referenced it in its brief, the Federal Defendants merely note that missing from the January 20, 2015 letter is any revised labeling for Envarsus specific to the conversion use; the only labeling FDA has received from Veloxis to date encompasses use in both *de novo* and conversion kidney transplant patient populations.

[9] Plaintiff's complaint was filed on December 16, 2014, before FDA issued a final decision in this matter. Although Plaintiff has not filed an amended complaint in this case, based on Plaintiff's summary judgment brief, the parties appear to agree that, as a factual matter, the agency action challenged in this lawsuit is FDA's January 12, 2015 decision in which the agency declined to grant full and immediate approval to Envarsus based on Astagraf's exclusivity. To the extent Plaintiff raises any allegations based solely on FDA's October 30, 2014 tentative

ARGUMENT

I. VELOXIS' COMPLAINT SHOULD BE DISMISSED OR SUMMARY JUDGMENT SHOULD BE ENTERED FOR THE FEDERAL DEFENDANTS

A motion to dismiss under Fed. R. Civ. P. 12(b)(6) tests the legal sufficiency of a complaint. *Browning v. Clinton*, 292 F.3d 235, 242 (D.C. Cir. 2002). Dismissal is appropriate when a plaintiff fails to allege "enough facts to state a claim to relief that is plausible on its face." *Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 570 (2007). "A claim has facial plausibility when the plaintiff pleads factual content that allows the court to draw the reasonable inference that the defendant is liable for the misconduct alleged." *Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009). When reviewing a Rule 12(b)(6) motion, a court must accept as true all of the plaintiff's well-pled factual allegations; however, courts "accept neither 'inferences drawn by plaintiffs if such inferences are unsupported by the facts set out in the complaint,' nor 'legal conclusions cast in the form of factual allegations.'" *Browning*, 292 F.3d at 242 (quoting *Kowal v. MCI Communications Corp.*, 16 F.3d 1271, 1275 (D.C. Cir. 1994)); *see also Ashcroft*, 556 U.S. at 678 ("Threadbare recitals of the elements of a cause of action, supported by mere conclusory statements, do not suffice."). Dismissal is appropriate when, as here, the plaintiff's complaint is "legally insufficient to state claims upon which relief can be granted." *Trudeau v. FTC*, 456 F.3d 178, 191 (D.C. Cir. 2006).

The D.C. Circuit has clearly set forth "the role the district court plays when it reviews agency action." *Marshall Cnty. Health Care Auth. v. Shalala*, 988 F.2d 1221, 1225 (D.C. Cir. 1993). "The district court sits as an appellate tribunal, not as a court authorized to determine in a trial-type proceeding whether the [agency's] study was factually flawed." *Id.* "The entire case on

---

approval letter, they are mooted by Plaintiff's November 14, 2014 request, and FDA's January 12, 2015 response. AR at FDA 00001–57; FDA 01626-1738.

review is a question of law, and only a question of law." *Id.* at 1226. Because of the nature of Administrative Procedure Act ("APA") review, the Court can decide this case on a motion to dismiss. *Id.* ("[T]he district court can consult the [administrative] record [on a Rule 12(b)(6) motion to dismiss] to answer the legal question before the court – in this case whether the agency adhered to the standards of decision making required by the APA."). Whether the arguments are addressed in a motion to dismiss or a motion for summary judgment, the legal standards are the same. *Id.* at 1222–23 ("[W]hen a district court is reviewing agency action . . . the legal questions raised by a 12(b)(6) motion and a motion for summary judgment are the same.").

Alternatively, because the facts necessary for resolution of this case are not disputed, this Court should grant summary judgment to the Federal Defendants pursuant to Fed. R. Civ. P. 56. The usual summary judgment standard does not apply in cases involving review of final agency action under the APA "because of the limited role of a court in reviewing the administrative record." *Coal for Common Sense in Gov't Procurement v. United States*, 821 F. Supp. 2d 275, 280 (D.D.C. 2011). In such cases, "the agency resolves factual issues to arrive at a decision that is supported by the administrative record," and summary judgment is "the mechanism for deciding whether as a matter of law the agency action is supported by the administrative record and is otherwise consistent with the APA standard of review." *Id.*; *see also Hi-Tech Pharmacal Co. v. FDA*, 587 F. Supp. 2d 13, 18 (D.D.C. 2008) (same); *Fund for Animals v. Babbitt*, 903 F. Supp. 96, 105 (D.D.C. 1995) (summary judgment is "an appropriate procedure for resolving a challenge to a federal agency's administrative decision" when, as here, "review is based upon the administrative record.") (citing *Richards v. INS*, 554 F.2d 1173, 1177 (D.C. Cir. 1977)); *cf.* LCvR 7(h) (Comment) ("This provision recognizes that in cases where review is based on an

administrative record the court is not called upon to determine whether there is a genuine issue of material fact, but rather to test the agency action against the administrative record.").

The administrative record here demonstrates that FDA has reasonably interpreted the FDCA and its implementing regulations in these circumstances to conclude that Envarsus is blocked from approval for use in *de novo* kidney transplant patients until Astagraf's three-year exclusivity expires because the two drugs share an exclusivity-protected condition of approval. The Court should therefore grant the Federal Defendants' motion to dismiss, or alternatively for summary judgment.

A. FDA's Administrative Decision Is Entitled to Deference

1. The APA standard of review

FDA's administrative decisions are subject to review under the APA, and may be disturbed only if "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A).[10] This standard is highly deferential to the agency. *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971). The agency's administrative decision is entitled to a presumption of validity. *See Fla. Power & Light Co. v. Lorion*, 470 U.S. 729, 743 (1985); *Camp*, 411 U.S. at 142. The reviewing court must consider whether the agency's decision was based upon consideration of the relevant factors and whether there has

[10] Counts I and II of Plaintiff's complaint are brought under 5 U.S.C. § 706(2)(C), claiming that FDA's actions "exceed[] Defendants' statutory authority." (Pl's. Compl., Dkt. No. 1, ¶¶ 116 & 121.) Although this APA provision uses different language, courts have adopted the same deferential standard of review as with the more familiar "arbitrary and capricious" provision, 21 U.S.C. § 706(2)(A). *E.g.*, *Apotex, Inc. v. FDA*, 2006 U.S. Dist. LEXIS 20894, at *23 (D.D.C. Apr. 19, 2006), *aff'd Apotex, Inc. v. FDA*, 449 F.3d 1249, 1251 (D.C. Cir. 2006) (explaining in the face of a challenge under 5 U.S.C. §§ 706(2)(A) & 706(2)(C) that the "[a]gency actions are entitled to much deference, and the standard of review is narrow.") (citing *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971)); *see also Wright v. Foreign Serv. Griev. Bd.*, 503 F. Supp. 2d 163, 172 (D.D.C. 2007) (noting the "deferential standard of review" for an APA case brought under 5 U.S.C. § 706(2)(C)).

been a clear error of judgment. *Overton Park*, 401 U.S. at 416. However, a reviewing court is not empowered "to substitute its judgment for that of the agency," *id.*, and must uphold the agency's action so long as it is "rational, based on consideration of the relevant factors and within the scope of the authority delegated to the agency by the statute." *Motor Vehicle Mfrs. Ass'n of the United States, Inc., v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 42-43 (1983). In applying the arbitrary and capricious standard, the court reviews the administrative record assembled by the agency and does not undertake its own fact finding. *See, e.g.*, *Camp,* 411 U.S. at 142.

2. FDA's interpretation of the FDCA and its implementing regulations is entitled to deference under *Chevron*

This action challenges FDA's interpretation of statutory provisions the agency is charged with implementing. Well-established precedent instructs this Court to defer to FDA in this context.

The Supreme Court's decision in *Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837 (1984), and its progeny set forth a two-step framework for reviewing an administrative agency's interpretation of its statute. Under *Chevron* step one: "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. *Chevron* step two applies when Congress has not directly addressed the issue or has done so ambiguously. In that event, the court may not "simply impose its own construction on the statute," but rather must determine whether the agency's construction is based on a permissible interpretation of the statute. *See id.* at 843, 843-44 n.11 (in case of ambiguity, the court must uphold the agency's interpretation if construction is permissible under the statute; a court need not conclude that

agency construction was the only one it permissibly could have adopted or even the reading the court would have reached); *see also Barnhart v. Walton*, 535 U.S. 212, 218 (2002) (reviewing court must decide: (1) whether the statute unambiguously forbids agency interpretation, and (2) whether the agency interpretation exceeds the bounds of the permissible).

Courts have repeatedly given *Chevron* deference to FDA's interpretation of the FDCA, as well as the agency's own implementing regulations. *See, e.g.*, *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 764 (D.C. Cir. 2010); *Novartis Pharms. Corp. v. Leavitt*, 435 F.3d 344, 349 (D.C. Cir. 2006); *Mylan Labs., Inc. v. Thompson*, 389 F.3d 1272, 1281 (D.C. Cir. 2004); *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1319, 1320 (D.C. Cir. 1998) (citing *Auer v. Robbins*, 519 U.S. 452, 461(1997)). Indeed, when, as here, a court is evaluating an agency's interpretation of its own regulations, the agency is entitled to "substantial deference." *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994) ("[t]his broad deference is all the more warranted when . . . the regulation concerns 'a complex and highly technical regulatory program,' in which the identification and classification of relevant 'criteria necessarily require significant expertise and entail the exercise of judgment grounded in policy concerns.'") (quoting *Pauley v. BethEnergy Mines, Inc.*, 501 U.S. 680, 697 (1991)); *Troy Corp. v. Browner*, 120 F.3d 277, 283 (D.C. Cir. 1997) (Courts "review scientific judgments of the agency 'not as the chemist, biologist, or statistician that [they] are qualified neither by training nor experience to be, but as a reviewing court exercising [its] narrowly defined duty of holding agencies to certain minimal standards of rationality.'") (quoting *Ethyl Corp. v. EPA*, 541 F.2d 1, 36 (D.C. Cir. 1976).

Chevron deference also extends to administrative determinations that are not embodied in rulemaking or formal adjudication. As the Supreme Court made clear in *Barnhart*:

> [T]he fact that the Agency previously reached its interpretation through means less formal than "notice and comment" rulemaking . . . does not automatically

> deprive that interpretation of the judicial deference otherwise its due. . . . If this Court's opinion in [*Christiansen v. Harris Cnty.*, 529 U.S. 576 (2000)] suggested an absolute rule to the contrary, our later opinion in [*United States v. Mead Corp.*, 533 U.S. 218 (2001),] denied the suggestion. Indeed, *Mead* pointed to instances in which the Court has applied *Chevron* deference to agency interpretations that did not emerge out of notice-and-comment rulemaking.

535 U.S. at 221–22 (citations omitted).

In *Mylan Labs.*, 389 F.3d at 1279–80, for example, the D.C. Circuit extended *Chevron* deference to the agency's interpretation of ANDA exclusivity provisions that was expressed in a letter decision. The court explained that deference was appropriate because of "the complexity of the statutory regime . . . , the [presence of] FDA's expertise or the careful craft of the scheme it devised to reconcile the various statutory provisions." *See also Novartis*, 435 F.3d at 351-52 (deferring to FDA's interpretation of a statute without notice-and-comment rulemaking).[11]

B. FDA Properly Determined that Envarsus' Approval for the *De Novo* Kidney Patient Population is Blocked by Astagraf's Exclusivity

1. Astagraf's exclusivity was appropriately granted under 21 U.S.C. § 355(v)

Veloxis challenges FDA's decision to grant Astagraf exclusivity under the FDCA in the first instance, claiming that because an initial NDA for Astellas' once-daily extended-release tacrolimus product was pending before the date of the QI Act, Astagraf is ineligible for exclusivity under 21 U.S.C. § 355(v). Pl's Br. at 40–41. As a factual matter, Veloxis does not

[11] Veloxis intimates that the Court should ignore or somehow minimize FDA's January 12 decision because it was a "post hoc" rationalization of the agency's decision. Pl.'s Mem. P. & A in Supp. of Pl's. Mot. for Summ. J. ("Pl's. Br.") at 2, 26, 28. But where FDA has issued its "considered views . . . announced at the usual point in the agency's decision-making process (the end) . . . '[t]here is simply no reason to suspect that the interpretation does not reflect the agency's fair and considered judgment on the matter in question,'" and the D.C. Circuit has accordingly concluded that "timing isn't everything." *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1325 (D.C. Cir. 1998) (quoting *Auer*, 519 U.S. at 462). Similar to the facts in *Serono*, that Veloxis filed for injunctive relief before the agency ruled on its November 14, 2014 "Request for Final Approval" does not change the thoughtful and well-considered nature of FDA's January 12, 2015 decision, nor the deference accorded to it. *Id.*

dispute that Astellas withdrew this initial NDA in 2009, and submitted a new NDA in 2012—four years after the QI Act was passed. Pl's Br. at 41. Because the statute permits exclusivity for an Old Antibiotic if its application was submitted after the date of the QI Act, and because Astellas' 2012 NDA for Astagraf undoubtedly satisfies this requirement, Veloxis' challenge is contrary to the plain statutory language and should be dismissed under *Chevron* step one. *See* 21 U.S.C. §§ 355(v)(1)(A), 355(v)(1)(B)(i).

While the Federal Defendants believe the text of the QI Act is clear, and thus this matter can be resolved under *Chevron* step one, should the Court consider the statute ambiguous, FDA's interpretation of this provision is entitled to deference under *Chevron* step two for the following three reasons.

First, had Congress intended to restrict exclusivity for Old Antibiotics such that applications previously-submitted but withdrawn were ineligible for exclusivity when resubmitted as Veloxis suggests, it could have addressed these applications in a manner similar to the way it addressed pre-FDAMA pending applications in the *following* subsection of the *same statutory provision*. *See* 21 U.S.C. § 355(v)(2) ("antibiotic drugs submitted before November 21, 1997 but not approved. . .").[12]

Second, contrary to Veloxis' assertions, Astellas submitted new study data and information with its 2012 NDA, including: complete justification for non-inferiority margins for both studies essential to the approval of the application (Studies 158 and 12-03); final reports and analyses for additional studies (Studies 02-0-131, FG 506E-12-02 and FG 506EKT0); results from the OSAKA Study, which was a European post-marketing study conducted in the *de novo* setting on the version of Astagraf approved in Europe); and additional safety analyses. AR at

[12] Congress also explicitly distinguished applications based on the timing of submission and approval in FDAMA sections 125(d)(1) and 125(d)(2). AR at FDA00031 n. 132.

FDA 00032; FDA 00888–906. This information had not been submitted to the previously-filed and withdrawn NDA, *id.*, and therefore it bolsters FDA's position that the new NDA submitted by Astellas in 2012 should be treated as such under 21 U.S.C. § 355(v).

Third, in a last ditch attempt to foster an argument under the QI Act, Veloxis cites to the legislative history, arguing that FDA's position to allow Astagraf exclusivity is contrary to Congress' goals because only "new and innovative antibiotic therapies" are entitled to such exclusivity. Pl's Br. at 42. On the contrary, FDA's interpretation of this provision *is* consistent with Congress' intent to balance the need to encourage development of new antibiotic drugs with its desire to ensure access to previously-approved antibiotics. If instead, FDA adopted the limitation advocated by Veloxis, public health could be adversely affected by discouraging sponsors from continuing to study, analyze data, and submit an NDA for an antibiotic drug product in situations where the drug product had been the subject of a previously-submitted and withdrawn NDA. Further, Veloxis' position here cannot be squared with its claims that Envarus, which is also a once-daily extended-release Old Antibiotic, is an "innovative product." Pl's Br. at 1.

2. The scope of Astagraf's three-year exclusivity is based on its "conditions of approval"

After concluding that Astagraf is eligible for three-year exclusivity under 21 U.S.C. § 355(v), FDA determined the scope of that exclusivity under 21 U.S.C. § 355(c)(3)(E)(iii). The parties here agree that exclusivity hinges on the "conditions of approval" per the statutory language. Pl's Br. at 29. Because the FDCA does not define "conditions of approval," the agency's interpretation is entitled to deference under *Chevron* step two. *See supra* p. 20. In the 1989 Proposed Rule, FDA explained that the scope of three-year exclusivity covers "the

innovative change" that is supported by the new clinical investigations. 1989 Proposed Rule at 28896–97; *supra* p. 5. Veloxis does not dispute this interpretation. *See* Pl's Br. at 29, 35.

> Under this legal framework, FDA concluded in its January 12, 2015 decision that:
>
> Because Prograf capsules had been previously approved as a twice-daily, IR [immediate-release] dosage form of tacrolimus for prophylaxis of organ rejection in *de novo* kidney transplant patients, the change in Astagraf XL for which new clinical investigations were needed was the change to a once-daily, ER [extended-release] version of tacrolimus for prophylaxis of organ rejection in *de novo* kidney transplant patients. Studies 158 and 12-03 were essential to the approval of Astagraf XL for this change.

AR at FDA000036.

Veloxis agrees with the Federal Defendants on the legal standard (*i.e.*, that exclusivity is governed by "conditions of approval," determined by the "new clinical investigations" essential to that approval); however, it raises a two-prong attack on Astagraf's exclusivity under this framework, flagrantly contradicting the position it took in its November 14, 2014 Request for Final Approval. *See* AR FDA AR at FDA 00034 n.146; FDA 01636 ("Veloxis does not dispute that Astagraf XL is entitled to three-year exclusivity under 505(c)(3)(iii) of the Act, or that such exclusivity would bar the approval of any ANDA or 505(b)(2) application that relies upon the new clinical investigations essential to the approval of the Astagraf XL NDA."). Moreover, it bases this challenge on an extra-record (though publicly-available) document.[13]

[13] Plaintiff's citation to Exhibit 6, FDA's Statistical Review for the Prograf supplemental NDA ("sNDA"), in support of this argument is improper under well-established administrative law principles. *Hill Dermaceuticals, Inc. v. FDA*, 2012 U.S. Dist. LEXIS 171955, at *27–29 (D.D.C. May 18, 2012), *aff'd*, 709 F.3d 44, 47 (D.C. Cir. 2013); *United Space Alliance, LLC, v. Solis* 812 F. Supp. 2d 68, 88 (D.D.C. 2011) ("[T]he Court of Appeals has 'repeatedly applied [the 'whole record' rule] to bar introduction of litigation affidavits to supplement the administrative record.'" (quoting *AT&T Info. Sys., Inc. v. Gen. Servs. Admin.*, 810 F.2d 1233, 1236 (D.C. Cir. 1987)); *see also Camp v. Pitts*, 411 U.S. 138, 142 (1973) ("the focal point for judicial review should be the administrative record already in existence, not some new record made initially in the reviewing court."). Veloxis has not asserted any of the factors required for extra-record supplementation. *IMS, P.C. v. Alvarez*, 129 F.3d 618, 624 (D.C. Cir. 1997); *see also Theodore Roosevelt*

CONFIDENTIAL INFORMATION – FILED UNDER SEAL

First, Veloxis challenges the agency's interpretation of "new clinical investigation," claiming that Study 158 does not qualify under the definition contained in FDA's regulation. Second, Veloxis asserts that, if Study 158 is not a "new clinical investigation," then only Study 12-03 remains to support Astagraf's exclusivity, and that study alone does not support FDA's determination regarding the scope of Astagraf's exclusivity.

The backbone of Veloxis' argument is the definition of "new clinical investigation," which appears in the three-year exclusivity provision, 21 U.S.C. § 355(c)(3)(E)(iii), and is defined by regulation, in part, as follows:

> *New clinical investigation* means an investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product.

21 C.F.R. § 314.108(a). Veloxis asserts that because Study 158 had been previously-submitted to FDA in support of a Prograf sNDA, that study cannot be a "new clinical investigation" that supports Astagraf's approval. Pl.'s Br. at 30–31.

The fact that FDA reviewed one arm of a study in conjunction with a different application is not dispositive. FDA was aware at the time it reviewed the Astagraf NDA that one arm of Study 158 was reviewed in conjunction with the Prograf sNDA, s*ee* Astagraf Exclusivity Summary and attachments, AR at FDA 01082–1098; FDA 02068–02082, and ultimately concluded in assessing exclusivity for Astagraf that Study 158 was a "new clinical investigation"

Conservation P'ship v. Salazar, 616 F.3d 497, 514 (D.C. Cir. 2010); *Cape Hatteras Access Pres. Alliance v. United States*, 667 F. Supp. 2d 111, 116. Nor can it. Moreover, "'if the reviewing court simply cannot evaluate the challenged agency action on the basis of the record before it, the proper course, except in rare circumstances, is to remand to the agency for additional investigation or explanation.'" *PBGC v. LTV Corp.*, 496 U.S. 633, 654 (1990) (quoting *Fla. Power & Light Co. v. Lorion*, 470 U.S. 729, 744 (1985)).

within the meaning of its regulation, 21 C.F.R. § 314.108(a). Veloxis fails to show that FDA erred in reaching this conclusion.

Because FDA properly concluded that Study 158 is a "new clinical investigation," and it concluded that Astagraf's exclusivity covered once-daily extended-release use in *de novo* kidney transplant patients, Veloxis' argument regarding Study 12-03 need not be considered. Pl's Br. at 34. In any event, Veloxis' argument related to Study 12-03 can be concisely stated as this: the Court should substitute Veloxis' views of the scientific studies underlying Astagraf's approval for the agency's. But FDA, and not Veloxis, is in the proper position to determine what the submitted studies demonstrate and the scope of Astagraf's exclusivity. The Court should not allow Veloxis to usurp FDA's position as the proper evaluator of the scientific data supporting drug approvals. *Graceway Pharms., LLC v. Sebelius*, 783 F. Supp. 2d 104, 110–111 (D.D.C. 2011) (noting the "high level of deference" to which Courts routinely give "FDA's evaluations of scientific data within its area of expertise") (citing *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1320 (D.C. Cir. 1998)).

3. Because Envarsus and Astagraf share exclusivity-protected "conditions of approval," Envarsus is blocked by Astagraf's three-year exclusivity under the FDCA

Veloxis asserts that Envarsus is not blocked by Astagraf's exclusivity because, although it admittedly shares some conditions of approval with Astagraf, it does not share all of Astagraf's conditions of approval. Pl's Br. at 1, 35. Specifically, Veloxis argues that Envarsus differs from Astagraf in pharmacokinetic ("PK") profile, dosage form, dosage strengths and dosing regimen, and that these differences take Envarsus outside the scope of Astagraf's exclusivity. *Id*. at 36–40.

As explained above, the relevant analysis for exclusivity is whether Envarsus shares exclusivity-protected conditions of Astagraf's approval. *See supra* p. 25. Astagraf received exclusivity neither for the capsule nature of its dosage form (Prograf had been previously-approved as a capsule) nor for the particular strengths for which it was approved (Prograf had been approved previously in the same strengths as Astagraf. AR at FDA 00188–00230. Astagraf also did not obtain exclusivity for its precise PK profile, as the agency has not yet determined, and no sponsor has yet established, the correlation between changes in PK profile and clinically significant differences in safety and effectiveness for tacrolimus products. AR at FDA 00093–94, 01903–01906.[14] Instead, Astagraf's innovation is its extended-release nature that permits once-daily dosing (whereas Prograf was an immediate-release dosage form with twice-daily dosing). AR at FDA 00095. The new clinical investigations essential to this innovation studied Astagraf for the prophylaxis of organ rejection in *de novo* kidney transplant patients. AR at FDA 00559–60. Astagraf's exclusivity is circumscribed by the scope of these new clinical investigations. Because Envarsus shares the exclusivity-protected conditions of approval—*i.e.*, the once-daily, extended-release dosage form of tacrolimus to prevent organ rejection in *de novo* kidney transplant patients— with Astagraf , Envarsus is blocked from approval for this use until Astagraf's exclusivity expires in July 2016.

[14] Veloxis takes out of context the Agency's explanations regarding clinical significance and inappropriately attempts to conflate the issues. Pl's Br. at 36. The Agency stated, in the context of *eligibility* for 3-year exclusivity, that it 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 condition of use* for exclusivity purposes under *21 U.S.C. § 355(v)*. AR at FDA00034 n. 145. This is consistent with the Agency's position that the *scope* of exclusivity under a different provision (i.e., 21 U.S.C. § 355(c)(3)(E)(iii)) is related to the scope of the new clinical investigations essential to approval which is a fact-specific inquiry. The Agency's position is perfectly sound.

As noted above, *see supra* pp. 5–6, under the agency's interpretation, a 505(b)(2) application can differ in certain ways from the previously-approved drug product with exclusivity and nonetheless be blocked if it shares the conditions of approval for which exclusivity was granted. Veloxis disagrees with this position, but the legal support for its position is unsurprisingly lacking. Pl's Br. at 35. Veloxis argues, without support, that only drugs that share *all* "approval characteristics" can be blocked by the three-year exclusivity of a previously-approved drug. But Congress has established a separate pathway for such drugs (also known as duplicates or generics) under 21 U.S.C. § 355(j) and had it intended to limit the scope of exclusivity to block approval only of drugs approved under this pathway, it would not have needed the exclusivity provision in 21 U.S.C. § 355(c)(3)(E)(iii). *See supra* p. 3. Veloxis' interpretation of the FDCA would render 21 U.S.C. § 355(c)(3)(E)(iii) superfluous, and therefore is ill-favored. *Singer v. United States*, 323 U.S. 338, 344 (1945); *Haase v. Sessions*, 893 F.2d 370, 374 n.5 (D.C. Cir. 1990) ("it is a well-settled principle of statutory construction that all words in a statute are to be assigned meaning and not to be construed as duplicative or surplusage.") (citing *United States v. John Peter McGoff*, 831 F.2d 1071, 1083 (D.C. Cir. 1987)).

Moreover, FDA is not "cherry-picking" conditions of approval, as Veloxis asserts. Pl's. Br. at 35, 40. Rather, after examining the conditions of approval for which tacrolimus had been approved previously and the scope of the clinical studies and the changes for which the clinical studies were essential, the agency has determined, consistent with the statutory language, that Astagraf's innovative change for which new clinical investigations were needed was the change from twice daily, immediate-release dosage form to its once-daily, extended-release dosage form. The agency then carefully examined the new studies, concluded that they were essential to Astagraf's approval, and thus determined the scope of Astagraf's exclusivity based on those

studies. FDA's analysis in support of this conclusion is robust and well-documented. There is nothing arbitrary or capricious about FDA's analysis, and FDA's interpretation of "conditions of approval" is entitled to deference under *Chevron* step two.

Further, the differences Veloxis highlights could not, under the agency's interpretation of the FDCA, serve as the basis for exclusivity, given the new clinical investigations submitted by Astellas and Veloxis in support of their applications. For example, while FDA acknowledges that there are some differences in Astagraf's and Envarsus' PK profiles, the clinical significance of those differences has not been demonstrated in clinical studies. AR at FDA 000037; FDA 001903-1906. Veloxis has not provided studies demonstrating the clinical significance of Envarsus' PK profile , and FDA need not speculate whether such a difference would affect whether Envarsus would be blocked by the scope of Astagraf's exclusivity. Envarsus is blocked by Astagraf's exclusivity because it shares at least one exclusivity-protected condition of approval with Astagraf.

Similarly, Astagraf's exclusivity is not based on the capsule aspect of its dosage form. Contrary to Veloxis' assertion, Astagraf was *not* granted exclusivity for its capsule formulation. This is because Astagraf's capsule form was not the innovative change for which the new clinical studies were essential, as Prograf, Astagraf's predecessor drug, is also a capsule. Hence, at the time Astellas obtained exclusivity for Astagraf, the capsule aspect of the dosage form was not eligible for exclusivity protection.[15]

[15] Veloxis also argues that "new dosage form" or "NDF" is not the appropriate Orange Book code to designate Astagraf's exclusivity. Pl's Br. at 8, 38–39; 39 n.29; *see* AR at FDA 00016; FDA 001090–1100. That the Orange Book did not list a more specific code, such as "capsule, extended-release," as Veloxis suggests it could have, only supports FDA's view that Astagraf's exclusivity encompassed something broader, namely the extended-release, once-daily dosage form. Similarly, the "once daily dosing" or "once-a-day dosing regimen" that Veloxis suggests

The same is true regarding the dosage strength. Although Envarsus and Astagraf share one common dosage strength, the clinical investigations for Astagraf did not evaluate the specific strengths or starting doses for that product because Prograf had been previously-approved for those strengths. Further, dosing for tacrolimus products is individually titrated for each patient.

Simply put, given what the new clinical investigations supporting approval of Astagraf and Envarsus demonstrate (and what they do not), FDA concluded that they share conditions of approval that were supported by new clinical investigations: namely the extended-release, once-daily formulation of tacrolimus for use in *de novo* kidney transplant patients to prevent organ rejection even though they may differ in certain other aspects. Accordingly, under 21 U.S.C. § 355(c)(3)(E)(iii), FDA is prohibited from approving Envarsus, the later-in-time 505(b)(2) application based on its current labeling until Astagraf's three-year exclusivity expires in July 2016.

C. The listed drug a 505(b)(2) applicant chooses to rely on does not affect FDA's exclusivity determinations under section 355(c)(3)(E)(iii)

1. Reliance is not a prerequisite for exclusivity under the unambiguous statutory text

As noted above, a 505(b)(2) applicant can choose the listed drug that it seeks to rely on in its 505(b)(2) application. It would be nonsensical if in choosing the listed drug, the 505(b)(2) applicant could also choose whether or not it would be subject to a previously-approved drug's exclusivity. The FDCA *does not* state that only 505(b)(2) NDAs that rely on a particular drug with exclusivity are blocked.

Rather, the operative statutory provision here, 21 U.S.C. § 355(c)(3)(E)(iii), states:

If an application submitted under subsection (b) [of this section] for a drug, which

---

as better alternatives would not have been more appropriate exclusivity codes, because these codes would not have captured the extended release nature of Astagraf's dosage form.

> includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) [of this section], is approved after [September 24, 1984,] and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) for the *conditions of approval* of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) *if* **the investigations described in clause (A) of subsection (b)(1) and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.**

(emphasis added). To be eligible for three-year exclusivity under 21 U.S.C. § 355(c)(3)(E)(iii), an application must meet four factors: (1) be a 505(b)(1) or 505(b)(2) NDA; (2) have been approved after the enactment of the Hatch-Waxman Amendments (in 1984); (3) be for a drug that contains a previously-approved active ingredient; and (4) contain at least one new clinical study that is not a bioavailability study that is essential to approval of the application. Here, Astagraf easily meets each of these requirements as it: (1) is a 505(b)(1) NDA; (2) that was approveed in 2013; (3) contains tacrolimus, the active ingredient in the previously-approved product Prograf; and (4) was approved based on two controlled clinical trials, Studies 158 and 12-03. Because Envarsus shares Astagraf's exclusivity-protected conditions of approval and because Veloxis submitted a 505(b)(2) application (*i.e.*, did not conduct the investigations or obtain a right of reference for the investigations necessary for Envarsus' approval), Envarsus is blocked, pursuant 21 U.S.C. § 355(c)(3)(E)(iii), by Astagraf's exclusivity.

Desperate to avoid the consequences of having submitted Envarsus as a 505(b)(2) application and *not* a 505(b)(1) NDA (which plainly would not have been blocked), Veloxis profers a construction of the the statutory language that twists it into a meaning that it simply does not have. Veloxis challenges the agency's interpretation of 21 U.S.C. § 355(c)(3)(E)(iii) by

seizing on the phrase "relied upon," trying to load that phrase with a meaning belied by the plain statutory text. *See* Pl.'s Br. at 18. The phrase "relied upon" *does not*, as Veloxis asserts, mean that reliance is required to trigger exclusivity. Pl.'s Br. at 18. Nowhere in this provision does Congress say that an applicant will be blocked only if the studies it "relied upon" were conducted by a particular sponsor, or included in the blocking drug's application.

Rather, "relied upon" is used only to distinguish 505(b)(1) applications from 505(b)(2) applications; the phrase "relied upon" is included in 21 U.S.C. § 355(c)(3)(E)(iii) only as part of the lengthier statutory definition of a 505(b)(2) application. This is apparent from a comparison of the bolded language below, which is the FDCA definition of 505(b)(2) applications, with the bolded language included in the 21 U.S.C. § 355(c)(3)(E)(iii) block quote, *see supra*, p. 32:

> An application submitted under paragraph (1) for a drug for which **the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted . . .**

21 U.S.C. § 355(b)(2) (emphasis added). That Congress has used different shorthand language to reference 505(b)(2) applications in later-enacted sections of the statute, as Veloxis notes, *see* Pl's Br. at 20, does not alter the identical language contained in 21 U.S.C. § 355(b)(2) and 21 U.S.C. § 355(c)(3)(E)(iii).

Veloxis also grasps at straws when it points to FDA's statements in another lawsuit involving whether and when a 505(b)(2) applicant is required to file a patent certification. *Takeda Pharms., U.S.A., Inc. v. Burwell,* 2015 U.S. Dist. LEXIS 5908 (D.D.C. Jan. 13, 2015). Such analyses focus on 21 U.S.C. § 355(b)(2)(A), a provision not at issue in this litigation. Further, that provision involves *patent* certification. This case involves three-year exclusivity only, and has nothing to do with patents or patent certification. Because *Takeda Pharms*. and

many of the citizen petition responses Veloxis cites in support of its reliance argument concern 505(b)(2) patent certification requirements, they are not controlling, or indeed even relevant, to the legal questions before the Court here.

2. The precedents Veloxis cites are unavailing

Veloxis has cited to two primary examples that it claims show that only where a 505(b)(2) applicant relies on a previously-approved drug will FDA conclude that the 505(b)(2) applicant is blocked by the previously-approved drug's exclusivity. Pl's Br. at 25–26. As explained above, and noted in the 1989 Proposed Rules, this is *not* the agency's long-standing interpretation.[16]

Further, the agency's review of the two examples Veloxis cites demonstrates that they are not inconsistent with the agency's position regarding reliance. In the Metadate CD/Concerta example, Veloxis notes that Concerta's exclusivity did not block approval of Metadate CD. In speculating why, Veloxis implies that Metadate CD was not blocked because it did not rely on Concerta's previous approval in its drug application. Pl's Br. at 24–25. Veloxis also surmises that FDA's approval of Metadate CD must have been because it was a capsule rather than a tablet. Pl's Br. at 25, 36-37. Yet Veloxis has pointed to nothing in the administrative record to confirm either of its hypotheses. AR at FDA 00049-FDA 00051. Veloxis' over-simplification omits key facts that explain why the agency was able to approve Metadate CD despite Concerta's three-year exclusivity. AR FDA000049–51. When Concerta was approved, a third methylphenidate product was already on the market—Ritalin, which had been approved in both

[16] The July 17, 1997 Meeting Minutes related to Duoneb, which Plaintiff improperly submitted as Exhibit 5 with its summary judgment motion, *see supra* n. 12, support FDA's position, not Veloxis'. *See* Pl's Ex. 5 at 6 ("[the applicant, Dey's] 505(b)(2) new drug application could not be approved pending expiration of [the approved product, Combivent's] exclusivity . . . *even if Dey does not reference the Combivent NDA and even if Dey provides data in support of the combination product from the literature and/or their own studies.*") (emphasis added).

immediate-release and extended-release tablet formulations (Ritalin and Ritalin SR, respectively). AR at FDA 00050. Concerta was therefore ineligible for exclusivity for its "tablet" condition of approval, or for being an extended-release dosage form of methylphenidate, and the fact that Metadate CD has an extended-release capsule form was irrelevant to the exclusivity analysis. This is exactly the case here. Astagraf did not receive exclusivity for its capsule formulation because Prograf, an earlier approved tacrolimus product, is also a capsule. *Id.* Accordingly, the fact that Envarsus is a tablet simply has no bearing on the exclusivity analysis.

FDA examined the new clinical investigations supporting Concerta's approval, and concluded that Concerta's condition of approval for which clinical investigations were essential was narrow—its exclusivity is limited to its specific PK profile. This conclusion is supported by the administrative record. AR at FDA 002843 (in describing the reason the new clinical study was essential, Concerta's Exclusivity Checklist, states, "[t]he new PK profile of formulation requires a clinical study.") While Veloxis asserts that Envarsus is different from Astagraf because it has a distinct PK profile, this difference is irrelevant for exclusivity purposes. Even if Envarsus were to have a different "condition of approval" from Astagraf based on a difference in its PK profile, Astagraf's exclusivity is not as narrow as Concerta's, which was limited solely to its unique PK profile (because methylphenidate had been previously-approved as a tablet in an extended release dosage form). Unlike Concerta, Astagraf was the first extended-release tacrolimus product, and the first with once-daily dosing, in *de novo* patients. Because these changes were supported by new clinical investigations, they are the "conditions of approval" for which Astagraf received exclusivity. As described previously, because Envarsus shares both of

these exclusivity-protected conditions of approval, the fact that it may differ in certain other conditions of approval does not provide a basis to approve Veloxis' 505(b)(2) application.

Veloxis also points to Testim 1%, a transdermal testosterone gel that was approved four months before the three-year exclusivity of Androgel 1% (another transdermal testosterone gel) expired. Pl's. Br. at 26. Again, Veloxis speculates that FDA approved Testim 1% because it did not rely on FDA's findings of safety and effectiveness for Androgel 1%. As with methylphenidate, the landscape of testosterone products is not as simple as Veloxis makes it appear. *See* AR at FDA 00051–53; FDA00055–56. Regardless, FDA reviewed the administrative record for Testim 1% and found no express statements indicating that the Testim NDA was approved because it did not rely on AndroGel 1%—nor has Veloxis cited any such statements. Further, some aspects of the administrative record indicate that there was uncertainty about whether Testim 1% was a 505(b)(1) or a 505(b)(2) application. AR at FDA00053; FDA 03512–13; FDA 03517. The agency notified the Testim sponsor that the Testim NDA had been reclassified before the expiration of exclusivity of Androgel 1%. AR at 03514–3515. This issue is significant because if FDA had believed that Testim was a 505(b)(1) NDA, its approval would not have been blocked by the three-year exclusivity of another drug.[17]

Finally, Veloxis' entire argument regarding precedents is self-contradicting: on the one hand, it cites to "thirty years of precedents" that it claims support its views, and demands that FDA explain its "departure from established precedent," but on the other, acknowledges that

[17] Moreover, even if Testim 1%'s approval was premature, this decision appears to be an outlier, and does not bind the agency. *See, e.g.*, *Aera Energy LLC v. Salazar*, 642 F.3d 212, 223 (D.C. Cir. 2011) ("we have never required a special procedure and instead have encouraged agencies to adapt established internal procedures to render fresh untainted decisions."); *Actavis v. FDA*, 689 F. Supp. 2d 174, 180 (D.D.C.), *aff'd*, 625 F.3d 760 (D.C. Cir. 2010) (rejecting Actavis' argument that FDA had been inconsistent and noting with approval FDA's decision to reverse course and render a decision that was consistent with the FDCA and its implementing regulations).

"[n]or do FDA's examples establish a clear FDA position on reliance." Pl.'s Br. at 24, 27 n. 19, 20, 28. It is inaccurate for Veloxis to imply that this situation arises routinely, and that the agency has, in every other situation, taken a position contrary to the one it takes here.

As FDA notes in its January 12, 2015 decision, the situation presented by this case does not arise often due to:

> a combination of several factors, including the rarity of the factual scenario and rational decision-making by knowledgeable industry actors. Three years is relatively short in relation to the time required to develop an NDA. It generally takes a longer time for an NDA to be developed, filed, and reviewed. Therefore, for this question to be presented, two applicants would generally have to proceed on parallel development paths for the same innovation. In addition, the later-in-time application would have to be a 505(b)(2) application, which would have to become ready for an approval decision during the pendency of the 3-year exclusivity period of a protected drug on which it did not rely. Moreover, for the question of reliance to arise, there must also exist another version of the exclusivity-protected drug (or a significant quantity of non-product specific published literature) such that the 505(b)(2) application is able to refer to the other drug as its listed drug or rely on the nonproduct specific published literature to fill gaps in its application, rather than relying on the exclusivity-protected drug product.

AR at FDA 00046. Moreover, in instances where this fact scenario has presented itself, "[s]ponsors have also developed alternative business arrangements to avoid conflicts involving three-year exclusivity issues for competing products." AR at FDA 00047. For example, in October 2014, two firms announced an exchange of waivers of exclusivity for their respective competing extended-release hydrocodone products. AR at FDA 00047; FDA 02133–36. FDA approved the later-in-time 505(b)(2) application that did not rely on the previously-approved drug's data shortly after the mutual waiver agreement was announced. AR at FDA 02151–52.

3. Under Chevron, FDA's interpretation of the FDCA's three-year exclusivity provision is reasonable and must be upheld

The agency has reasonably interpreted the statutory language regarding three-year exclusivity to conclude that reliance is not required for a subsequent 505(b)(2) application to be

blocked by a previously-approved drug's exclusivity-protected "conditions of approval." Because the interpretation flows from the plain text of the statute, the Federal Defendants need not discuss the second step of the *Chevron* analysis; however, should the Court find the statute ambiguous, it must defer to the agency's reasonable interpretation of the statute under *Chevron* step two. This interpretation is faithful to both the statutory text and the purpose of the Hatch-Waxman amendments, which were designed, in part, to incentivize drug manufacturers to engage in the "protracted, expensive, and risk-laden" full NDA process. Pl's Br. at 3. The agency's interpretation is also supported by the preamble to the 1989 Proposed Rule, which itself is entitled to deference under *Mead*. 533 U.S. at 227–28; *Barnhart*, 535 U.S. at 221–22. That proposed rule explains: "when exclusivity attaches to . . . an innovative change in an already approved drug, the . . . effective date of approval of . . . 505(b)(2) applications for a drug with that . . . innovative change will be delayed until the innovator's exclusivity has expired . . . *regardless of the specific listed drug product to which the . . . 505(b)(2) application refers*." 54 Fed Reg. 28897 (emphasis added). Moreover, the agency's well-considered and reasonable decision on this point further explains FDA's rationale for this interpretation. AR at FDA 00005–57; FDA 00058–116. Because that decision is well-reasoned and consistent with the statutory language and the administrative record in this case, the Court must afford the agency's interpretation deference. *Mead*, 533 U.S. at 228; *Mylan*, 389 F.3d at 1279–80.

II. THE INJUNCTIVE RELIEF VELOXIS SEEKS IS INAPPROPRIATE

In addition to asking this Court for declaratory relief, Veloxis' complaint seeks an injunction ordering FDA to "rescind the marketing exclusivity awarded to Astagraf XL and ordering FDA to grand immediate, final approval of the Envarsus XR NDA." Dkt. No. 1. It has renewed this request in its summary judgment motion. Pl's Br. at 1 ("Veloxis seeks declaratory

and injunctive relief requiring FDA to . . . grant immediate, full, and final approval to the Envarsus XR NDA.").

To obtain a permanent injunction, Veloxis must demonstrate: (1) success on the merits; (2) that it is likely to suffer irreparable harm in the absence of relief; (3) the balance of equities tips in its favor; and (4) an injunction would serve the public interest. *Winter v. NRDC*, 555 U.S. 7, 22, 32 (2008). Plaintiff is not entitled to injunctive relief here because it has not demonstrated success on the merits, *see supra*, and because it has failed to allege any harm in its motion for summary judgment. *Astellas Pharm. v. FDA*, 642 F. Supp. 2d 10, 16 (D.D.C. 2009) ("Indeed, if a party fails to make a sufficient showing of irreparable injury, the court may deny the motion for injunctive relief without considering the other factors."). While Veloxis did raise such matters in its motion for preliminary injunction and supporting attachments ("PI motion"), the Court denied Veloxis' PI motion without prejudice. Dkt. No. 9.

Finally, although FDA has no commercial stake in the outcome of this litigation, FDA's interest and the public's interest in drug approvals are the same. *See Serono*, 158 F.3d at 1326 (determining that the public interest is "inextricably linked" to Congress's purpose in passing the Hatch-Waxman Amendments). As such, both the balance of equities and the public interest weigh against the entry of injunctive relief.[18]

[18] As demonstrated above, the challenged FDA decision is well-reasoned and entitled to deference under steadfast administrative law principles. But even if Veloxis could succeed on the merits, which it cannot, the appropriate remedy here would be to remand this case to FDA for further consideration consistent with the Court's findings. *Hill Dermaceuticals, Inc. v. FDA*, 709 F.3d 44, 46 n.1 (D.C. Cir. 2013) ("Usually, where a district court reviews agency action under the APA, it acts as an appellate tribunal, so the appropriate remedy for a violation is 'simply to identify a legal error and then remand to the agency.'") (quoting *Bennett v. Donovan*, 703 F.3d 582, 589 (D.C. Cir. 2013)); *N. Air Cargo v. United States Postal Serv.*, 674 F.3d 852, 861 (D.C. Cir. 2012) (same); *see also Camp v. Pitts*, 411 U.S. at 143 (citing *SEC v. Chenery Corp.*, 318 U.S. 80 (1943)). On these reasons alone, Veloxis' request for injunctive relief should be denied.

CONCLUSION

Veloxis cannot have its cake and eat it too. It chose to file a 505(b)(2) application rather than undertaking the more costly route that would have required it to conduct all of its own studies to support its application. It now seeks to undo the incentives created by the Hatch-Waxman amendments by asking this Court to strip exclusivity from its competitor, Astellas, for its currently-marketed drug, Astagraf. Granting Veloxis' request would overturn FDA's reasonable interpretation of the FDCA and supplant its expert scientific judgment. This Court should not abandon core administrative law principles as Plaintiff asks, and should instead dismiss Veloxis' lawsuit, or alternatively, grant Defendants' summary judgment motion.

Respectfully submitted,

Of Counsel:

WILLIAM B. SCHULTZ
General Counsel

ELIZABETH H. DICKINSON
Associate General Counsel
Food and Drug Division

PERHAM GORJI
Deputy Chief Counsel, Litigation

SONIA W. NATH
Associate Chief Counsel for Enforcement
U.S. Dept. of Health & Human Services
Office of the General Counsel
10903 New Hampshire Ave.
White Oak 31, Room 4568
Silver Spring, MD 20993-0002
Tel. 301-796-8708

JOYCE R. BRANDA
Acting Assistant Attorney General

JONATHAN F. OLIN
Acting Assistant Attorney General

MICHAEL S. BLUME
Director

/S/ HEIDE L. HERRMANN
HEIDE L. HERRMANN
Trial Attorney
Consumer Protection Branch
U.S. Department of Justice, Civil Division
P.O. Box. 386
Washington, D.C. 20044
Tel. 202-532-4882
Heide.Herrmann@usdoj.gov

EXHIBIT A

NDA 206406

RESPONSE TO REQUEST FOR FINAL APPROVAL

Veloxis Pharmaceuticals, Inc.
Attention: Michelle A. McGuinness
VP Global Regulatory Affairs & Quality Assurance
499 Thornall Street
3rd Floor
Edison, NJ 08837

Dear Ms. McGuinness:

Please refer to your New Drug Application (NDA) dated December 28, 2013, received December 30, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) for Envarsus XR (tacrolimus extended-release tablets), 0.75 mg, 1 mg, and 4 mg.

We also refer to the Tentative Approval letter issued on October 30, 2014.

We acknowledge receipt of your November 17, 2014, Request for Final Approval and December 2, December 8, and December 12, 2014, amendments to the Request for Final Approval.

This NDA provides for the use of Envarsus XR (tacrolimus extended-release tablets), 0.75 mg, 1 mg and 4 mg for prophylaxis of organ rejection in kidney transplant patients.

We have completed our review of your Request for Final Approval, including the amendments subsequently made to that Request. At this time, your application will remain tentatively approved under 21 CFR 314.105 for use as described in the labeling included in the October 30, 2014 Tentative Approval letter ("TA Letter").

Below we describe two options for approval of this application. The first option provides for full approval on or after July 19, 2016 for use as described in the labeling included in the TA letter. The second option provides for approval now, subject to reaching agreement on revised labeling for the use of Envarsus XR only in patients converted from an immediate-release formulation of tacrolimus to Envarsus XR. If you pursue the second option now for approval, you can seek approval for the *de novo* use on or after July 19, 2016, as described in the labeling included in the TA letter.

(1) As noted in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), the listed drug product Astagraf XL (NDA 204096) is subject to a period of exclusivity protection under section 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the

Act. Envarsus XR shares conditions of approval with Astagraf XL for which new clinical studies were essential to the approval for Astagraf XL. Therefore, final approval of your application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until that product's exclusivity period has expired. Refer to the DTOP's separate letter to this NDA (206406) dated January 12, 2015, titled **GENERAL ADVICE**, regarding Envarsus XR; Request for Final Approval, for a complete discussion of this issue.

To obtain final approval of this application, submit an amendment two or six months prior to the: 1) expiration of the exclusivity protection or 2) date you believe that your NDA will be eligible for final approval, as appropriate. In your cover letter, clearly identify your amendment as **"REQUEST FOR FINAL APPROVAL."** This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of any relevant court order or judgment settlement, or licensing agreement, as appropriate. In addition, the amendment should include a safety update and also identify changes, if any, in the conditions under which your product was tentatively approved, i.e., updated labeling; chemistry, manufacturing, and controls data; and risk evaluation and mitigation strategy (REMS). If there are no changes, clearly state so in your cover letter. Any changes require our review before final approval and the goal date for our review will be set accordingly.

(2) During the telephone conference on December 5, 2014, between representatives from the Division of Transplant and Ophthalmology Products, the Office of Regulatory Policy, and the Office of the Chief Counsel, and representatives from Veloxis and Veloxis's legal counsel, the Agency proposed a potential option for final approval prior to July 19, 2016. Specifically, the Agency stated that Veloxis could submit revised draft labeling to the Envarsus XR NDA seeking approval only for patients seeking conversion from an immediate-release formulation of tacrolimus to Envarsus XR based on the clinical trials conducted by Veloxis and submitted to NDA 206406. On December 8, 2014, Veloxis informed the Agency that the company was declining this proposed option for approval.

This option would require Veloxis to submit revised draft labeling that omits references to the *de novo* patient population (Study 3002 and Study 2017), and only discusses the information relating to the conversion population (Study 3001). Approval of the application would be dependent upon reaching final agreement on labeling.

Until we issue a final approval letter, this NDA is <u>not</u> approved.

If you have any questions, call Ms. Lois Almoza, Regulatory Health Project Manager, at 301-796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RENATA ALBRECHT
01/12/2015

NDA 206406

GENERAL ADVICE

Veloxis Pharmaceuticals, Inc.
Attention: Michelle A. McGuinness
VP Global Regulatory Affairs & Quality Assurance
499 Thornall Street
3rd Floor
Edison, NJ 08837

Dear Ms. McGuinness:

Please refer to your New Drug Application (NDA) dated December 28, 2013, received December 30, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) for Envarsus XR (tacrolimus extended-release tablets), 0.75 mg, 1 mg, and 4 mg.

This letter documents the Food and Drug Administration's (FDA's or the Agency's) analysis and conclusions regarding the following issues: whether Astellas Pharma US, Inc. (Astellas) appropriately received 3-year exclusivity for the NDA for Astagraf XL (tacrolimus extended-release (ER) capsules) (NDA 204096), the scope of that exclusivity, and whether that exclusivity blocks approval of Veloxis Pharmaceuticals Inc.'s (Veloxis') NDA for Envarsus XR (NDA 206406).

FDA's consideration of the matter included evaluation of the arguments raised by Astellas and Veloxis; reexamination of the studies conducted to support both the Astagraf XL and Envarsus XR NDAs; review of the documents from NDAs for products cited as precedent regarding FDA's past treatment of the scope of 3-year exclusivity; and reevaluation of the Agency's prior determinations that Astagraf XL is entitled to 3-year exclusivity, that such exclusivity is not circumscribed by the limitations described in section 505(v) of the FD&C Act (21 U.S.C. 355(v)), and that this exclusivity blocks approval of the Envarsus XR NDA.

In summary, FDA confirms that 3-year exclusivity for Astagraf XL is proper under section 505(c)(3)(E)(iii) and 505(v) of the FD&C Act. This exclusivity is based on the new clinical investigations essential to the approval of the once-daily, ER dosage form of tacrolimus for prophylaxis of organ rejection for use in *de novo* kidney transplant patients. In addition, FDA

concludes that the Envarsus XR NDA is a once-daily, ER dosage form of tacrolimus for prophylaxis of organ rejection that is blocked from approval for *de novo* kidney transplant patients by Astagraf XL's exclusivity until that exclusivity expires on July 19, 2016. FDA also concludes, however, that the Envarsus XR NDA can be approved now for conversion of stable kidney transplant patients from tacrolimus immediate-release (IR) products to Envarsus XR (the *conversion use*), pending Veloxis' submission and FDA approval of an appropriate labeling amendment deleting reference to the *de novo* population and seeking approval for the conversion use only.

This decision has involved the intersection of complex legal, regulatory, policy, scientific, and technical issues. This decision was made with input from the Agency's scientific experts and policymakers from the Center for Drug Evaluation and Research (CDER), including representatives from the Office of the Center Director, Office of New Drugs (including scientific experts in the Office of Antimicrobial Products (OAP), Division of Transplant and Ophthalmology Products (DTOP)), Office of Clinical Pharmacology (OCP), CDER's Exclusivity Board, and other policy experts in the Office of Regulatory Policy (ORP) and the Office of Medical Policy, among others. Accordingly, this letter has been prepared in consultation with several components of the Agency.

I. BACKGROUND

A. Immunosuppression in Kidney Transplant Patients[1]

The immune system distinguishes *self* from *non-self*. When a kidney (or other organ) is transplanted from one person into another person, the immune system recognizes the transplanted organ as *non-self* and will try to attack and to reject the transplanted *non-self* organ. To prevent any rejection, drugs that suppress the immune system need to be given to organ transplant recipients. The drugs must be started at the time the organ is transplanted and continue to be taken as long as the transplanted organ (graft) is viable.

Kidney transplant patients are referred to as *de novo* patients at the time of transplant surgery. Because relying solely on one immunosuppressant drug has not been shown to be sufficient to provide adequate immunosuppression to these patients, multiple drugs are now included in the patient's immunosuppressive regimen. *Induction* generally refers to the intensive level of immunosuppression administered to *de novo* kidney transplant patients from the commencement

[1] This section has been derived from a compilation of sources. See, e.g., Morris, PJ and SJ Knechtle, 2014, Kidney Transplantation: Principles and Practice, 7th edition, Saunders; Kirk, AD, SJ Knechtle, CP Larsen, et al., 2014, Textbook of Organ Transplantation; HU Meier-Kriesche, S Li, RW Gruessner, et al., 2006, Immunosuppression: Evolution in Practice and Trends, 1994-2004, Am J Transplant, 6 (5 Pt 2):1111-1131; Hardinger, KL, DC Brennan, and CL Klein, July 2013, Selection of Induction Therapy in Kidney Transplantation, Transpl Int, 26(7):662-672; WH Lim, J Eris, J Kanellis, et al., Sept. 2014, A Systematic Review of Conversion from Calcineurin Inhibitor to Mammalian Target of Rapamycin Inhibitors for Maintenance Immunosuppression in Kidney Transplant Recipients, Am J Transplant,14(9):2106-2119; Holdaas, H, L Rostaing, D Serón, et al., Aug. 27, 2011, Conversion of Long-Term Kidney Transplant Recipients from Calcineurin Inhibitor Therapy to Everolimus: A Randomized, Multicenter, 24-Month Study, Transplantation, 92(4):410-418; Budde, K, J Curtis, G Knoll, et al., Feb. 2004, Enteric-Coated Mycophenolate Sodium Can Be Safely Administered in Maintenance Renal Transplant Patients: Results of a 1-Year Study, Am J Transplant; 4(2):237-243.

of the transplant surgery until early after the surgery. In all kidney transplant patients, induction involves, at a minimum, the use of a *triple combination* of a calcineurin inhibitor (CNI) (e.g., tacrolimus or cyclosporine) at a high initial dose; a mycophenolate preparation (which includes mycophenolate mofetil (MMF) or mycophenolate-sodium); and a higher dose of corticosteroids than regularly used for maintenance immunosuppression. In approximately 85% of *de novo* kidney transplant patients, induction involves the use of a four-drug (quadruple) combination, which includes one to six doses of an antibody preparation (antibody induction) in addition to the triple combination.[2]

During the early post-transplant period, the patient's regimen of these immunosuppressants is carefully and frequently monitored, which may include measuring drug trough (predose) concentrations in blood[3] and may be adjusted to minimize the development of adverse reactions while keeping the immune system from rejecting the kidney. The immunosuppressive regimen is adjusted according to the patient's individual course, including the occurrence of rejection episodes (signifying increased risk for rejection), and according to adverse events (signifying poor tolerance of the regimen). The goal is to customize the regimen to find the optimum balance between the efficacy and toxicity of the immunosuppressive regimen.

Kidney transplant recipients reach this optimum balance generally around 3 to 6 months (although sometimes it takes years) after kidney transplant. When patients have achieved this balance, they are no longer considered *de novo* patients and are considered maintenance patients. These maintenance patients are on a regimen that is both tolerated by their bodies and keeps their immune system from rejecting the organ. Maintenance patients are different from *de novo* transplant recipients, and thus are treated differently. For example, maintenance patients:

- Have lower risk of rejection episodes.
- No longer require treatment with induction antibodies or high dose corticosteroids (unless needed to treat an episode of a high-grade rejection). Are not receiving induction-level immunosuppression, meaning that (among other things) they are receiving lower doses of CNI and a zero to low dose of corticosteroids, and that the long-lasting immunosuppressive effects of the induction treatment received at the time of transplant are starting to disappear.

[2] Scientific Registry of Transplant Recipients, available on the Internet at http://srtr.org/annual_Reports/2011/506d_ki.aspx and http://srtr.org/annual_reports/2011/506a_ki.aspx.

[3] Calcineurin inhibitors, including tacrolimus, are considered narrow therapeutic index (NTI) drugs. See FDA's Bioequivalence Recommendations for Specific Products and draft guidances on Tacrolimus (recognizing that tacrolimus is an NTI drug based on certain evidence). FDA updates guidance documents periodically. To make sure you have the most recent version of a drug guidance or a product-specific bioequivalence study guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. The doses and resulting drug trough concentrations needed to achieve efficacy are often associated with toxicity. The goal of dosage adjustments of immunosuppressive drugs is to maintain efficacy and minimize toxicity.

- Receive an immunosuppression regimen that reflects their individual level of immunologic risk as informed by the post-transplant history or absence of rejection episodes.
- Have immunosuppressive drug dosing and targets used in therapeutic drug monitoring (TDM) of whole blood trough concentrations that are optimized for each patient.
- Have a reduced frequency of monitoring, including TDM, to maintain efficacy and minimize toxicity, compared to the early *de novo* post-transplant phase.

The term *conversion* is used to indicate that a kidney transplant patient who has been treated with a regimen of three to four immunosuppressive drugs has one of those drugs discontinued and replaced with another drug. The conversion may be initiated due to toxicity or inadequate efficacy; for example, if the patient is having very serious adverse reactions and cannot tolerate the drug, or if the patient is experiencing rejection. Alternatively, the conversion can be for other reasons, such as choice of once-daily (morning or evening) or twice-daily dosing regimens based on personal convenience or other considerations in the practice of medicine. When a patient is converted to another drug, clinical practice requires additional and/or more frequent monitoring, clinical visits, and laboratory tests (including whole blood trough concentrations), which would not be needed in maintenance patients who continue on their same regimen.

Because immunosuppression in kidney transplant patients is highly individualized and requires a delicate balance between adequate suppression to avoid rejection and adverse events inherent to immunosuppressive therapy, the clinical study design needed to demonstrate the safety and efficacy of immunosuppressants in certain populations is very specialized. Separate studies are needed to support approval in *de novo* patients and conversion patients because the populations, and their inherent risks and goals, are different.

The *de novo* patients start with intense induction regimens consisting of three to four drugs at the time of kidney transplant with the goal of achieving a customized optimum balance between efficacy and toxicity. Once an optimum balance between immunosuppressive toxicity and the risk of rejection has been established in maintenance patients, any disturbance, including a change of immunosuppression regimen (even if it is switching from the immediate release to extended release of the same active moiety), may affect this balance, resulting in organ rejection. Thus, clinical studies in *de novo* patients are designed to evaluate the efficacy and safety of the immunosuppressive regimen in providing adequate protection against rejection. These studies start at the time of transplant and patients are treated and the drug is evaluated for safety and effectiveness for a duration of 6 to 12 months.

The goal for studies conducted in conversion patients is to assess the safety and efficacy of conversion because there is a risk of an untoward outcome anytime an alteration, including a change in the immunosuppressive regimen, occurs. Patients who are at least 3 months post-transplantation can be enrolled in these conversion studies. In a clinical study for conversion, patients are randomized either to continue the maintenance regimen or to be converted to a new drug or formulation to evaluate whether conversion from one product to another (e.g., one tacrolimus formulation to another non-bioequivalent formulation) is safe and effective. Without a controlled clinical study, safety and effectiveness cannot be solely extrapolated from the

different pharmacokinetic (PK) characteristics of each product. FDA currently expects separate adequate and well-controlled clinical studies for approval of immunosuppressants in *de novo* and conversion kidney transplant patients.

B. Tacrolimus and Prograf NDA 050708

Tacrolimus is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*.[4] Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. Experimental evidence suggests that tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin inhibited. This effect may prevent the dephosphorylation and translocation of the nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (such as interleukin-2, gamma interferon). The net result is the inhibition of T-lymphocyte activation (i.e., immunosuppression). Tacrolimus prolongs the survival of the host and transplanted graft in animal transplant models of liver, kidney, heart, bone marrow, small bowel and pancreas, lung and trachea, skin, cornea, and limb. In animals, tacrolimus has been demonstrated to suppress some humoral immunity and, to a greater extent, cell-mediated reactions such as allograft rejection, delayed type hypersensitivity, collagen-induced arthritis, experimental allergic encephalomyelitis, and graft versus host disease.

The first NDA for tacrolimus was approved by FDA on April 8, 1994, under the trade name Prograf (NDA 050708). The Prograf NDA was submitted pursuant to section 505(b)(1) of the FD&C Act and is currently held by Astellas. Prograf is an IR capsule available in doses equivalent to 0.5, 1, or 5 milligram (mg) of anhydrous tacrolimus.[5] Prograf is indicated for the prophylaxis of organ rejection in patients receiving allogeneic liver, kidney, or heart transplants.[6] The recommended dosing frequency of Prograf is twice daily.[7] Prograf is also approved in an injectable dosage form (NDA 050709) that should be used only as a continuous IV infusion when the patient cannot tolerate oral administration of Prograf capsules.[8]

Tacrolimus is produced by *Streptomyces tsukubaensis* and meets the statutory definition of an *antibiotic drug*.[9] This definition turns on the nature of the drug substance rather than on the

[4] This paragraph has been excerpted from the Approved Product Labeling for Prograf (NDA 050708) (approved Sept. 4, 2013) (Approved Prograf Product Labeling) (Clinical Pharmacology and Description sections), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050708s043,050709s036lbl.pdf.

[5] Id. (Description section).

[6] Id. (Indications and Usage section). The kidney studies for Prograf were conducted in *de novo* patients as described in the Clinical Studies section.

[7] Id. (Dosage and Administration section).

[8] Id.

[9] Section 201(jj) of the FD&C Act (21 U.S.C. 321(jj)) defines *antibiotic drug* as:

> any drug . . . composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for human use containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy

indication of the drug product. Thus, even though tacrolimus was approved to prevent organ rejection rather than for antimicrobial use, it is considered an antibiotic drug.[10] Because tacrolimus is an antibiotic drug substance that was the subject of an application for marketing received by FDA before November 21, 1997 (i.e., before enactment of the Food and Drug Administration Modernization Act (FDAMA[11])), it is commonly referred to as an *Old Antibiotic*.[12] There are no patents or exclusivities listed for the Prograf NDA in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book).[13,14]

C. Astagraf XL

Astagraf XL (NDA 204096) is an oral dosage form (capsule) of tacrolimus developed as an ER formulation and intended for once-daily administration. The approved indication is for the prophylaxis of organ rejection in patients receiving a kidney transplant.[15] Astagraf XL capsules are available in doses equivalent to 0.5, 1 or 5 mg of anhydrous tacrolimus. The Astagraf XL NDA is currently held by Astellas. The Agency summarizes below the relevant history of the NDA.

1. Astagraf XL NDA 050811 and Withdrawal[16]

On December 19, 2005, Astellas submitted an NDA for Prograf XL (further developed as Advagraf and now approved as Astagraf XL) for once-daily dosing in the prophylaxis of organ rejection following kidney, liver, or heart transplantation (NDA 050811).[17] The NDA was

> micro-organisms in dilute solution (including a chemically synthesized equivalent of any such substance) or any derivative thereof.

[10] Letter from FDA to TG Mahn, JE Mauk, WS Vicente, et al. (Docket No. 2003P-0275/CP1 & PSA1) (Dec. 18, 2003) at 15, 29, and 32, available on the Internet at http://www.fda.gov/ohrms/dockets/dailys/04/apr04/042004/03p-0275-ref0001-090-Tab-39-vol6.pdf; see the proposed rule "Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs" (65 FR 3623 (Jan. 24, 2000)) (Proposed Rule on Old Antibiotics).

[11] Public Law 105-115.

[12] See, e.g., Proposed Rule on Old Antibiotics (listing tacrolimus as an *Old Antibiotic*). See also section II.C, infra, for a further discussion of antibiotics and exclusivity.

[13] See the Orange Book, available on the Internet at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Section 505(j)(7)(A) of the FD&C Act requires FDA to publish and make available to the public certain information, including a list in alphabetical order of the official and proprietary name of each drug that has been approved for safety and effectiveness under section 505(c) of the FD&C Act, the date of approval and application number, and certain patent information. FDA also makes other information, such as exclusivity codes, available in the Orange Book.

[14] FDA has approved several ANDAs referencing Prograf (NDA 050708). See the Orange Book.

[15] Approved Product Labeling for Astagraf XL (NDA 204096) (Feb. 28, 2014) (Indications and Usage section), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204096s002lbl.pdf.

[16] Initially, the proposed name for the drug product was Prograf XL and then Advagraf (not Astagraf XL), but for ease of reading, this memorandum refers to the drug product as Astagraf XL throughout.

[17] Astagraf XL Clinical Review (June 19, 2013) (Astagraf XL Clinical Review) at 12. The Agency administratively split the NDA into three separate NDAs for each indication: NDA 050811 (kidney), NDA 050815 (liver), and NDA

submitted pursuant to section 505(b)(1) of the FD&C Act. The NDA for Astagraf XL cross-referenced animal pharmacology/toxicology data in Astellas' NDA for Prograf IR capsules (NDA 050708).[18] NDA 050811 included one clinical study (Study 158) as primary confirmation of efficacy and supportive data from Phase 2 studies to support the proposed kidney indication.[19]

On January 19, 2007, FDA issued an approvable letter for NDA 050811 citing, among other things, deficiencies related to the kidney indication.[20] For example: (1) studies in *de novo* and stable kidney transplant patients did not provide sufficient data to support the safe and effective use of Astagraf XL for the prevention of graft rejection in kidney transplant patients or to conclude that the benefit of the drug outweighed its risks; and (2) studies did not demonstrate that the same daily doses of Astagraf XL and Prograf resulted in comparable tacrolimus exposures over the entire treatment period (and the clinical significance of these PK differences had not been fully characterized).[21] The Agency also advised Astellas to provide additional PK data to support use of an initial dose of Astagraf XL and to submit data from an ongoing clinical trial comparing Astagraf XL to Prograf (Study 12-03) that could provide the additional data needed to support the safety and efficacy of Astagraf XL.[22]

On September 12, 2007, Astellas submitted a complete response to the January 19, 2007, approvable letter for NDA 050811.[23] Astellas amended its NDA with results from the PK sub-study of Study 12-03,[24] as well as with some limited information on safety and efficacy in the population studied.[25]

Although this submission addressed the deficiency related to determination of an initial dose of Astagraf XL, it did not address the clinical deficiency.[26] In addition, upon reviewing data from NDA 050815 (liver indication), the Agency became concerned that gender-related differences in mortality and post-transplant diabetes mellitus between the Astagraf XL and Prograf treatment groups observed in liver transplant patients may also exist in kidney transplant patients.[27]

050816 (heart). Id. To date, Astagraf XL has not been approved for liver or heart transplant patients. Approved Product Labeling for Astagraf XL.

[18] Astagraf XL Clinical Review at 25-26. Manufacturing and controls information for Astagraf XL was incorporated into the application by reference to the Prograf NDA 050708 and the associated Type II DMF 16833. Astagraf XL Division Director Summary Review (July 19, 2013) (Astagraf XL Division Director Summary Review) at 7.

[19] Astagraf XL Division Director Summary Review at 6; Astagraf XL Cross-Discipline Team Leader Review (Astagraf XL CDTL Review) at 1 (citing Astagraf XL Clinical Review at 12-13).

[20] Astagraf XL CDTL Review at 1-2 (citing Astagraf XL Clinical Review at 12-13).

[21] Letter from DTOP to Astellas (Jan. 19, 2007) at 3.

[22] Astagraf XL CDTL Review at 2.

[23] Id.

[24] Astellas did not provide the full study report from Study 12-03 at that time.

[25] Astagraf XL CDTL Review at 2.

[26] Id.

[27] Id.

Specifically, while reviewing NDA 050815 (liver indication), FDA found that there was a substantial gender-related difference in 12-month mortality rates between the Astagraf XL and Prograf treatment groups and a gender difference in the onset of post-transplant diabetes mellitus.[28] The Agency concluded that data from a PK sub-study of Study 12-03 was insufficient to determine if the observed 20% higher AUC_{0-24} for Astagraf XL, compared with Prograf, was related to this clinically significant higher incidence of tacrolimus-related adverse events for Astagraf XL.[29] Although these adverse events were observed in the liver transplant setting, the Agency remained concerned that these adverse events could also exist in kidney transplant patients.[30] To address this deficiency in the kidney transplant context, the Agency requested that Astellas submit the full study report for Study 12-03 and study datasets that included, among other things, exposure-response analyses between safety outcomes (i.e., post-transplant diabetes mellitus, renal dysfunction, CMV and other infections, cardiac disorders, and glucose intolerance), efficacy outcomes, and C_{trough} (trough concentrations) as a function of gender and treatment group.[31] The Agency also requested that Astellas analyze by gender and treatment groups all "adverse events of special interest" for *all* existing Astagraf XL versus Prograf trials in solid organ transplantation, not just Study 12-03 or studies in kidney transplantation.[32]

On January 29, 2009, Astellas requested withdrawal of NDA 050811.[33] In a letter dated February 10, 2009, the Agency informed Astellas that if it decided to resubmit the application, the withdrawal would not prejudice any future decisions on filing.[34] The Agency also informed Astellas that it could reference information contained in the withdrawn application in any resubmission and that it should address the deficiencies identified during the Agency's review of the withdrawn application and described in the approvable letter dated March 13, 2008.[35]

2. Astagraf XL Pre-NDA/IND 64,148

Eight months after it withdrew NDA 050811, Astellas met with FDA on September 29, 2009, to discuss its development program for Astagraf XL under IND 64,148.[36] Astellas proposed that Study 158 would be the primary basis for the efficacy and safety evaluation of Astagraf XL in the kidney transplant setting and that Study 12-03 would serve as a supportive study.[37] Although

[28] Approvable letter from DTOP to Astellas (Mar. 13, 2008) at 1-2.

[29] Id.

[30] Id.

[31] Id. at 2.

[32] Id.

[33] Letter from Astellas to CDER (Jan. 29, 2009).

[34] Acknowledgement letter of NDA 050811 Withdrawal from FDA to Astellas (Feb. 10, 2009) at 1.

[35] Id.

[36] Agency preliminary responses to Astellas' briefing package dated Sep. 9, 2009, for IND 64,148 (Sept. 24, 2009) (Agency Prelim. Resp.). IND 64,148 is the same IND under which studies supporting NDA 050811 were conducted.

[37] Agency Prelim. Resp. at 1.

the Agency agreed that these studies were sufficient to support filing the NDA, it also requested data from PK Study FG-506E-12-01 (Study 12-01); and given the safety issues identified in the Astagraf XL liver transplant program, the Agency also requested a review of the liver studies (with particular attention to the different PK profiles exhibited by Astagraf XL in the liver and kidney patient populations) to augment the safety dossier of the drug in the kidney transplant setting.[38]

The Agency agreed with Astellas' proposal that the risk of mortality with the potential use of Astagraf XL for organ transplant recipients other than those in the kidney transplant setting could potentially be addressed through labeling and a Risk Evaluation and Mitigation Strategy (REMS), but emphasized that Astellas should continue to elucidate more completely the causes of the safety signals observed in the liver transplant program.[39] Given that a difference in the incidence of mortality between males and females was not observed for *de novo* kidney transplant recipients in Studies 158, 12-03, and 12-01, Astellas stated that it would provide the detailed analyses requested in the March 13, 2008, approvable letter to support the lack of clinically significant differences in the safety of Astagraf XL in male and female kidney transplant recipients.[40]

The Agency also agreed that it would review any collected data on dispensing/medication errors that resulted in serious adverse events from those jurisdictions where Astagraf XL had received approval (Europe, Canada, Japan) but also requested that Astellas provide additional information on the labeling and packaging for Astagraf XL in those jurisdictions.[41] The Agency further stated that it would have to review the adequacy of Astellas' strategies to prevent medication errors.[42] The Agency agreed that of the two possible approaches Astellas proposed for the resubmission of an NDA—(1) to cross-reference the withdrawn NDA and submit additional/updated summaries, analyses, and reports separately as an electronic common technical document (eCTD) format (Astellas' preferred approach) or (2) to submit an entire new NDA in eCTD—Astellas could adopt its preferred approach.[43] The Agency also stated that because Astellas withdrew the previous NDA, this application would be a new NDA with a new number and the review clock would be 10 months.[44]

On November 4, 2011, Astellas submitted a request to the Agency for a pre-NDA Type B meeting to discuss the submission of an NDA for Astagraf XL for the prophylaxis of organ rejection in adults (>18 years old) receiving allogeneic kidney transplants and for the prophylaxis

[38] Id.

[39] Id. at 3.

[40] Id. at 2.

[41] Id. at 3.

[42] Id.

[43] Id. at 3-4.

[44] Meeting minutes of Sept. 29, 2009, meeting between Astellas and FDA (Oct. 30, 2009) (Sept. 29, 2009, Meeting Minutes) at 7.

of organ rejection in men (>18 years old) receiving allogeneic liver transplants.[45] The pre-NDA meeting was held on January 31, 2012.

At this pre-NDA meeting, Astellas once again proposed that (1) Study 158 would be the primary basis to support the safety and efficacy of Astagraf XL in the kidney transplant setting and (2) not only Study 12-03, but also Study 12-01 (the PK study requested by the Agency at the September 29, 2009, meeting held with Astellas) and Study PMR-EC-1210 (or the OSAKA Study, which was a European post-marketing study conducted in the *de novo* setting on the EU-approved version of Astagraf XL (Advagraf)), would provide supportive evidence of efficacy.[46] Astellas chose to characterize Study 12-03 only as supportive because the Prograf regimen used in the control arm of Study 12-03 was different from the FDA-approved regimen.

At this pre-NDA meeting, the Agency generally agreed with Astellas' proposal to submit a new NDA.[47] The Agency agreed that the studies, including Study 158, could be submitted to support the filing of an NDA for an indication in *de novo* kidney transplant patients but declined to characterize Study 158 as the sole primary study.[48] Although Astellas characterized Study 12-03 as only a supportive study, the Agency declined to characterize it as such because the study was requested in the January 19, 2007, approvable letter and the full study reports for Study 12-03 had not been previously reviewed.[49] The Agency also requested that Astellas include a complete non-inferiority (NI) margin justification for both Study 158 and Study 12-03 and submit final reports for Studies 02-0-131, FG 506E-12-02, and FG 506E-KT01 in conversion kidney patients, including not only the results of the PK analyses, but also the 12-month results for the biopsy-proven acute rejection (BPAR) endpoint (including deaths, graft losses, and losses to follow-up imputed as failures).[50] Astellas agreed to these requests.[51]

To meet the requirements for pre-clinical information, Astellas proposed to cross-reference non-clinical data from its previously submitted NDAs for Prograf (NDAs 050708 Prograf capsules [S-008; S-021; S-022] and 050709 Prograf injection [S-006; S-013; S-016]), as well as an Astagraf XL-specific nonclinical pharmacology study (Study CCR980201) to support the NDA.[52]

3. Astagraf XL NDA 204096

[45] Meeting minutes of Jan. 31, 2012, meeting between Astellas and FDA (Feb. 28, 2012) (Jan. 31, 2012, Meeting Minutes).

[46] Id. at 6.

[47] Id. at 4.

[48] Id. at 7.

[49] Id.

[50] Id.

[51] Id.

[52] Id. at 5.

On September 21, 2012, Astellas submitted a new NDA for Astagraf XL (NDA 204096). The proposed indication was prophylaxis of organ rejection in adult patients receiving kidney transplants.[53]

On July 19, 2013, FDA approved Astagraf XL based on two Phase 3 controlled clinical trials (Studies 158 and 12-03), both of which demonstrated that Astagraf XL was non-inferior to Prograf on the endpoint of BPAR, when used with MMF and corticosteroids, in a regimen with or without basiliximab induction respectively.[54] Both studies were conducted in *de novo* kidney transplant patients. Consistent with FDA's practice of approving organ-based indications for transplant drug products, the Indications and Usage section of the approved labeling states, in part:

> ASTAGRAF XL is indicated for the prophylaxis of organ rejection in patients receiving a kidney transplant. It is recommended that ASTAGRAF XL be used concomitantly with mycophenolate mofetil (MMF) and corticosteroids, with or without basiliximab induction . . . . Therapeutic drug monitoring is recommended for all patients receiving ASTAGRAF XL . . . .

The clinical studies conducted by Astellas that were the basis for exclusivity were in *de novo* kidney transplant patients rather than in conversion patients.[55] The Astagraf XL Clinical Review described FDA's understanding that Astellas was seeking approval for Astagraf XL for the prophylaxis of organ rejection in patients receiving *de novo* kidney transplants.[56] The Astagraf XL Clinical Review indicates that in 2012, Astellas was not seeking a specific conversion indication,[57] but was requesting that certain information on Phase 2 PK conversion studies in kidney transplant patients be included in the labeling. The review states that the PK data from the conversion studies would be reviewed in the FDA clinical pharmacology review.[58] The review further stated that "these studies do not represent adequate well-controlled studies capable of providing substantial evidence of efficacy and safety of a potential 'conversion' indication."[59]

The PK section of the currently approved labeling includes only limited descriptive PK information from FG 506E-12-02 (a PK study in conversion kidney transplant patients) in the

[53] NDA 204096 was submitted with the proposed trade name Advagraf. Before approval, the trade name was changed to Astagraf XL.

[54] Astagraf XL Division Director Review at 4. Basiliximab is an antibody used in induction for kidney transplant patients.

[55] Astagraf XL Clinical Review at 32.

[56] Id. at 32. Section 5, entitled Sources of Clinical Data, includes the following sentence: "The Applicant is seeking approval for tacrolimus XL for prophylaxis of organ rejection in patients receiving *de novo* kidney transplants." (italics added). Studies 158 and 12-03 are also described in section 5.

[57] Id. at 39.

[58] Id.

[59] Id. (italics omitted).

last row of Table 6.[60] This information was not intended to and does not imply approval of Astagraf XL for the conversion use. The text of the Clinical Studies and Dosing and Administration sections of the Astagraf XL labeling not only is silent on the conversion use but also is specific to *de novo* use in kidney transplant patients.

When Astagraf XL was approved, FDA determined that the NDA should receive 3-year exclusivity because Astellas conducted new clinical investigations essential to approval (Studies 158 and 12-03). This exclusivity covers the once-daily, ER dosage form for the prophylaxis of organ rejection for use in *de novo* kidney transplant patients and is reflected in the Orange Book with the exclusivity code *NDF* or *new dosage form*. The exclusivity expires on July 19, 2016.[61]

D. Envarsus XR

Envarsus XR is an ER tablet formulation of tacrolimus in doses equivalent to 0.75, 1, or 4 mg of anhydrous tacrolimus. Envarsus XR is intended to be dosed once-daily, and the proposed labeling from Veloxis states that it is indicated for the prophylaxis of organ rejection in kidney transplant patients in combination with other immunosuppressants.

1. Envarsus XR NDA 206406

On December 28, 2013, Veloxis submitted NDA 206406 for Envarsus XR pursuant to section 505(b)(2) of the FD&C Act. The Envarsus XR NDA relies on the listed drug Prograf (NDA 050708), which currently is not protected by any patents or exclusivities. Specifically, Envarsus XR relies on FDA's findings of safety and/or effectiveness for Prograf with respect to nonclinical and certain clinical pharmacology information.

To support the Envarsus XR NDA, Veloxis also submitted results from Phase 1, 2, and 3 studies, including two Phase 3 clinical studies: one study in *de novo* kidney transplant recipients (Study 3002)[62] and one study in stable kidney transplant recipients converted from Prograf to Envarsus XR (≥3 months to 5 years post-transplant) (Study 3001).[63] For both studies, the primary endpoint was the rate of treatment (efficacy) failure, defined as BPAR, graft loss, death, or loss to follow-up by the 12-month post-transplant visit.[64]

The study in the *de novo* population compared Envarsus XR (starting dose of 0.17 mg/kg/day given once daily) to Prograf, (starting dose of 0.1 mg/kg/day given twice daily) with subsequent

[60] Approved Product Labeling for Astagraf XL (Pharmacokinetics section, Table 6, Pharmacokinetic Parameters of Astagraf XL Once Daily in Healthy Subjects and in Kidney Transplant Patients (Under Fasted Conditions) and Statistical Comparison of PK Parameters with Prograf Twice Daily (Table 6)).

[61] See the Orange Book.

[62] We note that Veloxis submitted a June 18, 2010, request for a Special Protocol Assessment for Study 3002. FDA reviewed the protocol and, based on the information submitted, agreed that the design and planned analysis of the study adequately addressed the objective to support a regulatory submission. See Letter from DTOP to R Guido (Aug. 5, 2010) (Special Protocol Agreement); see also FDA's guidance for industry, *Special Protocol Assessment* (May 2002).

[63] Envarsus XR Clinical Review (Sept. 25, 2014) (Envarsus XR Clinical Review) at 8.

[64] Id. at 60.

dosage adjustments based on the attainment of the protocol-specified target tacrolimus trough concentration ranges of 6-11 ng/mL in the first 30 days and 4-11 ng/mL thereafter. Because the trough concentrations in *de novo* patients taking Envarsus XR were higher than observed in *de novo* patients taking IR tacrolimus during the first 2 weeks and higher than the protocol specified target range during the first week post-transplant, the Agency questioned whether the 0.17 mg/kg/day starting dose of Envarsus XR used by Veloxis in Study 3002 would be safe and effective.[65] A Phase 2 PK study (Study 2017) provided support for a lower 0.14 mg/kg/day starting dose for Envarsus XR in *de novo* patients, which is currently in the proposed labeling.[66] Separately, in Study 3001, Envarsus XR was studied for converting patients who had previously been stable on Prograf. In the conversion study, stable kidney transplant patients receiving stable doses of Prograf twice daily and having tacrolimus trough concentrations within 4-15 ng/mL at the end of the 7-day run-in period were randomized (1:1) at baseline either to continue treatment with Prograf twice daily at the current dose or to switch to Envarsus XR once daily. Study 3001 and Study 2011, a PK study in stable kidney transplant patients, provided support for a recommended Prograf-to-Envarsus XR daily dose conversion ratio of 1:0.8.[67]

In Study 3002, Envarsus XR was shown to be non-inferior to Prograf in *de novo* kidney transplant patients, and the outcome met the pre-defined non-inferiority margin. In Study 3001, comparable efficacy was shown between the Prograf and Envarsus XR arms in conversion patients. Overall, the reviewers concluded that the benefits of Envarsus XR outweighed its risk in the prophylaxis of organ rejection in kidney transplant recipients, and that Envarsus XR represented a safe and effective treatment option for the prophylaxis of organ rejection in kidney transplant patients in *de novo* and conversion settings.[68] The Indications and Usage section of the proposed labeling currently states that Envarsus XR is indicated for the prophylaxis of organ rejection in kidney transplant patients in combination with other immunosuppressants. The Clinical Studies and Dosage and Administration sections of the proposed labeling include information for the safe and effective use for the prophylaxis of organ rejection in *de novo* and conversion kidney transplant patients.

[65] Budde, K, S Bunnapradist, JM Grinyo, et al., Dec. 2014, Novel Once-Daily ER Tacrolimus (LCPT) Versus Twice-Daily Tacrolimus in *De Novo* Kidney Transplants: One-Year Results of Phase III, Double-Blind, Randomized Trial, Am J Transplant, 14(12):2796-2806.

[66] Veloxis initially submitted its IND results from a Phase 2 PK study conducted in stable kidney transplant patients (Study 2011). FDA, however, requested information in *de novo* transplant patients (End-of-Phase 2 meeting (May 20, 2008)). A protocol for Study 2017 was then submitted on August 13, 2008. One of the key issues identified during the review of the application was that the starting dose of 0.17 mg/kg/day used in Study 3002 resulted in patients having levels above the target trough concentrations (up to 52 ng/mL for the first 2 weeks post-transplantation), whereas in Study 2017, the starting dose of 0.14 mg/kg/day was not associated with trough concentrations significantly outside the target range.

[67] In Study 2011, the steady state AUC-C_{trough} correlation lines of Envarsus XR and Prograf were found to be superimposable (i.e., the slopes of the lines were comparable and the data points comprising each line overlapped substantially), and the AUC-C_{trough} correlation coefficients ($r \geq 0.79$) were found to be satisfactory. These observations suggested that targeting the same tacrolimus trough concentration range as Prograf would be appropriate for stable kidney transplant patients who had switched from Prograf to Envarsus XR at a daily dose conversion ratio of 1:0.8. Envarsus XR Clinical Review at 41.

[68] Id. at 9-10.

On October 30, 2014, FDA concluded that NDA 206406 for Envarsus XR was safe and effective for the prophylaxis of organ rejection in both *de novo* and conversion kidney transplant patients and issued a tentative approval for use in both of these settings. The Envarsus XR NDA would have been fully approved at that time but for a determination that the approval was blocked by the exclusivity of Astagraf XL, as described more fully below.

2. Veloxis' Request for Orphan Designation

On July 16, 2013, Veloxis requested orphan designation for tacrolimus for "prophylaxis of organ rejection in patients receiving allogeneic kidney transplant" based on a "plausible hypothesis" that its product in development (then referred to as LCP-tacro and later known as Envarsus XR) was clinically superior to Prograf. [69] Orphan designation was granted on December 20, 2013.[70] Astagraf XL had not been approved when the request for designation was made; neither the request for designation nor the reviews of that request considered whether Envarsus XR had a plausible hypothesis of clinical superiority to Astagraf XL.[71]

E. Summary of Communications between FDA, Veloxis & Astellas Regarding the Scope of Astagraf XL's Exclusivity and of FDA's Initial Consideration of the Scope of Exclusivity

As noted above in section I.C., FDA determined that the NDA for Astagraf XL was eligible for 3-year exclusivity because Astellas conducted new clinical investigations essential to approval of the NDA. The Orange Book lists the exclusivity code as *NDF*, and the exclusivity expires on July 19, 2016.

On September 12, 2014, Astellas submitted a letter to FDA requesting that the Agency clarify the scope of Astagraf XL's exclusivity.[72] As stated in the letter, Astellas believes that Astagraf XL's "conditions of approval protected by [section 505(c)(3)(E)(iii) of the FD&C Act] encompass the once[-]daily formulation of tacrolimus indicated for the prophylaxis of organ rejection in transplant recipients regardless of patient setting, and no application for those conditions can be approved until expiration of the exclusivity period on July 19, 2016."[73] The letter also conveyed Astellas' belief, based on public information, that the Envarsus XR NDA covers the same active ingredient and dosing frequency and asked whether another once-daily tacrolimus product (e.g., Envarsus) can be approved by FDA during the period of Astellas' exclusivity.

[69] Letter from R Guido to G Rao re: Request for Designation of an Orphan Drug (July 16, 2013).

[70] Letter from G Rao to R Guido re: Designation Request # 13-4071 (Dec. 20, 2013).

[71] A sponsor who seeks orphan-drug designation for a drug that is the same drug (same active moiety) as a previously approved drug for the same rare disease or condition as that previously approved drug must submit a plausible hypothesis that it is clinically superior to the previously approved drug (21 CFR 316.20(a)). If FDA agrees that the hypothesis is plausible and that the drug otherwise meets all the applicable statutory and regulatory requirements for designation, the Agency will grant the request for designation.

[72] Letter from Astellas to DTOP (Sept. 12, 2014) (indicating that in August 2014 there was a conversation between a representative from FDA and a representative from Astellas, during which the company first posed the issue).

[73] Id. at 2.

On October 17, 2014, the CDER Exclusivity Board issued a letter to Astellas seeking additional information regarding exclusivity for Astagraf XL.[74] On October 27, 2014, Astellas' outside counsel submitted a letter asserting that the Agency had properly determined that Astagraf XL was eligible for 3-year exclusivity under section 505(c)(3)(E)(iii) and 505(v) of the FD&C Act.[75]

After receiving Astellas' letter, on October 27, 2014, FDA sent an Information Request to Veloxis, requesting the company's position on whether approval of the Envarsus XR 505(b)(2) NDA would be affected by Astagraf XL's exclusivity.[76] On October 29, 2014, Veloxis responded by submitting a letter to the Envarsus XR NDA stating that Astagraf XL's "exclusivity does not affect the type of action letter FDA can issue for Envarsus XR, which has a different dosage form and different proposed conditions of use."[77] Further, Veloxis claimed that the "Envarsus XR development program did not rely upon any of the studies Astellas performed which were essential to the approval of Astagraf XL."[78]

FDA considered Veloxis' reply in determining whether the Envarsus XR NDA was blocked by Astagraf XL's exclusivity. FDA concluded that the exclusivity for Astagraf XL covers its ER dosage form and its once-daily dosing regimen, both of which were changes from the previously approved tacrolimus drug, Prograf, and were supported by new clinical investigations essential to the approval of Astagraf XL. Because Envarsus XR is also an ER dosage form of tacrolimus with a once-daily dosing regimen, FDA determined at that time that Envarsus XR shares Astagraf XL's exclusivity-protected conditions of approval.

On October 30, 2014, FDA issued a tentative approval letter to Veloxis for Envarsus XR, stating that, "[a]s noted in the . . . Orange Book . . ., the listed drug product Astagraf XL (NDA 204096), with which you share conditions of approval for which new clinical studies were essential, is subject to a period of exclusivity protection under section 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the Act. Therefore, final approval of your application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until that product's exclusivity period has expired."[79]

Counsel for Veloxis contacted the Office of the Chief Counsel (OCC) on October 31, 2014, requesting a meeting with FDA and asking FDA to retract its tentative approval and to issue a letter approving the Envarsus XR NDA. On November 6, 2014, representatives of Veloxis met with representatives of FDA, including representatives from DTOP, OAP, OCP, ORP, and OCC. At this meeting, Veloxis explained that it believed FDA had issued the tentative approval letter for Envarsus XR in error because the "[c]onditions of approval of Envarsus XR do not overlap

[74] Letter from CDER Exclusivity Board to Astellas (Oct. 17, 2014).

[75] Letter from Covington & Burling to CDER Exclusivity Board (Oct. 27, 2014).

[76] Letter from DTOP to Veloxis (Oct. 27, 2014).

[77] Letter from Veloxis to DTOP (Oct. 29, 2014) at 1.

[78] Id. at 1-2.

[79] Letter from DTOP to Veloxis (Oct. 30, 2014) at 1-2.

with Astagraf XL."[80] Specifically, Veloxis claimed that Envarsus XR differs from Astagraf XL in, among other things, its dosage form, dosing regimen, strengths, and PK profile. Veloxis identified examples of past drug approval actions that it believed support approval of Envarsus XR, notwithstanding Astagraf XL's exclusivity. Veloxis also brought to the meeting a kidney transplant physician, Dr. Roy Bloom, who discussed the anecdotal benefits he observed using Envarsus XR, particularly in African-American patients whom he characterized as "rapid metabolizers" of tacrolimus.[81] Further, Veloxis reiterated that Envarsus XR's development program did not rely on the Astagraf XL NDA.

On November 10, 2014, FDA issued a General Advice/Information Request letter to Veloxis, explaining that at the November 6 meeting, Veloxis had presented new information for the Agency to evaluate and had asked FDA to reconsider its decision to tentatively approve the Envarsus XR NDA.[82] FDA requested that this new information be submitted as an amendment to the Envarsus XR NDA, identified as a "Request For Final Approval." Veloxis submitted the "Request For Final Approval" on November 14, 2014.[83] This submission contained an 18-page letter with six exhibits detailing Veloxis' position that FDA should immediately approve the NDA. The submission also included declarations from Dr. Bloom and a representative of the National Kidney Foundation.[84]

On December 2, 2014, Veloxis submitted an amendment to its "Request For Final Approval."[85] In this letter, Veloxis asserted for the first time that Astagraf XL was ineligible to receive 3-year exclusivity under section 505(v) of the FD&C Act because Astagraf XL (NDA 050811) was the subject of a pending application prior to October 8, 2008, the date of enactment of the QI Program Supplemental Funding Act of 2008 (QI Act),[86] and was therefore specifically excluded from eligibility for 3-year exclusivity under the timing provisions of the QI Act.[87] Veloxis claimed that Astellas performed no new studies in support of its application between the time of withdrawal and submission of the Astagraf XL NDA in 2012. According to Veloxis, its NDA for Envarsus XR could not be blocked by Astagraf XL's exclusivity because Astagraf XL was not entitled to any exclusivity under this QI Act limitation. Veloxis again urged FDA to immediately approve the Envarsus XR NDA.

[80] Veloxis subsequently submitted the meeting slides as part of a submission to its NDA. Veloxis Submission (Nov. 14, 2014) (Veloxis Submission) (Exhibit 4 at slide 4).

[81] Veloxis also submitted a declaration by Dr. Bloom. Veloxis Submission (Exhibit 2).

[82] Letter from DTOP to Veloxis (Nov. 10, 2014).

[83] Veloxis Submission.

[84] Id. (Exhibit 1).

[85] Letter from Veloxis to DTOP (Dec. 2, 2014).

[86] QI Program Supplemental Funding Act of 2008, Public Law 110-379, section 4, entitled "Incentives for the Development of, and Access to, Certain Antibiotics."

[87] Letter from Veloxis to DTOP (Dec. 2, 2014) at 1.

After meeting with Veloxis on November 6, 2014, and receiving its subsequent submissions, FDA had numerous internal meetings. On December 2, 2014, Agency representatives met with Astellas regarding the scope of exclusivity for Astagraf XL.

While reviewing the issues raised by Veloxis and Astellas, FDA preliminarily determined that the new clinical investigations essential to Astagraf XL's approval demonstrated the safety and effectiveness of the drug only in *de novo* patients but not in conversion patients and that, therefore, Envarsus XR's approval for conversion use would not be blocked by Astagraf XL's exclusivity. To that end, FDA held a teleconference with Veloxis on December 5, 2014, in which FDA suggested that Veloxis seek approval only for conversion of patients who are stable on IR tacrolimus to Envarsus XR, subject to submission and approval of revised labeling for Envarsus XR. In response to Veloxis' questions, FDA discussed potential revised labeling for Envarsus XR that would omit the information regarding use of Envarsus XR in *de novo* patients while permitting approval for the conversion use.

On December 8, 2014, Veloxis sent a letter to FDA declining to pursue the proposed option discussed on December 5, 2014.[88] In its letter, Veloxis reiterated its position that FDA should immediately approve Envarsus XR for all of the uses reflected in the labeling previously submitted in the Envarsus XR NDA. With the December 8, 2014 submission, Veloxis also submitted a declaration from Dr. Anthony Langone regarding the Envarsus XR NDA. Veloxis later submitted a letter on December 12, 2014, containing an additional exclusivity precedent for the Agency's consideration.[89]

On December 12, 2014, FDA sent a letter to Veloxis indicating that although FDA had initially estimated that it could respond during the week of December 8, the Agency had not had adequate time to fully consider the entire record and all of Veloxis' submissions.[90] The Agency's letter detailed the activity that had taken place since Veloxis' initial request on October 31, 2014, and indicated that due to the complexity of the issues involved, the Agency was not issuing a final decision at the time and intended to respond no later than January 12, 2015.

Veloxis' counsel requested a call with OCC on December 14, 2014. During that call, Veloxis' counsel requested immediate final approval by December 23, 2014. On December 15, 2014, OCC responded by letter conveying that the Agency could not commit to the time frame requested by Veloxis and referred to FDA's December 12, 2014, letter for additional explanation.

On December 16, 2014, Veloxis sent a letter to the Agency stating the company's intent of pursuing "court intervention" to require FDA to "grant final approval to the Envarsus XR NDA."[91] Veloxis filed a complaint in the U.S. District Court for the District of Columbia on the same day. On December 17, 2014, FDA moved to stay the proceedings pending final Agency action. The Court granted FDA's motion to stay on December 18, 2014.

[88] Letter from Veloxis to DTOP (Dec. 8, 2014).

[89] Letter from Veloxis to DTOP (Dec. 12, 2014).

[90] Letter from DTOP to Veloxis (Dec. 12, 2014).

[91] Letter from Veloxis to DTOP (Dec. 16, 2014).

II. STATUTORY AND REGULATORY BACKGROUND

A. Drug Approval Pathways Under the FD&C Act

Section 505 of the FD&C Act establishes approval pathways for three categories of drug applications: (1) 505(b)(1) NDAs, (2) 505(b)(2) NDAs, and (3) abbreviated new drug applications (ANDAs).

1. 505(b)(1) NDAs: Stand-Alone Approval Pathway

Section 505(b)(1) of the FD&C Act requires that an application contain, among other things, "full reports of investigations" to show that the drug for which the applicant is seeking approval is safe and effective.[92] NDAs that are supported entirely by investigations either conducted by the applicant or to which the applicant has a right of reference are referred to as *505(b)(1) NDAs* or *stand-alone NDAs*.

A 505(b)(1) NDA must also include:

- a full list of the articles used as components of such drug;
- a full statement of the composition of such drug;
- a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug;
- samples of the drug as necessary;
- proposed labeling for the drug; and
- pediatric assessments.[93]

FDA will approve a 505(b)(1) NDA if it finds the information and data provided by the applicant demonstrate that the drug product is safe and effective for the conditions prescribed, recommended, or suggested in the proposed labeling.[94]

2. 505(b)(2) NDAs and ANDAs: Abbreviated Pathways

The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments)[95] created section 505(b)(2) and 505(j) of the FD&C Act. These provisions established abbreviated pathways for 505(b)(2) NDAs and ANDAs, respectively.[96] The Hatch-

[92] See section 505(b)(1)(A) of the FD&C Act.

[93] See section 505(b)(1) of the FD&C Act.

[94] See, e.g., section 505(b)(1), 505(c) and 505(d) of the FD&C Act and 21 CFR part 314.

[95] Public Law 98-417.

[96] Section 505(j) of the FD&C Act generally requires that an applicant for an ANDA demonstrate that its product is bioequivalent to the listed drug it references (RLD) and is the same as the RLD with respect to active ingredient(s),

Waxman Amendments reflected Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure" with new incentives for drug development in the form of marketing exclusivity and patent term extensions.[97] These pathways permit sponsors to rely on what is already known about the previously approved drug, which allows for a speedier market entry than would be possible under the 505(b)(1) pathway and leads to increased competition.[98]

Like a stand-alone NDA, a 505(b)(2) NDA is submitted under section 505(b)(1) of the FD&C Act and approved under section 505(c) of the FD&C Act and must meet the "full reports" requirement in 505(b)(1)(A). Unlike a stand-alone NDA, in a 505(b)(2) NDA some or all of the safety and/or effectiveness information relied upon for approval comes from investigations not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use.[99] Thus, the difference between a 505(b)(2) NDA and a stand-alone NDA is the source of the information relied on for approval. Whereas a stand-alone NDA is supported entirely by studies that the sponsor owns or to which it has a right of reference, the 505(b)(2) applicant may conduct its own studies; rely on published reports of studies to which the applicant has no right of reference; rely on Agency findings of safety and/or effectiveness for a previously approved drug, i.e., a listed drug; or use a combination of these sources to support approval.[100] When the sponsor of a 505(b)(2) NDA chooses to rely on a listed drug, the 505(b)(2) pathway allows the sponsor to streamline drug development by relying on the Agency's finding of safety and effectiveness for the listed drug to the extent it is applicable and only requiring a sponsor to conduct the studies necessary to support any differences between the drug proposed for approval and the listed drug relied on.

Consistent with Congress' goal to advance both competition and innovation, the Hatch-Waxman Amendments balance the competitive advantages that an abbreviated pathway provides by also imposing on a 505(b)(2) applicant "additional requirements with respect to patent certification, notification of such certification to the patent owner, and exclusivity."[101] These additional requirements, which are designed to recognize certain market protections for previously

dosage form, route of administration, strength, conditions of use, and, with certain exceptions, labeling. As the pending matter involves only 505(b)(1) and 505(b)(2) NDAs, it is not necessary to discuss the ANDA pathway here.

[97] See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

[98] See *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990); see also *Bristol-Meyers Squibb Co. v. Royce Laboratories, Inc.*, 69 F.3d 1130, 1132-34 (Fed. Cir. 1995).

[99] Section 505(b)(2) of the FD&C Act provides for approval of an application:

> for a drug for which the [safety and efficacy investigations] . . . relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted . . . .

[100] See FDA's Response to Sanzo, Chasnow, Lawton, et al. (Docket Nos. 2001P-0323, 2002P-0047, and 2003-0408) (Oct. 14, 2003).

[101] Proposed rule "Abbreviated New Drug Application Regulations." (54 FR 28872 (July 10, 1989)) (1989 Proposed Rule).

approved drugs, have the potential to delay approval of 505(b)(2) applications but do not apply to delay approval of stand-alone NDAs.

B. 3-Year Exclusivity

The Hatch-Waxman Amendments provide NDA holders (including 505(b)(2) NDA holders) with certain periods of limited protection from competition from certain potential competitors for the innovation represented by the NDA holders' approved products. These periods are referred to generally as *exclusivity*.

At issue here is 3-year exclusivity, which operates by delaying the date that FDA can give final, effective approval to a 505(b)(2) NDA for the conditions of approval for which exclusivity was granted.[102] Specifically, section 505(c)(3)(E)(iii) of the FD&C Act states:[103]

> If an application submitted under subsection (b) [of this section] for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) [of this section], is approved after [September 24, 1984,] and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) [of this section] for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) [of this section] if the investigations described in clause (A) of subsection (b)(1) [of this section] and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

Thus, to be eligible for 3-year exclusivity under this provision, an application must have met each of the following requirements:

- be a 505(b)(1) or a 505(b)(2) NDA (submitted under subsection (b) of this section)
- have been approved after the enactment of the Hatch-Waxman Amendments (approved after September 24, 1984)
- be for a drug that contains a previously approved active moiety (an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section)
- contain at least one new clinical study that is not a bioavailability study that is essential to approval of the application and was conducted by or for the sponsors (reports of new

[102] 1989 Proposed Rule at 28896 ("Section[] 505(j)(4)(D) and 505(c)(3)(D) of the [FD&C Act] partially protect certain listed drugs, or certain changes in listed drugs, from competition in the marketplace for specified periods . . . by delaying the effective date of approval of ANDAs and 505(b)(2) applications for those listed drug products").

[103] A parallel provision applies 3-year exclusivity to ANDAs, but it is not relevant here. See section 505(j)(5)(F)(iii) of the FD&C Act.

> clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant).

FDA's implementing regulations further interpret certain aspects of the statutory language regarding eligibility for 3-year exclusivity. They define a *clinical investigation* as "any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects."[104] They further define *new clinical investigation* to mean:

> an investigation in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product.[105]

FDA regulations also define what *essential to approval* means with regard to an investigation, i.e., "there are no other data available that could support approval of the application."[106]

After FDA determines that new clinical investigations have qualified an application for exclusivity, FDA determines the scope of that exclusivity. Section 505(c)(3)(E)(iii) of the FD&C Act provides that, if the NDA receives 3-year exclusivity, the Agency may not approve a 505(b)(2) NDA for the "conditions of approval" of such drug for a period of 3 years. The regulations similarly state that if an application submitted under section 505(b) contained new clinical investigations that were essential to approval and conducted or sponsored by the applicant, the Agency "will not make effective for a period of 3 years after the date of approval of the application a 505(b)(2) application or an [ANDA] for the conditions of approval of the original application . . . ."[107]

Although neither the statute nor the regulations defines the phrase *conditions of approval* for purposes of determining the scope of 3-year exclusivity,[108] the preamble to the 1989 Proposed Rule provides the Agency's interpretation. It makes clear FDA's view that 3-year exclusivity covers the innovative change that is supported by the new clinical investigations:

> Exclusivity provides the holder of an approved new drug application limited protection from new competition in the marketplace for the innovation represented by its approved drug product. Thus, if the innovation relates to a new active moiety or ingredient, then exclusivity protects the pioneer drug product from other competition from products containing that moiety or ingredient. If the innovation is a new dosage form or route of administration, then exclusivity protects only that aspect of the drug product, but not the active ingredients. If the

[104] 21 CFR 314.108(a).

[105] Id.

[106] Id.

[107] 21 CFR 314.108(b)(4)(iv).

[108] 21 CFR 314.108(a) and 314.108 (b)(4)(iv).

> innovation is a new use, then exclusivity protects only that labeling claim and not the active ingredients, dosage form, or route of administration.[109]

FDA thus interprets the scope of exclusivity to be related to the scope of the underlying *new clinical investigations* that were essential to the approval. Exclusivity does not extend beyond the scope of the approval and does not cover aspects of the drug product for which new clinical investigations were not essential. Courts have upheld FDA's view of the relationship between *new clinical investigations* that were essential to the approval and the scope of 3-year exclusivity.[110]

Because the relevant conditions of approval for exclusivity purposes are those changes for which the new clinical investigations were essential, under the Agency's interpretation, a 505(b)(2) NDA can differ in certain respects from the previously approved product with exclusivity and nonetheless be blocked. If the 505(b)(2) NDA shares the exclusivity-protected conditions of approval, the NDA may differ in other ways from the exclusivity-protected product and nonetheless be blocked from approval for the exclusivity-protected approval conditions.

This interpretation strikes a balance between rewarding innovation and increasing access as Congress intended. If the Agency was to take the position that any differences between two products, including differences in aspects of the product for which new clinical investigations were not essential, means that the two products do not share conditions of approval and that the second product is not blocked, the 3-year exclusivity provision governing the approval of 505(b)(2) NDAs could be rendered meaningless. Under this hypothetical interpretation, only a true duplicate version of the product would be blocked. Subsequent 505(b)(2) sponsors could make simple changes that make little therapeutic difference (including changes that could be approved in a suitability petition, such as a change from tablet to capsule supported by no more than a PK study) to avoid being blocked. In rejecting this approach, the Agency's interpretation balances the dual goals of Hatch-Waxman to encourage innovation and to make available potentially less costly alternatives by providing exclusivity for the changes for which new clinical investigations were essential, by limiting that exclusivity to those changes, and by prohibiting other sponsors from easily circumventing that exclusivity by making minor changes to their drug products. It also recognizes that Congress created a separate pathway for true duplicates (i.e., ANDAs) and ensures the provisions of section 505(c)(3)(E)(iii) would not be superfluous.

[109] 1989 Proposed Rule at 28896-97.

[110] *Zeneca Inc. v. Shalala*, No. CIV.A. WMN-99-307, 1999 WL 728104, at *12 (D. Md. Aug. 11, 1999) *aff'd*, 213 F.3d 161 (4th Cir. 2000) ("The exclusivity extends only to the 'change approved in the supplement'"); *AstraZeneca Pharm. LP v. Food & Drug Admin.*, 872 F. Supp. 2d 60, 79 (D.D.C. 2012) *aff'd*, 713 F.3d 1134 (D.C. Cir. 2013) ("[T]he Court concludes that 21 U.S.C. § 355(j)(5)(F)(iv) is ambiguous. The FDA has reasonably interpreted and applied the applicable statute . . ."). Although these cases involved the parallel statutory provision for ANDAs, rather than the provision at issue here (i.e., section 505(c)(3)(E)(iii)), the provision pertaining to ANDAs interpreted by the courts includes the same language regarding the scope of 3-year exclusivity. The courts upheld as reasonable FDA's interpretation of the relationship between the scope of clinical studies that earned exclusivity, the change in the product that resulted, and the scope of the exclusivity earned.

FDA has also determined that if two 505(b)(2) applications are both under review, and the first to be approved receives exclusivity for an innovative change, the second will be blocked from obtaining approval for that innovative change during the exclusivity period. Specifically, the preamble to the 1989 Proposed Rule states:

> The exclusivity provisions . . . delay the effective date of approval of any 505(b)(2) application that is for the conditions of use of a previously approved application that contained new clinical investigations essential for approval. Consequently, if two 505(b)(2) applications are under review at the same time and one is approved before the other, the effective date of approval of the second application to be approved will be delayed, regardless of the date of submission, if the first contained new clinical investigations essential for approval and thereby qualified for exclusivity.[111]

FDA has also indicated more generally that if an application has 3-year exclusivity for a change to a previously approved drug product, a subsequent 505(b)(2) NDA containing that same change will be subject to the 3-year exclusivity regardless of whether the 505(b)(2) NDA relies on the product with exclusivity.[112] Specifically, in the preamble to the 1989 Proposed Rule, FDA considered and endorsed a broad view of 3-year exclusivity that "covers . . . changes in non-new chemical entities rather than covering only specific drug products." Under this view, the preamble states, "a 505(b)(2) application for a drug with . . . the innovator's change . . . could not be approved until the innovator's exclusivity expired, even if the . . . 505(b)(2) relied on another approved version of the innovator's drug."[113] It further states:

> [W]hen exclusivity attaches to . . . an innovative change in an already approved drug, the . . . effective date of approval of . . . 505(b)(2) applications for a drug with that . . . innovative change will be delayed until the innovator's exclusivity has expired . . . *regardless of the specific listed drug product to which the . . . 505(b)(2) application refers*.

(emphasis added).[114]

In sum, the Agency has interpreted the scope of 3-year exclusivity to cover the "innovative change" in the drug product and to be circumscribed by the scope of the "new clinical

[111] 1989 Proposed Rule at 28901.

[112] Notably, the regulation implementing the 3-year exclusivity provisions of the statute refers to reliance only in the context of applications approved under a suitability petition under section 505(j)(2)(C) of the FD&C Act. In discussing the scope of exclusivity, the regulation states that:

> the [A]gency will not make effective for a period of 3 years after the date of approval of the application a 505(b)(2) application or an [ANDA] for the conditions of approval of the original application *or an [ANDA] submitted pursuant to 505(j)(2)(C) of the act that relies on the information supporting the conditions of approval of an original new drug application.*

(emphasis added).

[113] 1989 Proposed Rule at 28897.

[114] Id.

investigations" essential to the approval of the change. A 505(b)(2) NDA for the conditions of approval that have received 3-year exclusivity will be blocked regardless of whether the 505(b)(2) NDA relies on the drug product with 3-year exclusivity.

C. Antibiotics and Exclusivity

As noted above in section I.B, tacrolimus is produced by *Streptomyces tsukubaensis,* and meets the statutory definition of an *antibiotic* drug.[115] This definition turns on the nature of the drug substance rather than on the indication of the drug product. Thus, even though tacrolimus was approved to prevent organ rejection rather than for antimicrobial use, it is considered an antibiotic.[116] This is relevant to this exclusivity inquiry because additional considerations apply to antibiotic drugs such as tacrolimus in determining eligibility for 3-year exclusivity as discussed below.

Before enactment of the FDAMA, antibiotic drugs were approved under section 507 of the FD&C Act and non-antibiotic drugs were approved under section 505 of the FD&C Act. The exclusivity and patent listing provisions of the Hatch-Waxman Amendments (Hatch-Waxman benefits) applied only to approvals under section 505 of the FD&C Act and therefore did not apply to antibiotic drugs approved under section 507 of the FD&C Act. In 1997, FDAMA repealed section 507 of the FD&C Act and required that all applications for antibiotic drugs be submitted under section 505 of the FD&C Act.[117] FDAMA included a transition provision declaring that an application approved under section 507 of the FD&C Act before enactment of FDAMA must be considered an application submitted, filed, and approved under section 505 of the FD&C Act (transition provision).[118] Congress created an exception to this transition provision in section 125(d)(2) of FDAMA, which exempted certain applications for antibiotic drugs from those provisions of section 505 of the FD&C Act that provide Hatch-Waxman benefits.[119] Specifically, section 125(d)(2) of FDAMA exempts an application from Hatch-Waxman benefits when "the drug that is the subject of the application contains an antibiotic drug[,] and the antibiotic drug was the subject of any application" received by FDA before the enactment of FDAMA (i.e., November 21, 1997).[120]

Thus, Congress created a distinction between antibiotic drugs for which the first application was received *after* FDAMA's effective date (November 21, 1997) and those antibiotic drugs for which the first application was received *before* that date (Old Antibiotics).[121] Initially, the

[115] Section 201(jj) of the FD&C Act (21 U.S.C. 321).

[116] Letter from FDA to TG Mahn, JE Mauk, WS Vicente, et al. (Docket No. 2003P-0275/CP1 & PSA1) (Dec. 18, 2003) at 15, 29, and 32, available on the Internet at http://www.fda.gov/ohrms/dockets/dailys/04/apr04/042004/03p-0275-ref0001-090-Tab-39-vol6.pdf; see Proposed Rule on Old Antibiotics (listing tacrolimus as an Old Antibiotic).

[117] Section 125(d)(1) of FDAMA.

[118] Section 125(d)(1) of FDAMA.

[119] Section 125(d)(2) of FDAMA.

[120] Id.

[121] *ViroPharma, Inc. v. Hamburg, et al.*, 898 F. Supp. 2d 1 (D.D.C. 2012) (*ViroPharma)* at 8.

former were eligible for Hatch-Waxman benefits and the latter were not.[122] FDA determined that the FDAMA exemption from Hatch-Waxman benefits for Old Antibiotics applied to all antibiotic moieties of antibiotic drugs that were the subjects of marketing applications received by FDA before November 21, 1997.[123]

On October 8, 2008, the FD&C Act was amended again through section 4 of the QI Act. The QI Act incorporated Old Antibiotics into the Hatch-Waxman regulatory scheme and provided certain Hatch-Waxman benefits for such Old Antibiotics for the first time. Among other things, it removed FDAMA's enumerated exemptions for Old Antibiotics and created an opportunity for an Old Antibiotic application to obtain Hatch-Waxman exclusivity if that application (or supplement thereto) was submitted after the QI Act's enactment. Thus, section 505(v)(1)(A) of the FD&C Act, as amended by the QI Act, provides that:

> Notwithstanding any provision of [FDAMA] or any other provision of law, a sponsor of [an Old Antibiotic] shall be eligible for, with respect to the drug, the 3-year exclusivity period referred to under clauses (iii) and (iv) of subsection (c)(3)(E) and under clauses (iii) and (iv) of section (j)(5)(F), subject to the requirements of such clauses, as applicable.

The statute further explains that such exclusivity applies to "an application . . . submitted . . . *after* the date of the enactment of [the QI Act] in which the drug that is the subject of the application contains [an Old Antibiotic]."[124]

However, the QI Act did not make applications for Old Antibiotics submitted after the date of enactment of the QI Act eligible for exclusivity and other Hatch-Waxman benefits to the same extent as other section 505 drugs. Instead, for Old Antibiotics, such as tacrolimus, the exclusivity described in section 505(v)(1) of the FD&C Act is subject to the limitation in section 505(v)(3)(B) of the FD&C Act, 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]."

In interpreting this language, FDA concluded that, for section 505(v)(3)(B) of the FD&C Act not to be rendered superfluous, Congress must have intended to create a higher hurdle for 3-year exclusivity for Old Antibiotics than exists for non-antibiotic drugs.[125] Thus, FDA interpreted

[122] Id.

[123] Proposed Rule on Old Antibiotics.

[124] Section 505(v)(1)(B)(i) of the FD&C Act (emphasis added).

[125] See Letter from FDA to ViroPharma, Inc. (Docket No. FDA-2006-P-0007) (Apr. 9, 2012) (Vancocin CP Response). In the Vancocin CP Response, the Agency stated:

> [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]."

section 505(v)(3)(B) to permit 3-year 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."[126]

The only court to have considered the matter has upheld this FDA interpretation as reasonable.[127] The court noted that the Agency's interpretation of "conditions of use" "encompass[ed] how, to whom, and for which purposes a drug product [was] used."[128] The court further noted that, in denying exclusivity for new labeling changes for the Old Antibiotic Vancocin under section 505(v)(3) of the FD&C Act, FDA had concluded, among other things, that the labeling changes for the Old Antibiotic at issue "did not prescribe a new dosing regimen." FDA's conclusion implied that if there had been a new dosing regimen, exclusivity would have been available despite the limitation in section 505(v)(3). In the court's opinion, FDA's conclusion confirmed that the Agency's interpretation of "significant new use" was broader than just a new indication.[129] As noted above, the court upheld that interpretation as reasonable.

III. DISCUSSION

Veloxis has made multiple assertions that Astagraf XL is not eligible for 3-year exclusivity and, in the alternative, even if it was eligible, that exclusivity does not block approval of Envarsus XR for use in *de novo* and conversion patients. In determining eligibility of Astagraf XL for 3-year exclusivity and in evaluating whether Envarsus XR is within its scope and therefore blocked, FDA has considered arguments from Veloxis and Astellas, the studies conducted to support both the Astagraf XL and Envarsus XR NDAs, and relevant precedent.

The Agency first evaluated whether Astagraf XL was ineligible for 3-year exclusivity due to the limitation on timing of the NDA submission under section 505(v) of the FD&C Act. Upon concluding that the timing of Astagraf XL's submission did not preclude eligibility for exclusivity, the Agency considered another issue that was not raised by Veloxis regarding whether Astagraf XL obtained approval only for a previously approved condition of use and therefore was ineligible for exclusivity under section 505(v)(3). After determining that Astagraf

> 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 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.

(emphasis added).

See also *ViroPharma* at 13 (quoting the Agency's position that "[t]o give content to this 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").

[126] Vancocin CP Response at 70 (emphasis added).

[127] *ViroPharma* at 22.

[128] Id.

[129] Id.

XL obtained approval for a new condition of use, was eligible for 3-year exclusivity, and was not otherwise barred by any of the limitations in section 505(v)(3), the Agency determined the scope of that exclusivity.

As described more fully below, FDA has concluded that Astagraf XL has exclusivity for a once-daily, ER dosage form of tacrolimus for prophylaxis of organ rejection for use in *de novo* kidney transplant patients. That exclusivity will block approval of Envarsus XR for use in *de novo* kidney transplant patients but will not block approval of Envarsus XR for the conversion use in kidney transplant patients stabilized on IR tacrolimus (i.e., Prograf and therapeutically equivalent generics).

A. Eligibility of Astagraf XL for Exclusivity Under Section 505(v) of the FD&C Act

1. Timing of Submission of Astagraf XL NDA

Veloxis has raised several arguments concerning Astagraf XL's exclusivity under section 505(v)(1) of the FD&C Act.

First, Veloxis asserts that the Astagraf XL NDA was not eligible for exclusivity under the timing limitations of the QI Act because the NDA was pending prior to the enactment of the QI Act.[130] FDA rejects this argument. Astellas submitted the NDA for Astagraf XL (NDA 204096) on September 20, 2012—a date four years *after* the QI Act was enacted. As noted above in section II.C, section 505(v)(1)(B)(i) of the FD&C Act only permits exclusivity under section 505(v) of the FD&C Act for Old Antibiotics with applications submitted after the date of enactment of the QI Act. On its face, Astagraf XL is an application submitted after enactment of the QI Act that is eligible for exclusivity under section 505(v) based on the plain text of section 505(v)(1)(B)(i).

Second, Veloxis argues that although "a separate but related" NDA for Astagraf XL was submitted after enactment of the QI Act, this NDA had been submitted before enactment of the QI Act and should be disqualified on this basis.[131] FDA does not agree. There is no indication in the text of the QI Act that a second application submitted after enactment would be disqualified if another related application was also submitted before enactment. Congress knew how to use different terms to capture the status of an antibiotic application that had previously been submitted for review before the QI Act was enacted but chose not to use such language in section 505(v)(1)(B)(i) of the FD&C Act.[132] Instead, Congress provided that any application

[130] Letter from Veloxis to DTOP (Dec. 2, 2014) at 1-2.

[131] Id. at 2.

[132] See, e.g., section 505(v)(2) of the FD&C Act (referring to *pending* applications). Congress also explicitly distinguished between different antibiotic applications based on the timing of submission and approval when it intended to do so. See, e.g., section 125(d)(1) of FDAMA (stating that an application approved by FDA before the date of enactment for the marketing of an antibiotic drug under section 507 of the FD&C Act is "in effect on the day before the date of enactment [of FDAMA]" and "shall on and after such date of enactment[] be considered to be an application that was submitted and filed under section 505(b)"); section 125(d)(2) of FDAMA (stating that certain sections of the FD&C Act shall not apply to "any application for marketing in which the drug that is the subject of the application contains an antibiotic drug and the antibiotic drug was the subject of any application for marketing received" by FDA under section 507 of the FD&C Act before the date of the enactment.).

submitted after enactment of the QI Act is eligible for exclusivity without regard to whether a version of such an application may have been previously submitted. Given that Congress has spoken to timing and does not explicitly exclude submissions of applications that have previously been submitted and withdrawn prior to approval, FDA declines to adopt this additional limitation here. FDA's interpretation of this provision is consistent with Congress' intent to balance the need to encourage development of new antibiotic drugs with its desire to ensure access to previously approved antibiotics through approval of generic versions of such antibiotics.[133] If, instead, FDA adopted the limitation advocated by Veloxis, public health could be adversely affected by discouraging sponsors from continuing to study, analyze data, and submit an NDA for an antibiotic drug product in situations where the drug product had been the subject of a previously submitted and withdrawn NDA.

Third, Veloxis states that although the subsequent application may have been assigned a new NDA number for administrative purposes, Astellas' second NDA must be treated as a continuation of the original NDA (submitted before enactment of the QI Act) for exclusivity purposes because Astellas performed no new studies in support of its second NDA between the time of withdrawal and resubmission of its NDA.[134] Specifically, Veloxis states that Studies 158 and 12-03 were cited by FDA as the clinical trials that had provided the basis for 3-year exclusivity and that the studies were completed before Astellas withdrew the original NDA in 2009.[135]

Contrary to Veloxis' assertions, Astellas was asked to, and did, submit in the new NDA the following studies and information: complete justification for non-inferiority (NI) margins for both Studies 158 and 12-03; final reports for Studies 02-0-131, FG 506E-12-02 and FG 506E-KT01 including not only the results of the PK analyses, but also the 12-month results for the BPAR endpoint (including deaths, graft losses, and losses to follow-up imputed as failures); results from the OSAKA Study; and additional safety analyses.[136] This information had not been submitted to the previously filed and withdrawn NDA.

Finally, Veloxis notes that although the Astagraf XL NDA that FDA ultimately approved was submitted after enactment of the QI Act, the FD&C Act user fee provisions "highlight[] the relatedness and connection between a withdrawn NDA and a subsequent application submitted by the same applicant for the same product."[137] Specifically, Veloxis notes that under the FD&C Act, if a sponsor pays an application fee for an initial NDA that is withdrawn prior to approval, a subsequent application "for the same product by the same person" shall not be subject to another application fee.[138] Veloxis states that the statute treats two applications as related, "recognizing

[133] *ViroPharma* 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").

[134] Letter from Veloxis to DTOP (Dec. 2, 2014) at 2-3.

[135] Id. at 3.

[136] Meeting Minutes (Jan. 31, 2012) at 6-7.

[137] Letter from Veloxis to DTOP (Dec. 2, 2014) at 1-2.

[138] Id.

that FDA's work reviewing the first application can be applied in large measure to its review of the subsequent related application[,] and thus that a separate fee is not warranted."[139] Veloxis also speculates that Astellas did not pay a user fee for its "subsequent NDA for Astagraf XL" submitted in 2012.[140]

As a factual matter, Astellas paid a user fee for the Astagraf XL NDA submitted after the enactment of the QI Act.[141] The user fee provision, however, has no bearing on exclusivity under section 505(v) of the FD&C Act. As noted above, the relevant factors for whether Astagraf XL was eligible for exclusivity under section 505(v) of the FD&C Act are: (1) whether the drug contains an Old Antibiotic; (2) whether the drug is the subject of an application for marketing approval submitted after October 8, 2008 (the date of enactment of the QI Act); and (3) whether the drug is seeking exclusivity for a condition of use approved before the date of enactment of the QI Act. In other words, regardless of whether Astellas paid a user fee for the Astagraf XL NDA, Astagraf XL would still be eligible for 3-year exclusivity under section 505(v) of the FD&C Act.

2. Approved Conditions of Use for Astagraf XL

Because Astagraf XL is an Old Antibiotic subject to section 505(v) of the FD&C Act, the drug product's exclusivity depends on whether it falls within the limitation described in section 505(v)(3) (i.e., whether it is approved for conditions of use that had not been previously approved for that Old Antibiotic). If the conditions of use for which Astagraf XL would otherwise have received exclusivity had been previously approved for Prograf or another tacrolimus product, Astagraf XL would not be entitled to 3-year exclusivity.[142]

In its submission of October 27, 2014, Astellas asserted that the clinical studies that were essential for Astagraf XL's approval established the safety and effectiveness of its once-daily dosing regimen, which is different from Prograf's previously approved twice-daily dosing regimen.[143] According to Astellas, Astagraf XL's new dosing regimen falls outside of the limitation under section 505(v)(3)(B) such that Astagraf XL's exclusivity is for a condition of use that was not approved before enactment of the QI Act.[144]

As explained in section II.C, FDA has interpreted the conditions of use in section 505(v)(3) of the FD&C Act to require a significant new use for an Old Antibiotic, not merely a refinement in labeling related to previously approved uses. Although the Agency does not agree with Astellas that the scope of exclusivity for Astagraf XL includes once-daily dosing for all kidney transplant patients, FDA agrees that for purposes of section 505(v)(3), the clinical studies conducted by

[139] Id.

[140] Id.

[141] Prescription Drug User Fee CoverSheet (Sept. 13, 2012).

[142] Although Veloxis did not raise this issue, the Agency nevertheless considered it as part of its review of the matter.

[143] Letter from Covington & Burling to CDER Exclusivity Board (Oct. 27, 2014) at 3.

[144] Id. at 4-5.

Astellas to demonstrate the safety and effectiveness of Astagraf XL for once-daily dosing of tacrolimus in the *de novo* kidney transplant population resulted in a significant new use of tacrolimus compared to the twice-daily dosing approved for Prograf in this patient population. Because this once-daily dosing regimen is not encompassed within the previously approved twice-daily dosing regimen for Prograf and represents a change in how, by whom, and for what purposes the drug is used, FDA has concluded that this change is eligible for exclusivity.[145]

B. Scope of 3-Year Exclusivity for Astagraf XL

Because we have determined that the limitations on exclusivity for Old Antibiotic drugs established under section 505(v) of the FD&C Act do not apply to the Astagraf XL NDA, the Agency must recognize 3-year exclusivity for the Astagraf XL NDA under subsections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the FD&C Act and the implementing regulations in 21 CFR part 314.108. Specifically, Study 158 and Study 12-03 were "new clinical investigations" (other than bioavailability studies) that were "essential to the approval of the application" and "conducted or sponsored" by Astellas within the meaning of the FD&C Act and implementing regulations.[146]

At issue here is the scope of 3-year exclusivity for Astagraf XL. The scope of exclusivity under section 505(c)(3)(E)(iii) turns on the key phrase "conditions of approval." Although the FD&C Act and implementing regulations do not define "conditions of approval," as discussed above in section II.B., the Agency interprets the scope of 3-year exclusivity to cover the "innovative change" which is related to the scope of the underlying "new clinical investigations" that were essential to the approval. Accordingly, the Agency must determine the innovation for which Astellas received exclusivity. Applying this interpretation to the facts at issue, we begin with a description of the "new clinical investigations" that were essential to the approval of Astagraf XL.

The approval of the Astagraf XL NDA for the prophylaxis of organ rejection in patients receiving kidney transplants was supported by two 12-month, Phase 3, randomized studies in *de novo* kidney transplant patients that included treatment arms for both Astagraf XL and Prograf: Study 158[147] and Study 12-03.[148]

[145] The Exclusivity Board acknowledged 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 Leader Review at 18, 37. However, the Exclusivity Board observed that the once-daily dosing for Astagraf XL is a new dosing regimen. The Exclusivity Board concluded that 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 under section 505(v). See Exclusivity Board Memorandum re Astagraf XL (tacrolimus extended-release capsules) 3-year exclusivity (Jan. 8, 2015).

[146] As no party disputes that Astagraf XL is entitled to 3-year exclusivity under section 505(c)(3)(E)(iii) of the FD&C Act (see Veloxis Submission at 11), it is not necessary to include a more detailed analysis of this provision here.

[147] Astagraf XL Clinical Review at 32.

[148] Id.

Study 158 was a comparative trial comprising three arms in *de novo* kidney transplant patients, all with basiliximab (antibody) induction: Astagraf XL (0.15-0.20 mg/kg once daily) + MMF + corticosteroids; Prograf (0.075-0.10 mg/kg twice daily) + MMF + corticosteroids; and the active comparator cyclosporine Neoral (4.5 mg/kg twice daily) + MMF + corticosteroids.[149] The study was designed to demonstrate non-inferiority of Astagraf XL/MMF and of Prograf/MMF to Neoral/MMF within a 10% margin in *de novo* kidney transplant patients such that the primary efficacy comparison was between the Astagraf XL and Neoral arms and that the comparison of Astagraf XL versus Prograf served as the secondary clinical endpoint.[150] The study included a 1-year primary analysis period and a clinical continuation period of treatment for up to 60 months post-transplant. The protocol-defined primary analysis was efficacy failure rate (biopsy-confirmed (Banff grade≥1) acute rejection (BCAR), graft failure, death or lost to follow-up at 1 year).[151]

Study 12-03 was conducted as a double-blind, double-dummy study during the first 24 weeks post-transplantation in *de novo* kidney transplant patients, continuing as an open-label study until the last patient completed the 12-month visit.[152] The study compared the efficacy and safety of Astagraf XL (0.2 mg/kg once daily) and Prograf (0.1 mg/kg twice daily), both in the presence of MMF and steroids, but without basiliximab induction. The intent of the study was to demonstrate that Astagraf XL was non-inferior to Prograf with respect to the primary endpoint, i.e., event rate of patients with BPAR within the first 24-weeks following transplantation.[153]

Although different primary endpoints were used in Studies 158 and 12-03, data for efficacy failures (BPAR, death, graft loss, or loss to follow-up) were collected and analyzed by the statistical reviewer for both studies.[154] Astellas considered Study 158 to be the primary study to support the demonstration of the efficacy and safety of Astagraf XL because the study was more consistent with the U.S. standard of care and population demographics. Study 12-03 provided information on a combination of tacrolimus + MMF without the use of antibody induction (which represents 15% of the use of this combination), and thus FDA also considered Study 12-03 to be a primary study to support the efficacy and safety of Astagraf XL in the *de novo* kidney transplant population.[155]

[149] Id..

[150] Id. at 42.

[151] Id. at 32 and 42. BCAR is synonymous with BPAR.

[152] Id. at 32.

[153] Id. at 32 and 51.

[154] Id. at 36. Data from the OSAKA Study on Advagraf, the EU-approved version of Astagraf XL, was also reviewed. The OSAKA Study was a non-IND, open-label, post-marketing study, exploring three different regimens using various doses and a combination of Advagraf compared to a Prograf + MMF + corticosteroids control arm that resembled the regimen used in the Prograf arm of Study 12-03 but without antibody induction. Although one of the Advagraf treatment arms approximated that used in the Astagraf XL treatment arm of Study 12-03, the open-label design, the limitation of assessment of efficacy and safety to 24 weeks, and the multiple comparisons involved limited the utility of this study to support labeling of the efficacy and safety of an Astagraf XL regimen in the U.S. Astagraf XL Clinical Review at 40.

[155] Id. at 38.

Because Prograf capsules had been previously approved as a twice-daily, IR dosage form of tacrolimus for prophylaxis of organ rejection in *de novo* kidney transplant patients, the change in Astagraf XL for which new clinical investigations were needed was the change to a once-daily, ER version of tacrolimus for prophylaxis of organ rejection in *de novo* kidney transplant patients. Studies 158 and 12-03 were essential to the approval of Astagraf XL for this change.[156]

C. Veloxis' Assertions That Approval of the Envarsus XR NDA Is Not Blocked

Veloxis has made several assertions that 3-year exclusivity for Astagraf XL does not block approval of the Envarsus XR NDA for use in *de novo* and conversion patients. FDA disagrees with these assertions.

1. Differences Between Envarsus XR and Astagraf XL

Veloxis asserts that Envarsus XR is not blocked by Astagraf XL's exclusivity because, although it shares some conditions of approval with Astagraf XL, it does not share all of the conditions of approval of Astagraf XL. Specifically, Veloxis argues that Envarsus XR differs from Astagraf XL in dosage form (capsule versus tablet), certain strengths, dosing regimen (although it is also a once-daily, ER dosage form, it has a different starting dose, target trough level, timing for step-down target trough levels), and PK profiles, and that these differences may have clinical significance, which take Envarsus XR outside the scope of Astagraf XL's exclusivity.[157]

We disagree with Veloxis as both a legal and factual matter. The differences that Veloxis refers to are not relevant to the exclusivity analysis in this case; moreover, they have not been demonstrated to be clinically meaningful. Astagraf XL received exclusivity neither for the capsule nature of its dosage form (Prograf had been approved previously as a capsule) nor for the particular strengths for which it was approved (Prograf had been approved previously in the same strengths: 0.5, 1, and 5 mg). Astagraf XL also did not obtain exclusivity for its precise PK profile as the Agency has not yet determined, and no sponsor has yet established, the correlation between the changes in PK profile and clinically significant differences in safety and effectiveness for tacrolimus products. Instead, Astellas' innovation for Astagraf XL was the ER nature of its dosage form that permitted once-daily dosing (whereas Prograf was an IR dosage form for twice-daily dosing). The new clinical investigations essential to this innovation studied Astagraf XL for the prophylaxis of organ rejection in *de novo* kidney transplant patients. Astellas' exclusivity is circumscribed by the scope of these new clinical investigations and cannot extend beyond this condition of approval. Therefore, Astellas' new clinical investigations supported and Astagraf XL got exclusivity for establishing the safety and effectiveness of a once-daily, ER dosage form of tacrolimus for prophylaxis of organ rejection in *de novo* kidney transplant patients.

Because Envarsus XR clearly shares with Astagraf XL the exclusivity-protected conditions of approval—i.e., once-daily, ER dosage form of tacrolimus for prophylaxis of organ rejection in *de novo* patients receiving kidney transplants—Envarsus XR is blocked from approval for this use.

[156] Astagraf XL Division Director Summary Review at 10-11.

[157] Veloxis Submission at 8-11.

As noted above in section II.B, under the Agency's interpretation, a 505(b)(2) application can differ in certain ways from the previously approved product with exclusivity and nonetheless be blocked if it shares the conditions of approval for which exclusivity was granted.

Because the Agency disagrees with Veloxis' interpretation that only an application that shares every condition of approval with an exclusivity-protected drug will be blocked,[158] and because the Agency notes that Envarsus XR shares the conditions of approval for which Astagraf XL obtained exclusivity, it is irrelevant whether Envarsus XR is different from Astagraf XL in the ways that Veloxis asserts. Nonetheless, for the sake of completeness, FDA notes that it also disputes many of the assertions made by Veloxis regarding the clinical significance of differences between the two products, as discussed below.

- *PK Profiles*

Veloxis asserts that Envarsus XR and Astagraf XL have "drastically different" PK profiles and that these PK differences "may" have clinical significance, particularly for African-American patients.[159] Although FDA acknowledges that there are some differences in the PK profiles for Astagraf XL and Envarsus XR, the clinical significance of the different tacrolimus PK profiles of Envarsus XR and Astagraf XL (and Prograf) has not been established. Specifically, despite Veloxis' claims, the clinical significance of the potential differences in PK profiles of these formulations *has not been demonstrated* in African-American patients in the Phase 3 clinical trials. A clinical study evaluating the significance of a potential difference of PK profiles between Envarsus XR and IR tacrolimus in African-American patients is underway but has not yet been completed. In particular, Veloxis has initiated a study entitled "Prospective, Randomized, Open-label, Single-center, Two Sequence, Three Period Crossover Study to Compare the Steady State Pharmacokinetics of Once-Daily-Extended Release Melt Dose Tacrolimus Tablets (LCP-Tacro) to Generic Tacrolimus Capsules Twice Daily in Stable African American Renal Transplant Patients."[160] This study is still ongoing, and whether the results will support a difference in PK between Envarsus XR and IR tacrolimus that is clinically significant is still unknown and will not be determined until after a review of the complete data and analyses. This study is not designed to detect the clinical significance, if any, of differences in PK profiles between Envarsus XR and Astagraf XL.

- *Tremors*

Veloxis claims that the results of the Envarsus XR STRATO Study (Study LCP-Tacro 3003) reveal that the majority of kidney transplant patients who were experiencing tacrolimus-induced

[158] As noted above in section II.B, such a narrow interpretation would render 3-year exclusivity virtually meaningless because any change (including changes that could be approved in a suitability petition such as a change from tablet to capsule supported by no more than a PK study) would be sufficient to take a subsequent drug outside the scope of another's exclusivity.

[159] Veloxis Submission at 8-9 (Exhibit 2).

[160] See "Crossover Study to Compare PKs of Once Daily [ER] Tacrolimus Tablets to Generic Tacrolimus Capsules Twice Daily," available on the Internet at https://www.clinicaltrials.gov/ct2/show/NCT01962922?term=LCP-tacro&rank=10.

hand tremors experienced significant improvement after conversion to Envarsus XR.[161] The claim of reduction in tremors is not supported by data from adequate and well-controlled trials. The two Phase 3 studies of Envarsus XR (LCP-Tacro 3002 and LCP-Tacro 3001) compared Envarsus XR to Prograf (not Astagraf XL) and did not show a reduction in tremors in the Envarsus XR group. Additionally, the STRATO Study was a Phase 2 study and was not considered by FDA to be an adequate, well-controlled study designed to support a claim for the reduction of tremor in kidney transplant recipients who had switched to Envarsus XR from a tacrolimus IR product. In particular, the STRATO Study did not have a double-blind design that would have been needed to minimize the potential for bias, as had been recommended by the Agency.[162]

- *Dosage Forms, Strengths, and Dosing Regimens*

Veloxis argues that Envarsus XR and Astagraf XL have different dosing regimens, dosage strengths, and dosage forms.[163] Contrary to Veloxis' assertions, Envarsus XR and Astagraf XL are both once-daily, ER dosage forms of tacrolimus. As noted above, even though Astagraf XL is a capsule and Envarsus XR is a tablet, these differences are not relevant for exclusivity purposes because neither Astellas' nor Veloxis' Phase 3 clinical investigations evaluated the safety and effectiveness of the specific dosage form (i.e., the capsule property of Astagraf XL and the tablet property of Envarsus XR). Rather, the focus of the clinical investigations was the once-daily, ER aspect of the drugs for the specific population. Astagraf XL did not get exclusivity for the capsule aspect of its dosage form. Similarly, although Envarsus XR and Astagraf XL share only one common dosage strength,[164] the Phase 3 clinical investigations for both drug products did not evaluate the specific strengths for each product because dosing for tacrolimus products is individually titrated based on the patient's weight. Moreover, although the two products have different starting doses, target trough levels and timing for step-down target trough levels, Veloxis has not demonstrated that Envarsus XR and Astagraf XL dosing regimens are clinically different. Astellas obtained exclusivity for the ER dosage form that permitted once-daily dosing for Astagraf XL, a characteristic that Envarsus XR shares. If FDA were to accept Veloxis' arguments for why Envarsus XR should not be blocked by Astagraf XL's exclusivity, 3-year exclusivity would block only ANDAs approved under section 505(j) of the FD&C Act and the provisions of section 505(c)(3)(E)(iii) would then be superfluous.

2. Orphan Designation

Veloxis attempts to make much of its receipt of orphan designation for Envarsus XR.[165] To the extent Veloxis argues that this orphan designation means that the approval of Envarsus XR

[161] Letter from Veloxis to DTOP (Dec. 8, 2014) (Declaration of Dr. Anthony Langone).

[162] Letter from DTOP to Veloxis re: IND 75,250 (Oct. 18, 2011).

[163] Veloxis Submission at 9-11.

[164] Astagraf XL is available in 0.5, 1, and 5 mg strengths. Envarsus XR has 0.75, 1, and 4 mg strengths. The Agency requested that Veloxis develop different strengths from Prograf due to concerns about the potential for medication errors. Letter from DSPTP to LifeCycle Pharma re IND 75350 (Oct. 27, 2009).

[165] Veloxis Submission at9-11.

should not be blocked by the exclusivity of a previously approved drug product, this argument has no merit.

Envarsus XR's status as an orphan-designated drug has no bearing on whether, if approved, the drug product would be approved for the exclusivity-protected conditions of approval for Astagraf XL. The conditions of approval for which Astagraf XL has exclusivity are once-daily, ER dosage forms of tacrolimus for prophylaxis of organ rejection for use in *de novo* kidney transplant patients. To be blocked by 3-year exclusivity, a drug need not share all of the conditions of approval (i.e., be a duplicate).

Moreover, even if Veloxis' view that a superior product should not be blocked by exclusivity was to prevail, Veloxis' orphan designation does not establish that FDA has concluded that Envarsus XR is a superior product to Astagraf XL. FDA acknowledges that Envarsus XR was designated for an indication for which tacrolimus had previously been approved and notes that a sponsor who seeks orphan-drug designation for a drug that is otherwise the same drug (same active moiety) as a previously approved drug for the same indication as that previously approved drug must submit a "plausible hypothesis" that it is clinically superior to the previously approved drug to obtain orphan designation.[166] If FDA agrees that the hypothesis is in fact plausible and that the drug otherwise meets all the applicable statutory and regulatory requirements for designation, the Agency will grant the request for designation. However, orphan designation does not indicate that, if approved, the relevant conditions of approval of Envarsus XR will differ from those of Astagraf XL. The "plausible hypothesis" standard for orphan designation presents a relatively low threshold and is not the same standard that would need to be met for a superiority claim in labeling.[167] Specifically, although more than "a hypothetical claim of clinical superiority" is needed to receive orphan designation, clinical superiority has not been proven at this stage in the process.[168] When FDA designates a drug, such as Envarsus XR, based on a plausible hypothesis of clinical superiority over a previously approved drug, the Agency makes no determination that the drug is in fact clinically superior to the previously approved drug or whether its ultimate approval would result in a different condition of approval.

[166] 21 CFR 316.20(a) ("[A] sponsor of a drug that is otherwise the same drug as an already approved drug may seek and obtain orphan-drug designation for the subsequent drug for the same rare disease or condition if it can present a plausible hypothesis that its drug may be clinically superior to the first drug"); 21 CFR 316.25(a)(3); see 21 CFR 316.3(b)(3) and (14).

[167] See the proposed rule "Orphan Drug Regulations" (56 FR 3338, 3340 (Jan. 29, 1991)):

> FDA considered proposing a rule under which it would designate drugs apparently the same as drugs that already have orphan-drug exclusive approval only where the agency believed that there was a high probability of eventual approval. FDA decided on a liberal designation policy, however, because the agency wants to encourage research whose aim is to produce safer and more effective drugs, even if FDA believes that the prospects are dim (because of the anticipated difficulty of demonstrating clinical superiority) for eventual marketing approval.

See also Letter from L Kux to P Turner, (Docket No. FDA-2011-P-0213) (Aug. 8, 2012) (Wilate CP response) at 4 ("Though the sponsor of a subsequent orphan drug must set forth a plausible hypothesis of clinical superiority over the previously approved drug at the designation stage, such a sponsor faces a higher standard at time of approval" (footnote omitted)).

[168] Wilate CP Response at 13.

Further, in applying for orphan designation, Veloxis hypothesized that Envarsus XR would be clinically superior to Prograf, the older, IR formulation of tacrolimus that was approved at the time the orphan designation was requested, not to Astagraf XL. FDA reviewed the Veloxis designation request on this basis and agreed that there was a plausible hypothesis that Envarsus XR would be clinically superior to Prograf. FDA's decision to designate Envarsus XR as an orphan drug did not involve any comparison of Envarsus XR to Astagraf XL.

For these reasons, although Envarsus XR has orphan-drug designation for the prophylaxis of organ rejection in patients receiving an allogeneic kidney transplant, this has no impact on the analysis of whether its conditions of approval differ from those of Astagraf XL and, more specifically, of whether Envarsus XR can be approved in the face of Astagraf XL's exclusivity.

3. Lack of Reliance on Astagraf XL

Veloxis asserts that because Envarsus XR did not reference or rely on the Agency's previous findings of safety and/or effectiveness for Astagraf XL, it should not be blocked.[169] Veloxis argues that section 505(c)(3)(E)(iii) uses the term "relied upon"[170] and that therefore the plain language of the statute requires reliance on a drug with exclusivity for a subsequent 505(b)(2) NDA to be blocked by that drug's exclusivity.

The scope of 3-year exclusivity for Astagraf XL does not depend on whether Envarsus XR relies on Astagraf XL for approval. Veloxis' assertion is misplaced because the phrase "relied upon," in section 505(c)(3)(E)(iii) of the FD&C Act, does not indicate that only drugs that rely on a particular drug with exclusivity are blocked; it simply distinguishes a 505(b)(2) NDA from a stand-alone NDA (and thereby identifies 505(b)(2) NDAs as those that have the potential to be blocked under that provision). This is plain from a review of the statutory text below.

Section 505(b)(2) of the FD&C Act provides that a 505(b)(2) NDA is

> [a]n application submitted under paragraph (1) for a drug for which the *investigations described in clause (A)* of such paragraph *and relied upon by the applicant for approval of the application were not conducted by or for the applicant and* for which *the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted* . . . .

(emphasis added). In describing what applications are blocked by exclusivity, section 505(c)(3)(E)(iii) of the FD&C Act mirrors this language as follows:

> If an application submitted under subsection (b) [of this section] for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) [of this section], is approved after [September 24, 1984,] and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the

[169] Veloxis Submission at 11-14.

[170] Id. at 11.

> applicant, the Secretary may not make the approval of an application submitted under subsection (b) [of this section] for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) [of this section] if the *investigations described in clause (A)* of subsection (b)(1) [of this section] *and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.*

(emphasis added). Although Veloxis misquotes the statute to read in an element of *reliance* on the drug with exclusivity, the plain text of the statute does not include such an element.

Similarly, in FDA regulations, the use of the words "relies on" in 21 CFR 314.108(b)(4)(iv) only modifies ANDAs submitted under suitability petitions pursuant to section 505(j)(2)(C) of the FD&C Act. Neither the statute nor the regulation requires a 505(b)(2) NDA to rely on a drug with exclusivity for that 505(b)(2) NDA to be blocked. To the contrary, the operative statutory term for the scope of exclusivity is "conditions of approval"; this phrase and others in section 505(c)(3)(E)(iii) and in the sections of the regulation at 314.108(b)(4)(iv) that apply to 505(b)(2) NDAs do not refer to any such reliance.

Veloxis also refers to the structure and purpose of the Hatch-Waxman Amendments to support its argument that an application cannot be blocked by a drug with exclusivity if it did not rely on the finding of safety or effectiveness for the exclusivity-protected drug. Even assuming *arguendo* that the statute is ambiguous, the Agency's interpretation is reasonable; the Agency interprets 3-year exclusivity to protect the change supported by the new clinical investigations regardless of reliance, thereby preserving the incentive to make exclusivity-protected changes.

In fact, as noted above, FDA specifically stated in the Preamble to the 1989 Proposed Rule describing the Agency's interpretation of 3-year exclusivity that

> when exclusivity attaches to an active moiety or to an innovative change in an already approved drug, the submission or effective date of approval of ANDAs or 505(b)(2) applications for a drug with that active moiety or innovative change will be delayed until the innovator's exclusivity has expired, whether or not FDA has approved subsequent versions of the drugs entitled to exclusivity, *and regardless of the specific listed drug product to which the ANDA or 505(b)(2) application refers*.[171]

The Agency's interpretation balances the goals of the Hatch-Waxman Amendments by giving full effect to protections available for innovative changes and by preventing those protections from being undercut by a competitor's simple decision to reference a different listed drug.

Finally, Veloxis asserts that FDA has previously taken the position that a 505(b)(2) NDA is barred by another drug's marketing exclusivity only if it relies upon the subject drug. Veloxis

[171] See 1989 Proposed Rule at 28897 (emphasis added).

refers to the Parkman Letter, the 505(b)(2) guidance, and certain citizen petition responses in support of this assertion.[172] For example, in its November 14 submission, Veloxis quotes a Citizen Petition response where FDA stated: "A 505(b)(2) applicant is subject to applicable periods of marketing exclusivity *granted to the listed drug relied upon . . . .*"[173] This statement (and other similar statements in other Agency documents) is correct (a 505(b)(2) applicant is subject to exclusivity granted to the listed drug relied upon), but does not describe the entire universe of ways in which a 505(b)(2) application can be blocked.[174] These statements merely address the most common scenario that arises – where a 505(b)(2) NDA that relies, in part, on a listed drug will be subject to the exclusivity periods covering the listed drug. These documents do not address the circumstance at issue here where a 505(b)(2) NDA may be blocked regardless of whether it relies on the exclusivity-protected drug – an interpretation supported by the statutory language and clearly contemplated by the Agency's preamble statements.[175] As noted above, there is nothing in this statement that precludes the Agency from concluding that a 505(b)(2) NDA is also blocked from approval, in whole or part, by the exclusivity of a drug product that it did not rely upon.

4. The Orange Book Exclusivity Code

Veloxis also asserts that it relied, to its detriment, on the NDF exclusivity code in the Orange Book, which put applicants on notice regarding the scope of exclusivity.[176] Veloxis asserts that because the NDF exclusivity code suggests that Astagraf XL obtained exclusivity for its dosage form and because Astagraf XL's dosage form is an ER capsule and Envarsus XR is an ER tablet,

[172] Veloxis Submission at 13-14.

[173] Veloxis Submission (Exhibit 4 at slide 15) (citing Letter from J. Woodcock to D. Clissold, Docket Nos. FDA-2011-P-0869 & FDA 2013-P-0995, September 18, 2013) (Suboxone CP Response) (emphasis added by Veloxis).

[174] We note as an aside that in responding to that petition, FDA was not considering directly whether a 505(b)(2) NDA would be blocked by 3-year exclusivity for buprenorphine/naltrexone, only whether such an NDA must reference Suboxone sublingual film and certify to its patents. We further note that in answering that petition, FDA did state, "During [the 3-year exclusivity] period, the Agency will not make effective the approval of a 505(b)(2) application for the conditions of approval of the application covered by the exclusivity." Suboxone CP Response at 5.

[175] We note that Veloxis' citation to language in FDA Response to Kevin McKenna, Ph.D., Docket No FDA 2011-P-0662 (March 27, 2012), is also inapposite, since this petition dealt with patent certifications not exclusivity considerations and involved interpretation of a statutory provision that is different than the one at issue here. In contrast to the 3-year exclusivity provision at 505(c)(3)(E)(iii), which prohibits approval for the conditions of approval for which exclusivity was granted without reference to reliance on the exclusivity-protected drug, section 505(b)(2)(A) regarding patent certifications for 505(b)(2) applications specifically ties the need for certification to the listed drug relied on for approval. It states, that an application "for which the investigations described in clause (A) . . . and relied on upon by the applicant for approval of the application were not conducted by of for the applicant . . . ." shall include a patent certification "for each patent which claims the drug for which such investigations were conducted." The latter thus links the investigations relied on for approval with the patent certifications that are required. Because a 505(b)(2) NDA cannot rely for approval on investigations in another NDA without citing that NDA as a listed drug, the patent certification provision necessarily limits the patent certification obligation to a listed drug relied upon.

[176] Veloxis Submission at 8.

these two products do not share the same condition of approval and Envarsus XR should therefore not be blocked.[177]

The NDF code corresponding to "new dosage form" in this case refers to the approval of an ER dosage form.[178] It is clear that the NDF code was not intended to refer to the capsule nature of the Astagraf XL product because Prograf had been previously approved for the same indication in capsule form; therefore, the capsule aspect of the product could not have been the innovation protected by exclusivity.

In any event, FDA notes that the scope of 3-year exclusivity is not intended to be defined or circumscribed by the exclusivity code listed in the Orange Book. In fact, "[i]t has been FDA's long-standing position that the exclusivity code listed in the Orange Book does not necessarily identify, with specificity, the actual scope of exclusivity (i.e., the conditions of approval for which new clinical investigations were essential and which are therefore protected)."[179]

As discussed above, FDA determined that the new clinical investigations essential to the approval of Astagraf XL, Studies 158 and 12-03, encompassed the once-daily, ER dosage form of tacrolimus for prophylaxis of organ rejection for use in *de novo* kidney patients. Both Astagraf XL and Envarsus XR are once-daily, ER dosage forms of tacrolimus for the prophylaxis of organ rejection for use in *de novo* kidney patients.

D. Conversion Kidney Transplant Setting Is Not Within the Scope of 3-Year Exclusivity for Astagraf XL

Astellas argues that the scope of its exclusivity for Astagraf XL encompasses and prevents approval of any once-daily dosage form of tacrolimus indicated for prophylaxis of organ rejection in kidney transplant patients "regardless of patient setting."[180] However, Astellas did not obtain approval of Astagraf XL in conversion patients and thus its exclusivity cannot extend to block approval for this population.

The Astagraf XL Clinical Review indicates that Astellas was not seeking a specific conversion indication.[181] Upon review of the data, however, the Agency concluded that Astellas' studies in stable patients converted from Prograf to Astagraf XL were not adequate and well-controlled trials for the purpose of supporting approval for conversion of kidney transplant patients from an

[177] Id.

[178] The Patent and Exclusivity Terms section of the Orange Book does not have an exclusivity code that is more specific to ER dosage forms. See the Orange Book (Patent and Exclusivity Terms).

[179] FDA Response to GL Veron (Docket No. FDA-2010-P-0614) (May 25, 2011) at 22-23 (FDA determined that although the descriptor in the Orange Book stated that Colcrys' exclusivity covered "gout flares," the single clinical trial essential to the approval of Colcrys was for the treatment of acute gout flares, not prophylaxis of gout flares. and therefore acute gout flairs was the exclusivity-protected indication).

[180] Letter from Astellas to DTOP (Sept. 12, 2014) at 2.

[181] Astagraf XL Clinical Review at 39 and 41.

IR version of tacrolimus to Astagraf XL (and vice versa) in proposed labeling.[182] Not only were the studies single arm and not randomized, they were also inherently not designed to meet the standard of providing substantial evidence of safety and efficacy of conversion from Prograf to Astagraf XL (i.e., not designed to collect systematic long-term information on BPAR), and thus were not reviewed for safety and efficacy.[183]

The PK section of the currently approved labeling includes only limited descriptive PK information from Study FG 506E-12-02 in the last row of Table 6.[184] The Clinical Studies and Dosing and Administration sections of the Astagraf XL labeling are not only silent on the conversion use, but are specific to *de novo* use.[185] The PK studies conducted in the conversion population were relative bioavailability studies and they were not "new clinical investigations" essential to the approval of Astagraf XL within the meaning of the statute and regulations.

Further, it is clear that the new clinical investigations (Studies 158 and 12-03) for which Astagraf XL received exclusivity did not also demonstrate the safety and effectiveness of the Astagraf XL once-daily, ER dosage form for every use (or even just for conversion use), but rather only for *de novo* use in kidney transplant patients.[186] FDA has previously required adequate and well-

[182] Id. at 22 and 41 (stating that the issue of making recommendations for conversion of stable transplant patients from Prograf to Astagraf XL in the proposed label is moot because Studies 02-0-131, FG 506E-12-02, and FG 506E-KT01, which are single arm and non-randomized, do not represent adequate well controlled studies).

[183] Id. at 41. Although Astellas submitted some 12-month follow-up data from these short studies, FDA concluded that such data was neither readily interpretable without a randomized concurrent control group nor included a systematic collection of safety data, or episodes of allograft rejection, beyond the completion of the short period of PK sampling. In addition, FDA concluded that the range of duration from time-of-transplant to time-of-conversion rendered data on 12-month graft and patient survival even more difficult to interpret in a clinically meaningful way that could inform an individual clinician or patient on the safety or efficacy of such conversion. Id.

[184] Approved Product Labeling for Astagraf XL (PK section, Table 6). FDA also notes that the same table includes PK information in healthy subjects as well.

[185] For example:

- The *Dosage in Adult Kidney Transplant Recipients* subsection of the Dosage and Administration section, describes dosing and administration instructions with and without basiliximab induction, which is specific to *de novo* kidney transplant patients. The use of the phrase "with or without basiliximab induction" implies that Astagraf XL is indicated for use in *de novo* patients because basiliximab (Simulect) induction refers to the two doses of basiliximab administered during the first week after kidney transplantation. The use of that phrase also reflects that both studies 158 and 12-03 were essential to approval.
- The Clinical Studies section specifically states that "[t]he efficacy and safety of ASTAGRAF XL in *de novo* kidney transplantation were assessed in two randomized, multicenter, active-controlled trials [(Studies 158 and 12-03)]."

[186] Astellas recognized the limitations of the Astagraf XL once-daily, ER dosage studies in its August 2012 submission:

> In this NDA, Astellas is providing two new clinical investigations (one for the *de novo* kidney transplant indication [Study 158] and one for the *de novo* male liver transplant indication[,] and each one is essential to the approval of the application . . . [so that 3-year] exclusivity can be obtained for the *de novo* kidney and the *de novo* male liver transplant indication.

See Exclusivity Request submitted Aug. 2012 at 7-8, available on the Internet at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204096Orig1s000AdminCorres_.pdf.

controlled studies to demonstrate safety and effectiveness of other immunosuppressants for the conversion use[187] and such studies would have been needed for approval for conversion for Astagraf XL as well. Astellas did not conduct those clinical investigations that would have been necessary to support that use. Consequently, the scope of 3-year exclusivity for Astagraf XL does *not* extend to a once-daily, ER dosage form of tacrolimus for prophylaxis of organ rejection for converting kidney transplant patients who are stable on IR tacrolimus.

While reexamining these exclusivity issues at the request of Veloxis, on December 5, 2014, the Agency informed Veloxis that before the expiry of Astagraf XL's exclusivity, Envarsus XR could potentially be approved for prophylaxis of organ rejection for conversion use only in kidney transplant patients who were stable on IR tacrolimus. This is because, in contrast to the studies Astellas submitted for Astagraf XL, Veloxis submitted to the Envarsus XR NDA the results of a clinical study for conversion use, i.e., kidney transplant recipients converted from Prograf to Envarsus XR (Study 3001). This study (along with the other studies submitted in the Envarsus XR NDA) provided substantial evidence of the effectiveness and safety of Envarsus XR to support approval in the conversion population.[188] Study 3001 also provided adequate data and information to support the appropriate dosing and administration of Envarsus XR for conversion use and the other necessary aspects of the labeling.[189] The Agency determined, as a preliminary matter, that it was feasible for Veloxis to obtain approval for the once-daily, ER dosage form of tacrolimus for conversion use only during the Astagraf XL exclusivity period and that such use would not be blocked by Astagraf XL's exclusivity. In short, the Agency concluded that the conversion use is a different "condition of approval" from the *de novo* use for which Astagraf XL received exclusivity and that Astagraf XL did not conduct new clinical investigations essential to the approval of Astagraf XL for the conversion use. Therefore, FDA informed Veloxis of its preliminary determination that Envarsus XR would not be blocked for

[187] As noted above in section I.A, immunosuppressants indicated for prophylaxis of organ rejection in patients receiving kidney transplants include organ-based indications. Because *de novo* patients and conversion patients are considered two distinct populations, however, the Agency generally expects adequate and well-controlled clinical studies to support the safe and effective (and approved) use in each respective population. See, e.g., Approved Product Labeling for Myfortic (mycophenolic acid) (NDA 50791) (approved Sept. 27, 2013), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050791s019lbl.pdf. The Indications and Usage section of that label states, in part, that Myfortic is indicated for the prophylaxis of organ rejection in adult patients receiving a kidney transplant. Specifically, the conversion study (conducted in adults) was one in which renal transplant patients (ages 18-75 years), who were at least 6 months post-transplant receiving MMF (brand name, Cellcept) 2 g/day in combination with cyclosporine with or without corticosteroids for at least two weeks prior to entry in the study were randomized to Myfortic 1.44 g/day or MMF 2 g/day for 12 months. In that approved labeling, the Clinical Studies section, for example, includes conversion information.

[188] Envarsus XR Clinical Review at 8.

[189] The Tentatively Approved Product Labeling for Envarsus XR (NDA 206406) (October 30, 2014), states, in relevant part: "To convert from a tacrolimus immediate release product to ENVARSUS XR, administer an ENVARSUS XR daily dose that is 80% of the total daily dose of the tacrolimus immediate release product. Monitor tacrolimus whole blood trough concentrations and titrate ENVARSUS XR dosage to achieve target whole blood trough concentration ranges of 4 to 11 ng/mL."

this condition of approval and asked Veloxis to submit proposed labeling seeking approval only for the conversion use.[190] Veloxis declined to pursue this option.

IV. ANALYSIS OF PRECEDENT CITED BY VELOXIS

The Agency has reviewed its prior actions regarding 3-year exclusivity in light of Veloxis' arguments. The fact that Veloxis has not identified any examples where FDA tentatively approved (rather than fully approved) a 505(b)(2) NDA based on a determination that the 505(b)(2) application was blocked by 3-year exclusivity for a listed drug on which it did not rely does not establish that the Agency interprets the relevant statutory and regulatory provisions such that a 505(b)(2) NDA cannot be blocked by 3-year exclusivity for a listed drug on which it did not rely. Indeed, FDA's policy as stated in preamble statements is the opposite — that a 505(b)(2) NDA can be blocked by the exclusivity of another NDA even if there is no reliance.[191] Our review of Agency precedent provides no indication that the Agency has abandoned this explicitly stated interpretation.

Questions about the scope of 3-year exclusivity and its potential to block approval of 505(b)(2) NDAs are not presented often, which can be explained by a combination of several factors, including the rarity of the factual scenario and rational decision-making by knowledgeable industry actors. Three years is relatively short in relation to the time required to develop an NDA. It generally takes a longer time for an NDA to be developed, filed, and reviewed. Therefore, for this question to be presented, two applicants would generally have to proceed on parallel development paths for the same innovation. In addition, the later-in-time application would have to be a 505(b)(2) NDA, which would have to become ready for an approval decision during the pendency of the 3-year exclusivity period of a protected drug on which it did not rely. Moreover, for the question of reliance to arise, there must also exist another version of the exclusivity-protected drug (or a significant quantity of non-product specific published literature) such that the 505(b)(2) NDA is able to refer to the other drug as its listed drug or rely on the non-product specific published literature to fill gaps in its application, rather than relying on the exclusivity-protected drug product.

Even in the relatively rare cases where a 505(b)(2) NDA has the potential to be blocked by exclusivity for a previously approved application on which it did not rely because it seeks approval for an exclusivity-protected condition of approval, it is likely that sponsors and applicants will strategically avoid situations where FDA must determine whether their applications fall within the scope of another sponsor's exclusivity. For example, applicants may shape their NDA submissions to avoid submitting an application that may be delayed by existing exclusivity. Similarly, because (in contrast to an ANDA) a 505(b)(2) NDA is not required to be

[190] The Agency informed Veloxis of this option after extensive consideration of the issues prompted by meetings with Veloxis and Astellas, respectively, and review of Veloxis' submissions and other relevant information in the respective NDAs. The Agency considered, for example, the October 30, 2014, CDER Memorandum summarizing the Agency's conclusion that Envarsus XR was blocked by Astellas' 3-year exclusivity. At that time, however, Veloxis was seeking approval of Envarsus XR for prophylaxis of organ rejection for both conversion use and for use in *de novo* kidney transplant patients. The Agency's further consideration of the issues prompted a closer review of the nature of the studies conducted by Astellas and of the scope of 3-year exclusivity for Astagraf XL.

[191] 1989 Proposed Rule at 28872, 28897.

the same as any previously approved application in any respect, in many cases a 505(b)(2) applicant can seek approval for conditions of approval that are no longer (or never were) protected by exclusivity. For example, Veloxis had the opportunity to do that here by seeking approval only for the unprotected conversion use but chose not to do so.

Sponsors have also developed alternative business arrangements to avoid conflicts involving 3-year exclusivity issues for competing products. For example, two firms recently announced an exchange of waivers of exclusivity for their respective competing single entity extended-release hydrocodone products.[192] Zogenix's single entity extended-release hydrocodone capsule, Zohydro ER (NDA 202880), was approved first and is listed in the Orange Book as having 3-year exclusivity, which will expire on October 25, 2016.[193] Purdue's single entity extended-release hydrocodone tablet, Hysingla (NDA 206627), a 505(b)(2) NDA that did not rely on Zohydro for approval, was approved shortly after the mutual waiver agreement was announced.[194]

A search of the Agency's records has not produced another instance where FDA refused to fully approve a 505(b)(2) application due to the 3-year exclusivity of another NDA on which the subsequent application did not rely. However, in instances where the Agency has considered this situation, it has applied considerations consistent with this interpretation of the scope of 3-year exclusivity. For example, on October 24, 1996, FDA approved Combivent (NDA 020291), a metered dose aerosol for inhalation and the first fixed-combination drug of albuterol sulfate and ipratropium bromide for use in patients with chronic obstructive pulmonary disease on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator. Because its sponsor had conducted new clinical investigations essential to its approval, Combivent obtained 3-year exclusivity, which expired on October 24, 1999. The scope of Combivent's exclusivity was related to the new clinical investigations that studied the fixed-combination of albuterol sulfate and ipratropium bromide for use in patients with chronic obstructive pulmonary disease on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator.[195]

On May 27, 1999, FDA considered the approvability of Duoneb (NDA 020950), which was a solution for inhalation and also a fixed-combination of albuterol sulfate and ipratropium bromide

[192] E.g., Reuters, *Zogenix and Purdue Pharma Exchange Waivers of Regulatory Exclusivity for Extended-Release Hydrocodone Products* (Oct. 31, 2014), available at http://www.reuters.com/article/2014/10/31/idUSnGNXtRGsC+ed+GNW20141031 (last accessed on Jan. 11, 2015). The companies, Zogenix, Inc. and Purdue Pharma L.P., announced their decision the day after the PDUFA goal date for Hysingla had passed.

[193]The Orange Book, available at http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=202880&Product_No=006&table1=OB_Rx.

[194] CBS, *FDA approves new, hard-to-abuse hydrocodone painkiller* (Nov. 20, 2014), available at http://www.cbsnews.com/news/fda-approves-new-hard-to-abuse-hydrocodone-painkiller/ (last accessed onJan. 11, 2015).

[195] Combivent Exclusivity Summary and Approved Product Labeling for Combivent (NDA 020291) (approved Oct. 24, 1996); see also Combivent Division Director Review (Oct. 3, 1996).

for the same indication as Combivent. Duoneb had been submitted as a 505(b)(2) application that did not rely on Combivent.[196] FDA noted that the Duoneb applicant conducted its own clinical trials to establish the safety and effectiveness of the fixed-combination, but FDA concluded that it likely would not be able to fully approve Duoneb's 505(b)(2) NDA at that time due to Combivent's existing exclusivity, which was due to expire on October 24, 1999.[197]

Similarly, in May 2010, when considering whether Cipher's tramadol hydrochloride ER capsules (NDA 022370) were blocked by exclusivity for Labopharm's Ryzolt (tramadol hydrochloride ER tablets) (NDA 021745), FDA noted that Cipher's product had the potential to be blocked if it was "seeking the same conditions of approval as are protected for Ryzolt."[198] FDA made this observation even though Cipher's product differed in dosage form from the Labopharm product and Cipher's product did not rely on Ryzolt for approval. Although the Agency ultimately concluded that Labopharm's clinical studies were essential only to approval of the specific titration schedule approved for Ryzolt and that Cipher's product (which had a different non-protected titration schedule previously approved for another tramadol product) was not blocked, the Agency's analysis contemplated that Cipher's product would have been blocked had it sought approval for the exclusivity-protected titration schedule. FDA further noted that although Cipher's tramadol product was an ER capsule and Ryzolt was an ER tablet, "[a] difference in dosage form alone for a proposed product would not necessarily be a basis for concluding that a previous applicant's exclusivity does not delay approval."[199]

In the case of colchicine products too, FDA acknowledged that exclusivity for a drug that a 505(b)(2) NDA did not reference nonetheless had the potential to block approval of that 505(b)(2) NDA. In that case, Mutual (the sponsor for Colcrys colchicine tablets) had exclusivity for use of colchicine for acute gout flares that was due to expire on July 30, 2012. Mutual submitted a citizen petition requesting that FDA "refrain from filing or approving any . . . 505(b)(2) application for a single-ingredient oral colchicine product that does not reference Colcrys" and further requested that FDA "[r]efrain from approving any . . . 505(b)(2) application for a single-ingredient oral colchicine product until the existing 3-year exclusivity awarded to Colcrys expires on July 30, 2012."[200] FDA denied Mutual's request that "any 505(b)(2) application for a single-ingredient oral colchicine product must necessarily cite Colcrys as its listed drug, irrespective of whether the proposed product shares the same strength, pharmacokinetic (PK) profile, or other characteristics such as dosage form or conditions of

[196] Duoneb (NDA 020950) Division Director's Memorandum (May 27, 1999) at 1, Administrative Documents, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/20950_DuoNeb_admindocs.pdf .

[197] Id. at 2. FDA also concluded that outstanding significant chemistry, manufacturing and controls issues precluded approval of Duoneb's application. By the time all outstanding issues were addressed and FDA was able to approve the application for Duoneb on March 21, 2001, Combivent's exclusivity had expired. FDA reached this conclusion despite the fact that Duoneb differed from Combivent in its dosage form and dosing regimen.

[198] See Memorandum from Division of Anesthesia and Analgesia Products to Office of Generic Drugs re: Scope of Three-year Exclusivity Granted to Ryzolt (tramadol hydrochloride) extended release tablets (May 7, 2010) at 3.

[199] See id. at 6, fn. 9.

[200] FDA Response to GL Veron (Docket No. FDA-2010-P-0614) (May 25, 2011) at 1-2.

use."[201] Nonetheless, the Agency found that "the labeling for a single-ingredient colchicine product seeking approval for prophylaxis of gout flares must inform healthcare providers that the lower dose colchicine regimen evaluated in the AGREE trial is adequate to treat an acute gout flare that may occur during chronic colchicine use, and thus *the approval of such a product must await expiration of Colcry's 3-year exclusivity for acute gout flares . . . .*"[202] Thus the Agency recognized that although a 505(b)(2) NDA that was not a duplicate of Colcrys tablets need not reference Colcrys as a listed drug, it might nonetheless be subject to exclusivity for Colcrys and would have to await expiration of that exclusivity before it could obtain approval.

These examples demonstrate that, although it does not arise often, when FDA is aware of exclusivity for a product on which a 505(b)(2) NDA did not rely, FDA has continued to interpret the 3-year exclusivity provisions in a manner consistent with the interpretation set forth in the Agency's preamble statements and consistent with its position set forth here.

The Agency has carefully evaluated the precedents cited by Veloxis.[203] As discussed below, we disagree that the only plausible explanation for approval of the products cited is that FDA interprets 3-year exclusivity such that it blocks only a 505(b)(2) NDA that relies on an exclusivity-protected drug.[204]

A. Methylphenidate

One of the precedents cited by Veloxis is the Agency's approval of a 505(b)(2) NDA for Metadate CD (ER methylphenidate capsules) (NDA 021259) on April 3, 2001, during the 3-year

[201] Id. at 3.

[202] Id. (emphasis added).

[203] Although the Veloxis letter cites only methylphenidate and testosterone as precedent for approving Envarsus XR, in its Exhibit 4, which includes slides from a presentation to FDA on November 6, 2014, Veloxis identified two additional examples: somatropin recombinant injections and timolol ophthalmic solution drops as support for its argument that a subsequent 505(b)(2) application is not blocked by 3-year exclusivity in the absence of reliance. The Agency has reviewed the administrative records for the somatropin and timolol NDAs cited by Veloxis and found that in each case, approval of the later-in-time 505(b)(2) NDA could be explained by a closer examination of the scope of the clinical studies that earned exclusivity for the previously approved product. For example, the two somatropin products in the somatropin example did not share the same indication and since the new clinical studies for the first product which earned exclusivity established the safety and effectiveness of the product for the indication, the second one was not blocked. The timolol ophthalmic solution example could also be explained by a narrow scope of exclusivity (i.e., once-daily dosing) that did not block the approval of the subsequent NDA which was administered twice daily. Thus, these examples do not demonstrate that FDA interprets 3-year exclusivity such that it blocks only a 505(b)(2) NDA that relies on the exclusivity-protected NDA. Because Veloxis focuses on methylphenidate and testosterone, the remainder of this discussion likewise focuses on those products.

[204] FDA makes exclusivity decisions in the context of individual applications because such decisions are fact- and circumstance-specific. Therefore, we have closely reviewed the records of the clinical studies essential to approval that gave rise to exclusivity and the basis for approval of a subsequently-approved 505(b)(2) NDA. We have reviewed the examples that Veloxis has cited, and we have not found a stand-alone document that summarizes FDA's reasoning why the particular drugs reviewed were or were not blocked. In addition, prior to the recent establishment of the CDER Exclusivity Board, there was no formal mechanism for vetting exclusivity decisions and their implications for approval of other applications. Many of the methylphenidate and testosterone products cited by Veloxis were approved more than a decade ago and all were approved prior to the establishment of the CDER Exclusivity Board so we have drawn reasonable conclusions based on the available records.

exclusivity period of another ER methylphenidate product, Concerta (ER methylphenidate tablets) (NDA 021121), that was approved on August 1, 2000.[205] Veloxis claims that "[l]ike Envarsus XR and Astagraf XL, Concerta and Metadate CD are approved to treat the same indication and both are once-daily extended-release formulations of the same active ingredient," but "[a]lso like the current situation, Concerta and Metadate CD are approved in different dosage forms (i.e., extended-release tablets and extended-release capsules, respectively)."[206] Veloxis, thus, concludes that "[a]s a result of this critical difference, Concerta's exclusivity did not block approval of Metadate CD."[207] In addition, Veloxis asserts that this example supports its view that a later-in-time 505(b)(2) NDA is not blocked if it does not rely on the NDA with exclusivity.[208]

The administrative records for the approvals of Concerta and Metadate CD do not, however, support Veloxis' conclusions. There is no evidence that FDA decided that Metadate CD was not blocked because it was a capsule rather than a tablet or because it did not rely on Concerta. Veloxis has not cited any evidence in the administrative record for Concerta that supports the notion that the ER tablet dosage form of Concerta was a condition of approval for which clinical studies were necessary, and that the exclusivity protected Concerta only against another ER tablet. In fact, given the prior approvals of Ritalin (an IR methylphenidate tablet) and Ritalin SR (an ER methylphenidate tablet), Concerta would not have obtained exclusivity for being a methylphenidate tablet or an ER methylphenidate tablet.[209] It follows that the scope of Concerta's exclusivity was narrower than the scope of Astagraf XL's exclusivity here because Astagraf XL was the first extended-release tacrolimus product and the first with once-daily dosing. It would be reasonable to conclude that Concerta's condition of approval for which clinical investigations were essential was the specific PK profile that results from its proprietary drug release mechanism that has both specific IR and ER release components.[210]

There is no explicit contemporaneous documentation in the record for why FDA determined that the subsequent methylphenidate product, Metadate CD, was not blocked by Concerta's exclusivity. However, Metadate CD had a different PK profile that was associated with a different drug release mechanism, and a clinical study that was essential for the approval of

[205] Veloxis Submission at 15.

[206] Id.

[207] Id.

[208] Id. at 15-16.

[209] FDA first approved methylphenidate on December 5, 1955, in an IR tablet form (Ritalin NDA 010187). Ritalin SR (NDA 018029), a sustained-release form of methylphenidate, was approved on March 30, 1982. Ritalin SR was designed to exert an effect equivalent to two 10 mg tablets of IR methylphenidate given 4 hours apart.

[210] See Concerta (NDA 021121) Exclusivity Checklist ("New PK profile of formulation requires a clinical study."), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-121_Concerta_admincorres.pdf. Unlike the methylphenidate products, which have a narrow scope of exclusivity related to the particular PK profile because an ER methylphenidate had already been approved by FDA, Astagraf XL had a broader scope of exclusivity because it was the first approved NDA for an ER tacrolimus product and Astellas conducted clinical studies that were necessary for the approval of its ER dosage form and once-daily dosing regimen for use in *de novo* kidney transplant patients.

Metadate CD was designed to demonstrate the safety and efficacy of the specific PK profile for Metadate CD. Consistent with the views stated here, it is reasonable to conclude that Concerta's exclusivity extended only to the specific PK profile associated with its formulation and drug release mechanism, and thus would not block the approval of Metadate CD.

B. Testosterone

Veloxis refers to FDA's approvals of certain NDAs for testosterone transdermal products during the 3-year exclusivity period of previously approved testosterone transdermal products and speculates that the NDAs were not blocked "presumably" because the applicants did not rely on the previously approved testosterone transdermal products with exclusivity.[211] The Agency disagrees that the only reasonable explanation for these approvals is that FDA interprets 3-year exclusivity such that it blocks only a 505(b)(2) NDA that relies on the exclusivity-protected product. The Agency's review shows that it has not abandoned its interpretation that a 505(b)(2) NDA can be blocked by the exclusivity of a previously approved product regardless of reliance on that product.

As a predicate to analyzing Veloxis' arguments, it is important to summarize some background regarding the approval of testosterone products. Testosterone was first approved in 1941 in the form of methyltestosterone (NDA 003158), and generally has been indicated as a replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. Prior to February 2000, i.e., before approval of the transdermal testosterone products cited by Veloxis, testosterone had been approved for this use in the form of intramuscular injectables, oral tablets, and transdermal patches.[212] Efficacy of testosterone products has generally been established by demonstrating serum testosterone levels within the normal ranges. Testosterone products have also been associated with certain safety issues, including the risk of secondary exposure to women and children for topically applied testosterone gels.[213]

Based on FDA's review of the record, FDA has prepared a table attached as an Appendix that includes for the relevant testosterone transdermal products the following information: the trade name, NDA number, date of approval, expiration date of exclusivity, exclusivity code, active

[211] Veloxis Submission at 15-16; letter from Veloxis to DTOP (Dec. 12, 2014).

[212] AndroGel 1% Medical Review dated February 25, 2000 at 7.

[213] For example, in 2009, FDA became aware of cases of secondary exposure of women and children to topical testosterone gel products caused by inadvertent drug transfer from adult males using the products ("risk of secondary transfer"). The risk of secondary transfer associated with testosterone gel products has been reported to cause virilization in women and children, some of which is irreversible. Signs and symptoms of secondary exposure have included enlargement of the penis or clitoris, development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age. FDA addressed this risk in April 2009, by requiring safety-related labeling changes, including requiring a boxed warning cautioning about secondary exposure to testosterone, and a Medication Guide (a form of FDA-approved patient labeling) discussing these risks. In light of this information, FDA determined, in the context of ANDAs for topical testosterone gel products, that some differences in inactive ingredients, including, but not limited to, differences in penetration enhancers, trigger the need for a study to evaluate the risk of secondary transfer (or transfer potential study), as well as a hand washing study to determine whether hand washing affects the amount of residual product on the skin. See, e.g., Letter from CDER to Auxilium Pharmaceuticals, Inc. (Docket No. FDA-2009-P-0123) (Aug. 26, 2009).

ingredient, indication, dosage form, strength, application site, and summary description of the new clinical investigations essential to approval. This table provides an overview of the testosterone products cited by Veloxis to aid in understanding how these products relate to each other and the nature of the new clinical investigations that were essential to approval. Given the number of products and the extensive record for each NDA, the table is a summary only and is not intended to be comprehensive.

In its initial submission, Veloxis cites as precedent for its view the approvals of NDAs for Axiron (NDA 022504), Fortesta (NDA 021463), and AndroGel 1.62% (NDA 022309).[214] Veloxis states that FDA approved the 505(b)(2) NDA for Fortesta notwithstanding exclusivity for the Axiron 505(b)(2) NDA, and FDA approved the 505(b)(2) NDA for AndroGel 1.62% notwithstanding exclusivity for the Axiron and Fortesta 505(b)(2) NDAs. Veloxis states that FDA did so even though Axiron, Fortesta, and AndroGel 1.62% all share active ingredients and indications; and the AndroGel 1.62% 505(b)(2) NDA was approved notwithstanding exclusivity for the Fortesta 505(b)(2) NDA even though they share the same dosage form (transdermal gel). Veloxis hypothesizes that the later-in-time approvals were permitted because they did not rely on the previously approved product(s) with exclusivity. FDA's review of the administrative records for each of these applications reveals that approval of the later-in-time 505(b)(2) NDA could be explained by the scope of the clinical studies that earned exclusivity for the previously approved product.

The Fortesta and AndroGel 1.62% approvals are consistent with the Agency's interpretation of the scope of 3-year exclusivity in that the approvals would not have otherwise been blocked due to the scope of 3-year exclusivity for the respective exclusivity-protected drugs. First, FDA has not uncovered any express statements in the record stating that approval of Fortesta or AndroGel 1.62% was permitted due to the fact that the later-in-time application did not rely on the exclusivity-protected drug in its 505(b)(2) NDA, nor has Veloxis cited any such statements. Second, Veloxis fails to consider that a subsequent 505(b)(2) NDA for testosterone would not be blocked if that drug did not share any exclusivity-protected conditions of approval with a previously approved drug. Axiron's 3-year exclusivity was not, as Veloxis suggests, for the active ingredient (testosterone) or indication (i.e., replacement therapy in males for conditions associated with deficiency or absence of endogenous testosterone) as those aspects of the drug product had been previously approved in other testosterone NDAs. As a result, sharing these characteristics would not have precluded approval of the Fortesta 505(b)(2) NDA. Likewise, the approval of AndroGel 1.62% would not have been blocked by virtue of sharing these characteristics (active ingredient and indication) with Axiron and Fortesta for the same reason. Furthermore, the fact that Fortesta and AndroGel 1.62% share the same dosage form (transdermal gel) is also irrelevant as this dosage form, too, was previously approved in the AndroGel 1% NDA in February 2000 and therefore was not the basis of exclusivity for the Fortesta 505(b)(2) NDA. Therefore, the fact that Fortesta and AndroGel 1.62% share the same dosage form would not have precluded approval of AndroGel 1.62% during Fortesta's exclusivity period.

[214] Veloxis Submission at 15-16;

Instead, FDA's review of the record shows the approval of 505(b)(2) NDAs for Fortesta and AndroGel 1.62% can be explained by the scope of 3-year exclusivity for the exclusivity-protected product supported by the new clinical investigations essential to the approval. The sponsors of the exclusivity-protected drugs conducted new clinical investigations to demonstrate, for example, the safety and effectiveness of each unique dosage form, formulation (e.g., strength), or application site for their particular testosterone product, and these new clinical investigations determined the scope of each product's exclusivity. Thus, a subsequent 505(b)(2) NDA for testosterone would not be blocked if that drug did not share exclusivity-protected conditions of approval with a previously approved drug.

In a later submission, Veloxis asserts that FDA approved Testim notwithstanding the exclusivity for AndroGel 1%; and that the Testim NDA did not reference AndroGel 1%, nor did it rely on any clinical studies performed in connection with the approval of AndroGel 1%.[215] Based on a Medical Officer's statements in the record relating to FDA's policy on the need for premarket approval site inspections, Veloxis speculates that "it would appear" that FDA concluded that the lack of reliance on AndroGel precluded the application of AndroGel's exclusivity to block final approval of Testim.[216]

Again, FDA's review has not uncovered any express statement in the record stating that approval of the Testim NDA was permitted due to the fact that it did not rely on AndroGel 1%, nor has Veloxis cited any such statements. To the extent Testim could be viewed as sharing certain characteristics with AndroGel 1% for which clinical investigations were essential and to the extent those characteristics could be viewed as exclusivity-protected conditions of approval, it is possible that Testim was approved prematurely four months before expiration of the 3-year exclusivity for AndroGel 1%. However, this single approval does not establish that FDA has interpreted the statute to require reliance for a subsequent 505(b)(2) application for the exclusivity-protected conditions of approval to be blocked. Instead, some aspects of the administrative record indicate the Testim NDA had been reclassified by the Agency as a 505(b)(1) NDA before expiration of exclusivity for AndroGel 1%.[217] Regardless of whether the application was correctly reclassified, this issue is significant because if FDA had believed that Testim was a 505(b)(1) NDA, its approval would not have been blocked by 3-year exclusivity of another drug. Finally, given that the Testim approval appears to be an outlier as described above, this example should not be viewed as precedent that binds the Agency.

[215] Letter from Veloxis to DTOP (Dec. 12, 2014) at 2.

[216] Id. (citing Medical Officer Review, "The decision to not have any site inspections was a result of the new draft policy from DSI which states that new NDAs do not automatically require clinical site inspections. Testim is not an NME, not first in its class, not intended for a novel population, not used for a new diagnostic category, and not delivered via new route of administration. Site inspections were not indicated under these circumstances." (italics omitted)).

[217] See, e.g., Testim (NDA 021454) Exclusivity Determination Checklist (stating that the NDA had been reclassified from a 505(b)(2) to a 505(b)(1)). Testim Supervisory Pharmacologist Memo to the NDA (Jan. 21, 2003) (stating that "[t]he literature cited by Auxilium did not contain investigations necessary to approval of the NDA"); Letter from CDER to Auxilium (Jan. 17, 2003) (stating that "[a]lthough the NDA was submitted as a 505(b)(2) application, it was determined that it was submitted under 505(b)(1)").

V. CONCLUSION

Based on a thorough review of submissions by Veloxis and Astellas, including the studies conducted in support of their applications, the relevant provisions of the FD&C Act and FDA regulations, and Agency precedent, FDA concludes that Astagraf XL obtained 3-year exclusivity for once-daily ER tacrolimus for prophylaxis of organ rejection in *de novo* kidney transplant patients and Envarsus XR is blocked from obtaining approval for that condition of approval until Astagraf XL's exclusivity expires on July 19, 2016. However, if appropriate labeling is submitted to the Agency, Envarsus XR may be approved now for its once-daily, ER dosage form of tacrolimus for conversion of stable kidney transplant patients from tacrolimus IR to tacrolimus ER. In approximately eighteen months, after the expiration of exclusivity for Astagraf XL, Envarsus XR can be approved for the prophylaxis of organ rejection in *de novo* and conversion kidney transplant patients.

If you have any questions, call Ms. Lois Almoza, Regulatory Health Project Manager, at 301-796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

APPENDIX

Drug Name/ NDA #	Approval/Exclusivity Expiration Date/Code	Active Ingredient/ Indication	Dosage Form, Strength, Application Site	New Clinical Investigations Essential to Approval[a]
AndroGel 1% NDA 021015	02/28/2000 2/28/2003 NDF	Testosterone Indicated for replacement therapy in males for conditions associated with deficiency or absence of endogenous testosterone	• Transdermal gel • 25 mg/2.5 g packet • 50 mg/5 g packet • Transdermal gel –- metered dose pump • 12.5 mg/1.25 g actuation (approved on 09/23/2003 in supplement 10) • shoulders, upper arms, and/or abdomen	UMD-96-017 Randomized, active-controlled, parallel-group trial that compared two doses of AndroGel with a testosterone patch (Androderm). Three treatment arms: 5gm of AndroGel daily (containing 50 mg of testosterone), 10 gm of AndroGel daily (containing 100 mg of testosterone), and two Androderm patches daily (containing total of 5 mg absorbed testosterone). Primary endpoint was proportion of patients in each treatment group with both C_{avg} and C_{min} values for serum testosterone within the normal range (298-1043 ng/dl) on Day 30.[b]
Testim [1%] NDA 021454	10/31/2002 10/31/2005 NP	Same	• Transdermal gel • 50 mg/5 g packet • Shoulders and upper arms	AUX-TG-201-02[c] Randomized, active-and placebo-controlled, four arm, parallel-group, multicenter trials in adult males with morning serum testosterone levels ≤ 300 ng/dL. Four treatment arms were Testim 50 and 100 mg gel, matching placebo gel, and Androderm transdermal patches (2 x 1.5 mg). Primary efficacy parameter was the C_{avg} and C_{min} of serum total testosterone levels within normal range. AUX-TG-207-01 Evaluated effect of washing on testosterone levels. AUX-TG-206-00 Evaluated potential for dermal transfer of testosterone. AUX-TG-209-00 Evaluated potential for dermal transfer of testosterone.[d]

Drug Name/ NDA #	Approval/Exclusivity Expiration Date/Code	Active Ingredient/ Indication	Dosage Form, Strength, Application Site	New Clinical Investigations Essential to Approval[a]
Axiron [2%] NDA 022504	11/23/2010 11/23/2013 NP	Same	• Transdermal solution – -metered • 30 mg/1.5 mL actuation (pump is capable of dispensing 90 mL of solution in 60 metered pump actuations) • Axillae (armpit)	MTE08 Phase 3, open-label titration trial to evaluate the effectiveness and safety of a dermal application of Axiron (testosterone transdermal solution) in hypogonadal men. Initial dose 60 mg to each axilla once daily. Primary efficacy endpoint was C_{avg} for testosterone in defined normal range.[e]
Fortesta [2%] NDA 021463	12/29/2010 12/29/2013 NP	Same	• Transdermal gel – metered • 10 mg/0.5 g actuation (60 g canisters, with 120 metered pump actuations) • Front and inner thighs	FOR01C Phase 3, open-label, non-comparative trial in hypogonadal males. Fortesta (testosterone gel) was applied to thighs at starting dose of 40 mg once daily. Primary efficacy endpoint was serum total testosterone C_{avg} within physiological range.[f]
AndroGel 1.62% NDA 022309	04/29/2011 4/29/2014 NP	Same	• Transdermal gel – metered • 20.25 mg/1.25 g actuation (pump can dispense 60 actuations) • Transdermal gel • 20.25 mg/1.25 g packet • 40.5 mg/2.5 g packet • shoulders and upper arms	S176.3.104 Phase 3, randomized, double-blind, placebo-controlled study in hypogonadal males. AndroGel 1.62% (testosterone gel) was applied at starting dose of 2.5g of testosterone which could, over any seven day period, be rotated between the upper arms/shoulders or abdomen provided correct application technique (arms/shoulder only application) occurred during PK visits. Primary efficacy endpoint was serum testosterone C_{avg} within normal serum testosterone range. Additional 6-month open-label extension.[g]

[a] Refers to new clinical investigations listed on Exclusivity Summary.

[b] AndroGel 1% Medical Officer Review (February 15, 2000) at 4, 9.

[c] Exclusivity Summary lists AUX-TG-201-02. The Testim NDA reviews refer to AUX-TG-202.01R or Study AUX-TG-202 (Study described in text). The NDA reviews also refer to AUX-TG-201.01 or Study AUX-201 (single-dose pharmacokinetic, crossover design with AndroGel active comparator). The Exclusivity Summary is likely referring to Study AUX-TG-202.

[d] Testim Medical Officer's Clinical Review (October 30, 2002) at 5, 7, 9, 11.

[e] Axiron Deputy Division Director Summary Review for Regulatory Action (November 23, 2010) at 5, 6, 7, 12.

[f] Fortesta Deputy Division Director Summary Review for Regulatory Action (December 29, 2010) at 7.

[g] AndroGel 1.62% Summary Review for Regulatory Action (April 29, 2011) at 9-10.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RENATA ALBRECHT
01/12/2015