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 (RBW) **HEARING REQUESTED**

PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

Plaintiff Veloxis Pharmaceuticals, Inc. ("Veloxis") moves the Court for a preliminary injunction ordering Defendant U.S. Food and Drug Administration ("FDA") to immediately grant final approval to Veloxis's New Drug Application ("NDA") for Envarsus® XR.

As set forth in the accompanying Memorandum of Points and Authorities, the FDA's denial of final approval of the Envarsus XR NDA based upon the exclusivity granted to Astagraf XL® is unlawful and must be set aside under the Administrative Procedure Act. Specifically, FDA's decision is erroneous as a matter of law for three independent reasons:

- *First*, according to the unambiguous statutory language of the Federal Food, Drug, and Cosmetic Act ("FDCA"), Astagraf XL was never entitled to three-year exclusivity. For drug products like Astagraf XL, exclusivity is only available if an application for approval was submitted to FDA *after* October 2008. Because the initial NDA for Astagraf XL was submitted in 2005, FDA's grant of exclusivity to Astagraf XL exceeded its statutory authority.

- *Second*, even if Astagraf XL is eligible for three-year exclusivity (and it is not), that exclusivity, as a matter of law, cannot block approval of Envarsus XR because the Envarsus XR NDA did not rely upon any of the studies or data supporting approval of Astagraf XL.

- *Third*, even if the reliance requirement was read out of the FDCA, Envarsus XR still would not be subject to the exclusivity granted Astagraf XL because Envarsus XR does not share conditions of approval with Astagraf XL. In this regard, FDA arbitrarily and capriciously concluded that the two drugs share the same conditions of approval, ignoring the significant clinical differences between the two drugs and the material differences in the package inserts, and abandoning more than 20 years of its own precedent.

For all these reasons, Veloxis is likely to succeed on the merits of its claims. Moreover, a preliminary injunction is warranted to prevent severe and irreparable harm to Veloxis, a small, single-drug company. It would also benefit the public interest by allowing numerous kidney transplant patients to take immediate advantage of the significant clinical advantages that may be realized with Envarsus XR.

Pursuant to Local Civil Rule 7(m), Veloxis has consulted with counsel for Defendants, who oppose this motion.

Dated: December 17, 2014

Respectfully submitted,
/s/ Mitchell S. Ettinger

Jennifer L. Bragg (D.C. Bar No. 488946)
Mitchell S. Ettinger (D.C. Bar No. 415451)
Lauryn K. Fraas (D.C. Bar No. 984887)
Colin V. Ram (D.C. Bar No. 989848) *pro hac vice and admission pending*
SKADDEN, ARPS, SLATE, MEAGHER & FLOM LLP
1440 New York Avenue, N.W.
Washington, DC 20005
(202) 371-7000 (tel.)
(202) 393-5760 (fax)

Maya P. Florence (D.C. Bar No. 986139)
SKADDEN, ARPS, SLATE, MEAGHER & FLOM LLP
500 Boylston Street
Boston, MA 02116
(617) 573-4800 (tel.)
(617) 573-4822 (fax)

Attorneys for Plaintiff Veloxis Pharmaceuticals, Inc.

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Defendants.	)	
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MEMORANDUM OF POINTS AND AUTHORITIES
IN SUPPORT OF PLAINTIFF'S MOTION FOR PRELIMINARY INJUNCTION

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INTRODUCTION

Plaintiff Veloxis Pharmaceuticals, Inc. ("Veloxis") seeks a preliminary injunction requiring the U.S. Food and Drug Administration ("FDA") to comply with its statutory mandate and grant immediate final approval to the New Drug Application ("NDA") for Envarsus® XR (tacrolimus extended-release tablets). Veloxis is a small, research-based pharmaceutical company seeking approval of its first innovative drug product after years of development and clinical testing. On December 28, 2013, Veloxis filed an NDA for Envarsus XR, an extended-release tacrolimus tablet for prophylaxis of organ rejection in kidney transplant patients. On October 30, 2014, FDA informed Veloxis that it had completed its review and had determined that the NDA met FDA's rigorous scientific standards for approval, *i.e.*, that Envarsus XR is safe and effective. Nevertheless, FDA refused to grant final, effective approval of the NDA for Envarsus XR because it erroneously concluded that such approval is blocked by the three-year exclusivity granted by FDA to another drug, Astagraf XL® (tacrolimus extended-release capsules). FDA's decision is erroneous as a matter of law for three reasons:

- *First*, according to the unambiguous statutory language of the Federal Food, Drug, and Cosmetic Act ("FDCA"), Astagraf XL was never entitled to three-year exclusivity. For drug products like Astagraf XL, exclusivity is only available if an application for approval was submitted to FDA *after* October 2008. Because the initial NDA for Astagraf XL was submitted in 2005, FDA's grant of exclusivity to Astagraf XL exceeded its statutory authority.

- *Second*, even if Astagraf XL is eligible for three-year exclusivity (and it is not), that exclusivity, as a matter of law, cannot block approval of Envarsus XR because the Envarsus XR NDA did not rely upon any of the studies or data supporting approval of Astagraf XL.

- *Third*, even if the reliance requirement was read out of the FDCA, Envarsus XR still would not be subject to the exclusivity granted Astagraf XL because Envarsus XR does not share conditions of approval with Astagraf XL. In this regard, FDA arbitrarily and capriciously concluded that the two drugs share

> the same conditions of approval, ignoring the significant clinical differences between the two drugs and the material differences in the package inserts, and abandoning more than 20 years of its own precedent.

It is undisputed that the Envarsus XR NDA meets all FDA requirements for demonstrating safety and efficacy for its intended use. If FDA's erroneous decision is permitted to stand, kidney transplant patients nevertheless will be denied access to Envarsus XR at least until July 2016. As explained below, the significant clinical advantages that may be realized through the use of Envarsus XR, especially in African-American patients, would be foreclosed without legal basis. During that 18-month period, Veloxis, which effectively is a single-drug company, also would suffer irreparable economic and reputational harm. For these reasons, Veloxis respectfully moves this Court to issue a mandatory injunction compelling FDA to grant immediate final approval of Envarsus XR.

STATEMENT OF FACTS

I. Statutory and Regulatory Background

A. Approval of Prescription Drugs

The FDCA requires FDA to approve a prescription drug before it may be distributed in interstate commerce. 21 U.S.C. § 355(a). Section 505 of the FDCA outlines three pathways for obtaining approval of a new drug. Under Section 505(b)(1), an NDA sponsor may conduct non-clinical and clinical studies to demonstrate the safety and effectiveness of a proposed new drug for its intended use and provide FDA with full reports of those studies. *Id.* § 355(b)(1).

Alternatively, under Section 505(b)(2), a sponsor may submit an application for a modification of a "listed drug" for which FDA already has made a finding of safety and effectiveness. *Id.* § 355(b)(2). A "505(b)(2)" application, unlike a 505(b)(1) "full NDA," relies in part on safety and/or efficacy data from a previously approved drug, coupled with data from

new studies required to support the change to the previously approved drug.[1] A 505(b)(2) application must identify the "listed drug" on which the applicant relies in seeking approval of its proposed drug product. 21 C.F.R. § 314.54(a)(1)(iii) (2014). Section 505(b)(2) is designed to encourage innovation without creating duplicative work, as Congress and FDA recognize that "it is wasteful and unnecessary to carry out studies to demonstrate what is already known about a drug." FDA 505(b)(2) Guidance at 3.

Finally, under Section 505(j), an "Abbreviated New Drug Application" ("ANDA") may be submitted for approval of a generic version of a drug that already has received FDA approval. 21 U.S.C. § 355(j). A drug submitted for approval under Section 505(j) typically must contain the same active ingredient, dosage form and strength, route of administration, labeling, quality, performance characteristics, and intended use as a previously approved drug. *Id.*; *see also* 21 C.F.R. § 314.92(a)(1) (2014).

B. Statutory Marketing Exclusivity

Pursuant to the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. § 156 (also known as the "Hatch-Waxman Amendments"), the FDCA was amended to provide periods of exclusivity to approved drugs in certain circumstances.[2] Exclusivity is intended to maintain incentives for companies to conduct time-consuming and costly clinical

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1 *See* FDA, *Draft Guidance for Industry*: *Applications Covered by Section 505(b)(2)* at 3 (Oct. 1999), *available at* www.fda.gov/downloads/drugs/guidancecomplianceregulatory information/guidances/ucm079345.pdf ("FDA 505(b)(2) Guidance").

2 *See* FDA, Center for Drug Evaluation and Research ("CDER"), *Small Business Assistance*: *Frequently Asked Questions for New Drug Product Exclusivity*, *available at* www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinesssAssistance/ucm069962.htm (last updated July 1, 2010) ("CDER FAQ") ("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.").

research by providing a window of time during which another company that relies on that research for FDA approval may not bring its drug to market. *See* CDER FAQ.

As an incentive to make significant improvements to existing drug products, the FDCA provides a three-year period of exclusivity for certain changes to already approved drug products. Three-year exclusivity is granted to drugs whose applications contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." 21 U.S.C. § 355(c)(3)(E)(iii). Changes that may be protected by three-year exclusivity include, among others, new dosage forms, new indications, new dosing regimens, new combinations, and different strengths.[3] The exclusivity period extends for three years from the date of the first drug's approval and prohibits FDA from granting final approval of a 505(b)(2) application "for the conditions of approval" of the first drug if the safety and effectiveness studies relied upon by the 505(b)(2) applicant "were not conducted by or for [the 505(b)(2) applicant] and if [that applicant] has not obtained a right of reference or use from the person by or for whom the investigations were conducted."[4] *Id.*

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[3] *See* Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,357 (Oct. 3, 1994) (FDA has identified "changes in active ingredient, strength, dosage form, route of administration, or conditions of use" and "changes in dosing regimen" as the "types of changes in a product" that may warrant three-year exclusivity); *see also* CDER FAQ ("[c]hanges in an approved drug product that affect its active ingredient(s), strength, dosage form, route of administration or conditions of use may be granted exclusivity if clinical investigations were essential to approval of the application containing those changes").

[4] Three-year exclusivity also blocks approval of ANDAs that rely upon the previously approved drug for approval. 21 U.S.C. § 355(j)(5)(F)(iii)-(iv).

C. Pre-Repeal Antibiotics

Antibiotics historically were not eligible for exclusivity under the Hatch-Waxman Amendments because they were approved under Section 507 of the FDCA rather than Section 505.[5] In 1997, Congress repealed Section 507 and directed FDA henceforth to approve all antibiotics under Section 505. *See* Food and Drug Administration Modernization Act of 1997 ("FDAMA"), Pub. L. 105-115, § 125(d)(1), 111 Stat. 2296, 2326-27. In so doing, Congress explicitly provided that certain Hatch-Waxman incentives, including three-year exclusivity, would not apply to any application for a drug product that contained a so-called "pre-repeal antibiotic," *i.e.*, an antibiotic drug that was the subject of an approved or pending application under Section 507 prior to November 21, 1997. *Id.* § 125(d)(2), 111 Stat. at 2327.

In 2008, Congress reversed course and amended the FDCA to spur research into new and innovative antibiotic therapies, particularly given the growing concern regarding antibiotic resistance. *See* 154 Cong. Rec. H10171 (daily ed. Sept. 27, 2008) (statement of Rep. Sullivan). As part of the QI Program Supplemental Funding Act of 2008 ("QI Act"), Pub. L. 110-379, 122 Stat. 4075, Congress provided that an NDA for a pre-repeal antibiotic could be granted exclusivity, provided it pertained to a new "condition of use." 21 U.S.C. §§ 355(v)(1)(A), 355(v)(3)(B). Recognizing that these incentives were not necessary for drug products that already had been developed, however, Congress provided that such exclusivity could be granted only to pre-repeal antibiotics that were the subject of new NDAs submitted to

[5] *See* FDA, *Guidance for Industry and Reviewers*: *Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act* (rev. May 1998), *available at* www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080566.pdf ("FDA Section 507 Repeal Guidance").

FDA after October 8, 2008, the enactment date of the QI Act. 21 U.S.C. §§ 355(v)(1)(B)(i), 355(v)(3)(B).

II. Factual Background

A. The Parties

Plaintiff Veloxis is a specialty pharmaceutical company based in Edison, New Jersey. (Polvino Decl. ¶ 1 (attached hereto as Exhibit 1).) Its corporate parent, Veloxis Pharmaceuticals A/S, is headquartered in Denmark. (*Id.*) On December 28, 2013, Veloxis filed an NDA for Envarsus XR, an extended-release tacrolimus tablet for prophylaxis of organ rejection in kidney transplant patients. (Mc Guinness Decl. ¶ 25 (attached hereto as Exhibit 2).)

Defendant HHS is a cabinet-level department of the United States Government. Defendant FDA is an agency of the United States and a division of Defendant HHS. FDA administers the FDCA and took the final agency action challenged in this case. Defendant Sylvia M. Burwell is the Secretary of HHS and ultimately is responsible for implementation and execution of the FDCA and associated regulations, including the approval of new drugs under Section 505 of the FDCA. Defendant Burwell is sued in her official capacity only. Defendant Margaret A. Hamburg is the Commissioner of Food and Drugs and is responsible for FDA's implementation and execution of the FDCA and associated regulations, including the approval of new drugs under Section 505. Defendant Hamburg is sued in her official capacity only.

B. Immunosuppressant Therapies Are Used to Prevent Rejection of Transplanted Kidneys

In 2013, there were 16,895 kidney transplants performed in the United States. (Weinberg Decl. ¶ 4 (attached hereto as Exhibit 3).) The average life expectancy of a transplanted kidney is approximately 10 years. (*Id.*) When a patient undergoes a kidney transplant, the patient's immune system attempts to reject the transplanted organ to protect itself

from foreign tissue. (*Id.* ¶ 5.) Immunosuppressive drugs are used to decrease the body's immune response and thus prevent the body from rejecting the transplanted organ, which can be fatal to the life-saving organ and the transplant recipient. (*Id.*) Tacrolimus was first approved by FDA for use as an immunosuppressant in 1994, and marketed by a predecessor of Astellas Pharma US, Inc. ("Astellas") under the brand name Prograf®. (*Id.* ¶ 9.) Tacrolimus is a pre-repeal antibiotic. *See* Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs, 65 Fed. Reg. 3,623, 3,627 (proposed Jan. 24, 2000). In 2013, FDA approved an extended-release capsule of tacrolimus, also marketed by Astellas, under the brand name Astagraf XL®. (Weinberg Decl. ¶¶ 10, 14.)

There have been few new immunosuppressive therapies in recent years and, unfortunately, the currently marketed immunosuppressive drugs can have serious side-effects for patients. (*Id.* ¶¶ 6, 8; Bragg Decl. (attached hereto as Exhibit 4) Ex. G at Ex. 2 ¶ 5 (hereinafter "Bloom Decl.").) Known side effects of tacrolimus include nephrotoxicity (drug toxicity affecting kidney cells and function), infectious complications, bone marrow suppression, hypertension, severe diarrhea, development of diabetes, electrolyte effects (hyperpotassium and hypomagnesium), severe tremors, seizures, blurred vision, insomnia, headaches, and forgetfulness. (Polvino Decl. ¶ 5; Bragg Decl. Ex. H at Ex. 1 ¶¶ 3, 18 (hereinafter "Langone Decl.").)

Tacrolimus is a "narrow therapeutic index" drug, meaning that the active ingredient must be maintained in the patient's blood within a narrow range throughout the lifetime of the transplanted organ. (Weinberg Decl. ¶ 17.) If the blood levels of the active ingredient fall below a minimum threshold, the drug is ineffective and the patient's immune system may reject the transplanted organ. (*Id.*) If blood levels of the active ingredient rise above

the prescribed range, however, there is an increased risk of the noted side effects. (*Id.*) For narrow therapeutic index drugs like tacrolimus, the range between these upper and lower limits is small.[6] As a result, the concentration and dosing of tacrolimus must be carefully managed and individually tailored for each transplant patient. (*Id.*; Langone Decl. ¶ 3.) To arrive at the appropriate dosing regimen, transplant patients typically are required to undergo regular monitoring for months after receiving a new organ to evaluate the blood level concentrations of tacrolimus. (Weinberg Decl. ¶ 17; Bloom Decl. ¶ 11.) This adjustment regimen requires repeated visits to the physician's office or a hospital, which may significantly impact a transplant recipient's quality of life. (Bloom Decl. ¶ 11.)

Improved immunosuppressive therapies can increase the survival of transplanted organs, thereby reducing the number of patients requiring re-transplants and, ultimately, enabling more people to receive organ transplants. (Weinberg Decl. ¶ 6.) In particular, new therapies that are less toxic and that reduce the number of doses a patient has to take each day can result in improved adherence to the medication regimen, which is crucial to maintaining kidney function. (Bloom Decl. ¶¶ 5, 12; Langone Decl. ¶ 12.)

New tacrolimus therapies may have particular benefits for African-American patients, whom studies have shown are at increased risk of acute kidney rejection when compared to other patient groups. (Bloom Decl. ¶ 8.) Data also shows that African-Americans are less likely to receive kidney transplants, and when they do, the average life span of the kidney is far less than for non-African-American patients. (*Id.*) This discrepancy has been attributed to the fact that 85% of African-Americans are rapid metabolizers of tacrolimus,

[6] FDA, *Draft Guidance on Tacrolimus* (rev. Dec. 2012), *available at* www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm181006.pdf

making it difficult to maintain appropriate concentrations of tacrolimus in a patient's blood. (*Id.*; Polvino Decl. ¶ 13.) Some rapid metabolizers require three doses per day in order to maintain minimum effective levels. (Bloom Decl. ¶ 9.) The use of larger doses can result in high peak levels of tacrolimus in the patient's blood and increase the risk of serious negative side effects due to the drug's toxicity. (Polvino Decl. ¶ 12.) As a result, therapies that increase the absorption of tacrolimus and maintain a steady-state blood level of the active ingredient may lead to improved clinical outcomes, especially for African-American patients. (Bloom Decl. ¶¶ 6-10, 13, 16; Polvino Decl. ¶ 14.)

C. History of the Envarsus XR NDA

Veloxis began clinical investigations of prototype formulations of Envarsus XR in Europe in November 2004. (Mc Guinness Decl. ¶ 8.) On December 20, 2006, Veloxis submitted an Investigational New Drug ("IND") application to FDA to conduct the first U.S. clinical trials in humans. (*Id.* ¶ 11.) The clinical program for Envarsus XR spanned nearly 10 years and cost Veloxis in excess of $200 million dollars. (*Id.* ¶ 23.) The clinical program included eighteen Phase I studies; six Phase II studies, and two Phase III studies, involving more than 1,000 patients and volunteers. (*Id.* ¶ 5.)

Throughout the Envarsus XR clinical program, Veloxis met with FDA to discuss the results of its trials and to explore what FDA would require to establish the drug's safety and effectiveness. (*Id.* ¶¶ 8-10, 12-13, 15-18, 20-22.) Veloxis repeatedly informed FDA that it would seek approval of Envarsus XR under Section 505(b)(2), and would reference Prograf as the listed drug. (*Id.* ¶¶ 9-10, 13, 15, 21, 26.) Veloxis specifically designed its pivotal double-blind, double-dummy Phase III clinical trial – Study 3002 – based upon rigorous requirements identified by FDA pursuant to a procedure known as a Special Protocol Assessment ("SPA"). (*Id.* ¶¶ 16-18.) The SPA process permits a drug manufacturer to propose a pivotal trial and

receive FDA feedback.[7] FDA's agreement to an SPA reflects its conclusion that the design and planned analysis of the proposed study adequately addresses the objectives necessary to support a drug approval if the study outcomes are as expected. (Mc Guinness Decl. ¶ 17.) Veloxis submitted an SPA for its proposed Phase III trial to FDA on March 31, 2010. (*Id.* ¶ 18.) FDA reviewed the design of the proposed Phase III trial and, on August 5, 2010, FDA and Veloxis reached agreement on the SPA. (*Id.*)

Veloxis's Phase III trial of Envarsus XR proved successful. On December 20, 2013, FDA designated Envarsus XR as an "orphan drug" pursuant to the Orphan Drug Act. (*Id.* ¶ 24.) The Orphan Drug Act is designed to incentivize companies to develop drug products for rare diseases or conditions that affect less than 200,000 people in the United States.[8] Because there were other tacrolimus products (Prograf and Astagraf XL) on the market for the same indication, FDA could only have designated Envarsus XR as an orphan drug based upon a plausible hypothesis that Envarsus XR was clinically superior to those other marketed products. *See* 21 C.F.R. § 316.20(b)(5) (2014). In designating Envarsus XR as an orphan drug, FDA specifically acknowledged that Envarsus XR was different from, and indeed plausibly superior to, Prograf and Astagraf XL. (Mc Guinness Decl. ¶ 24.)

On December 28, 2013, Veloxis submitted its new drug application for Envarsus XR pursuant to Section 505(b)(2) of the FDCA. (*Id.* ¶ 25.) The Envarsus XR NDA identified and relied upon a single listed drug, Prograf, for the limited purpose of making use of

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[7] FDA, *Guidance for Industry*: *Special Protocol Assessment* at 9 (May 2002), *available at* www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm080571.pdf.

[8] *See* FDA, *Developing Products for Rare Diseases & Conditions*, *available at* www.fda.gov/forindustry/developingproductsforrarediseasesconditions/default.htm.

pharmacology, clinical pharmacokinetic (*e.g.*, drug interaction studies), and pre-clinical animal toxicology data from studies conducted on Prograf. (*Id.* ¶ 26.) By relying on this data, Veloxis avoided having to conduct duplicative testing on animals or human volunteers to prove what already was known about the basic safety and pharmacokinetics of tacrolimus, which had been approved for use as an immunosuppressant since 1994. *See* FDA 505(b)(2) Guidance at 3.

Veloxis relied upon no other listed drug in pursuing its NDA for Envarsus XR. (Mc Guinness Decl. ¶ 26.) Most importantly, the Envarsus XR NDA *did not* (i) reference Astagraf XL as a listed drug, (ii) rely on any studies conducted to support the Astagraf XL NDA, or (iii) rely on FDA's findings of safety and effectiveness for Astagraf XL. (*Id.* ¶¶ 26, 28.) Instead, in order to establish the safety and effectiveness of its novel, extended-release tablet product, Veloxis relied upon its own extensive clinical trials conducted on the proprietary Envarsus XR formulation pursuant to its own longstanding development program and the SPA agreement with FDA. (*Id.* ¶¶ 16-18, 26.)

FDA's deadline for acting on the Envarsus XR NDA was October 30, 2014.[9] Three days before this deadline, on October 27, 2014, FDA for the first time raised with Veloxis the potential impact of Astagraf XL's three-year exclusivity, which had been granted in July 2013. (*Id.* ¶ 31; Bragg Decl. Ex. A.) FDA sent Veloxis an email noting that Astagraf XL had been granted three-year "new dosage form" exclusivity covering "the conditions of approval for the studies Astellas performed which were essential to the approval of Astagraf XL." (Bragg Decl. Ex. A.) FDA asked Veloxis "whether or not you believe that the scope of Astagraf XL's exclusivity does not affect the type of action letter FDA can issue for Envarsus XR." (*Id.*) Until

[9] Under the Prescription Drug User Fee Act of 1992 ("PDUFA"), Pub. L. 102-571, 106 Stat. 4491, FDA is committed to meeting certain time standards for completing its review of NDAs.

that time, Veloxis had no reason to believe that FDA was considering asserting Astagraf XL's exclusivity as a basis to delay final approval of Envarsus XR. (Weinberg Decl. ¶ 36.)

Veloxis responded preliminarily to FDA on October 28 and through a formal submission on October 29, 2014. (Bragg Decl. Ex. B.) Veloxis made clear that the Envarsus XR NDA did not reference Astagraf XL or rely on any Astagraf XL clinical studies. (*Id.*) Additionally, although FDA's October 28 email did not explain what it meant by the term "conditions of approval," Veloxis explained to FDA that Envarsus XR and Astagraf XL are substantially different products that do not share the same "conditions of approval" due to their different dosage forms, strengths, dosing regiments and pharmacokinetic profiles. (*Id.*)

On October 30, 2014, FDA made a final determination, issuing a "Tentative Approval" letter to Envarsus XR. The letter explained that FDA had found Envarsus XR to be eligible for approval under the FDCA, reflecting its conclusion that the drug is safe and effective. (Bragg Decl. Ex. C.) Nevertheless, FDA stated that it was delaying final marketing approval of Envarsus XR until the expiration of Astagraf XL's statutory exclusivity period because the drugs purportedly share the same "conditions of approval." (*Id.*) FDA did not identify the relevant "conditions of approval" that it believed were overlapping or explain why Astagraf XL's exclusivity should apply to Envarsus XR despite a lack of reliance on any of the Astagraf XL data or studies. (*Id.*)[10]

[10] An FDA "tentative approval" letter may be challenged as final agency action for purposes of the Administrative Procedure Act ("APA"), 5 U.S.C. § 706. *See e.g., Watson Labs., Inc. v. Sebelius*, No. 12-1344, 2012 WL 6968224 (D.D.C. Oct. 22, 2012) (finding FDA's decision to grant tentative approval to ANDA based on exclusivity issue was unlawful, arbitrary and capricious and ordering FDA to grant immediate final approval to ANDA); *TorPharm, Inc., v. Shalala*, No. 97-1925, 1997 WL 33472411 (D.D.C. Sept. 15, 1997) (granting preliminary injunction and ordering FDA to grant final approval after finding FDA's grant of tentative approval to ANDA based on exclusivity issue was unlawful).

D. Veloxis Attempts to Avoid Litigation With FDA

After receiving FDA's agency action, in an attempt to avoid litigation, Veloxis engaged in a series of communications with FDA in which Veloxis pointed out the factual and legal error in FDA's decision. On November 6, 2014, Veloxis met with FDA. (Bragg Decl. ¶ 5; *id*. Ex. D at 1.) Veloxis attendees included company personnel, a representative of the National Kidney Foundation, Dr. Roy Bloom, a leading kidney transplant physician, and outside counsel for Veloxis. (*Id.* ¶ 5; *id*. Ex. D at 1.) On November 10, 2014, FDA requested that Veloxis provide a copy of the materials presented at the meeting, and any additional data, information, or analysis regarding the implications of Astagraf XL's three-year exclusivity on the final approval of the Envarsus XR NDA. (*Id.* Ex. F.) Veloxis complied with FDA's request and on November 14, 2014, submitted an eighteen-page letter supported by six exhibits, including a declaration by Dr. Bloom, a written statement by the National Kidney Foundation representative who attended the meeting, and support from medical literature. (*Id.* Ex. G.)[11]

On December 5, 2014, FDA advised that if Veloxis amended its package insert to limit the NDA solely to patients being converted from Prograf, it would grant immediate final

[11] FDA specifically requested that Veloxis identify its submission as a "Request for Final Approval." (Bragg Decl. Ex. F.) Counsel for Veloxis spoke with FDA regarding this request and explained that although Veloxis was prepared to allow FDA a brief period of time to correct its erroneous action, Veloxis would not countenance a material delay in initiating its legal challenge to FDA's action. (*Id.* ¶ 8.) FDA assured Veloxis that it expected to be able to take action, if any, to correct or amend its decision within thirty calendar days. (*Id.*) Veloxis's subsequent November 14, 2014 submission served to document information conveyed during the November 6 meeting, which in turn was drawn from the Envarsus XR NDA. (*Id.* Ex. G.) That submission, which reflected an informal attempt to resolve the matter without resort to litigation, does not disturb the finality of FDA's Tentative Approval letter. *See CollaGenex Pharm., Inc. v. Thompson*, No. 03-1405, 2003 WL 21697344, at *4-5 (D.D.C. July 22, 2003) (plaintiff's communication with FDA after FDA decided issue adverse to plaintiff reflected "an effort to avoid litigation," which did not alter finality of prior agency action).

approval. (*Id.* ¶ 8; *id*. Ex. H.) On December 8, 2014, Veloxis declined to revise its NDA, noting that the suggested amendment would artificially limit the patient population that would benefit from Envarsus XR and would be inconsistent with the requirements of the FDCA. (*Id.* Ex. H.) On December 12, 2014, in a further attempt to avoid litigation, Veloxis provided FDA with additional FDA precedent supporting the immediate final approval of Envarsus XR. (*Id.* Ex. I.) The same day, FDA notified Veloxis that it did not intend to take any action to correct or amend its Tentative Approval letter within the thirty-day time period expressly agreed to by FDA, leaving the prior final agency action unaltered. (*Id.* Ex. J.)

E. FDA Engaged in Non-Public Communications With Astellas

FDA first raised the exclusivity issue with Veloxis on October 27, 2014, just three days before FDA was required to act on the Envarsus XR NDA. (Mc Guinness ¶ 31.) Unbeknownst to Veloxis, however, FDA had been discussing the scope of Astagraf XL's exclusivity with Astellas long before it raised the issue with Veloxis. (Bragg Decl. Ex. E.) As the manufacturer of Astagraf XL, Astellas stood to benefit from a continued monopoly on extended-release tacrolimus products if FDA blocked final approval of Envarsus XR.

After receiving FDA's Tentative Approval letter, Veloxis filed a Freedom of Information Act ("FOIA") request seeking FDA's Summary Basis of Approval for the Astagraf XL NDA as well as any communications from Astellas to FDA regarding the scope of Astagraf XL's exclusivity. (Bragg Decl. ¶ 6; *id*. Ex. E.) The documents produced by FDA reveal the previously non-public history of the Astagraf XL NDA, as well as a course of non-public communications between Astellas and FDA regarding Astagraf XL's eligibility for and scope of exclusivity.

As reflected in the documents Veloxis received, Astellas initially submitted an NDA for Astagraf XL in 2005. (*Id*. Ex. E, encl. 3 at 4 n. 4; *id*. Ex. K at 1, 7.) In 2009, Astellas

withdrew its NDA after FDA sent Astellas an "approvable letter" setting forth the deficiencies with the NDA. (*Id.* Ex. E, encl. 3 at 4 n.4; *id.* Ex. K at 7.) In 2012, Astellas resubmitted the Astagraf XL NDA.[12] (*Id.*; *id.* Ex. K.) Although Astellas filed its 2012 NDA as a separate NDA, Astellas did not complete any new studies necessary for the approval of Astagraf XL between withdrawing and resubmitting the Astagraf XL NDA. (*Id.* Ex. K at 7.)

The documents Veloxis received in response to the FOIA request also reflect that, in August 2012, Astellas argued to FDA that Astagraf XL was entitled to three-year exclusivity under Section 505(v) even though tacrolimus was a pre-repeal antibiotic because Astagraf XL's once-daily dosing constituted a new "condition of use." (*Id.* Ex. E, encl. 2.) On October 27, 2014, Astellas submitted a letter to FDA, apparently in response to an inquiry from FDA, in which it again asserted that Astagraf XL was entitled to exclusivity under Section 505(v). (*Id.* Ex. E, encl. 5.) Neither of these submissions addressed the scope of Astagraf XL's exclusivity or whether it would impact approval of Envarsus XR.

Separately, however, on September 12, 2014, Astellas sent a letter to FDA as a "follow up to a discussion" that Astellas's Head of Global Regulatory Affairs apparently had with Dr. Renata Albrecht, Director of FDA's division responsible for reviewing and approving the Envarsus XR NDA, at the World Transplant Congress in August 2014. (*Id.* Ex. E, encl. 4.) In the September 2014 letter, Astellas argued that its exclusivity "encompass[es] the once daily formulation of tacrolimus indicated for the prophylaxis of organ rejection in transplant patients regardless of patient setting, and no application for those conditions can be approved until the expiration of the exclusivity period on July 19, 2016." (*Id.*) Astellas specifically noted

[12] Astellas was not required to withdraw its original NDA or submit a related NDA to address the deficiencies identified by FDA.

Veloxis's filing of the NDA for Envarsus XR and asked FDA whether it agreed with Astellas's view of the scope of the Astagraf XL exclusivity. (*Id.*) Although this correspondence was intended to delay the approval of Envarsus XR, FDA did not require Astellas to submit it as a Citizen Petition as required by Section 505(q) of the FDCA. *See* 21 U.S.C. § 355(q).

F. There Are Clinically Significant Differences Between Envarsus XR and Other Tacrolimus Products

As FDA recognized in granting orphan drug status to Envarsus XR, Envarsus XR is different from Prograf and Astagraf XL. (Mc Guinness Decl. ¶¶ 23-24.) In particular, Veloxis's clinical trials establish that Envarsus XR and Astagraf XL are clinically different in ways that may significantly impact patient treatment. (Polvino Decl. ¶¶ 4-17; Weinberg Decl. ¶¶ 10, 18-31; Langone Decl. ¶ 16; Bloom ¶ 6-7, 10.)

Many of the key differences between Envarsus XR and Astagraf XL are reflected in the distinct FDA-approved package inserts for the drugs, which reflect their different dosage forms, different dosage strengths, and different dosing regimens. (Weinberg Decl. ¶ 35.) In particular, the package insert for Envarsus XR includes guidance on converting patients to the drug from twice-daily Prograf, which Veloxis specifically studied through a clinical trial. (*Id.* ¶¶ 34-35.) The Astagraf XL label contains no such instructions. (Bloom Decl. ¶ 12.) In the absence of clear instructions for converting patients safely from one drug to the other, patients are at risk of under-dosing, which may result in organ rejection. (Weinberg Decl. ¶ 32.)

Envarsus XR and Astagraf XL also have markedly different pharmacokinetic profiles. (*Id.* ¶¶ 18-27.) At the same dose as Astagraf XL, Envarsus XR shows greater but slower absorption, and a flatter profile, *i.e.*, less significant "peaks" and "troughs." (Bloom Decl. ¶ 6.) As a result, patients taking Envarsus XR can achieve comparable blood levels of tacrolimus using an approximately one-third lower dose of tacrolimus than if treated with Astagraf XL.

(*Id.*) A lower dose of tacrolimus may significantly reduce the drug's serious and sometimes debilitating side effects. (*Id.* ¶ 7.)

Envarsus XR was specifically engineered using Veloxis's patented MeltDose® technology, which results in the slow and uniform release of tacrolimus over time. (Weinberg Decl. ¶ 22.) Longer absorption (and increasing the lowest concentrations of tacrolimus in a patient's blood, *i.e.*, raising the "troughs") may prevent the level of tacrolimus in a patient's blood from falling below a therapeutic level. (*Id.* ¶¶ 23, 26-30.) It also may reduce the need for a patient to take additional doses of tacrolimus in order to maintain therapeutic levels (particularly patients who are rapid metabolizers, such as 85% of African-American patients). (Bloom Decl. ¶¶ 6, 8-9.)

G. Patients Are Deprived of the Clinical Advantages that May Be Realized With Envarsus XR

Envarsus XR's clinical differences from currently marketed tacrolimus drugs may offer significant benefits to patients. (*Id.* ¶ 5.) *First*, currently marketed tacrolimus drugs have many known, serious and sometimes debilitating gastrointestinal and neurological side effects for patients. (Polvino Decl. ¶ 5; Langone Decl. ¶ 3.) Envarsus XR, by virtue of its lower toxicity and lower required dose, may significantly reduce these side effects. (Polvino Decl. ¶ 5.) For example, in one blinded study, patients underwent a formal neurological assessment to evaluate the severity of tremors. (Bloom Decl. ¶ 7; Langone Decl. ¶¶ 9-10.) Patients experiencing severe tremors who were treated with Envarsus XR (in lieu of Prograf) uniformly improved, and most had dramatically reduced tremors. (Langone Decl. ¶ 11.)

Second, data from clinical trials conducted by Veloxis shows that Envarsus XR is absorbed more fully from the first day of treatment following transplant surgery, which may reduce the risk of early transplant rejections. (Polvino Decl. ¶ 7.) Early post-transplant

achievement of target levels of tacrolimus has the potential to safely reduce the length of hospital stays for new transplant patients whose transition to outpatient treatment often hinges on attaining therapeutic levels of tacrolimus. (Bloom Decl. ¶ 10.) In addition, once patients achieve target levels, they may not need daily blood testing, which often requires patients to stay within close proximity to the transplant center instead of returning home and imposes an increased financial burden on patients with diminished means. (*Id*. ¶ 11.)

Third, Envarsus XR may reduce the incidence of a concerning and common kidney transplant complication known as "delayed graft function," which may require a patient to undergo dialysis for a period of time after transplant and reduce the long-term survival rate of the transplanted organ. (Polvino Decl. ¶ 9.) Data from the Envarsus XR clinical trials revealed "delayed graft function" occurred less frequently with Envarsus XR than with Prograf. (*Id*.)

Fourth, as noted above, Envarsus XR's package insert provides guidance to convert patients from a twice-daily tacrolimus regimen to a once-daily extended-release tacrolimus product, whereas Astagraf XL's insert does not. (Bloom Decl. ¶¶ 12-13.)

Fifth, Envarsus XR specifically offers potential benefits to African-American patients and other rapid metabolizers of tacrolimus, who have high unmet needs with currently available therapies. (Polvino Decl. ¶¶ 11-16; Bloom Decl. ¶¶ 8, 13, 16.) Data analysis of patient sub-groups in Envarsus XR clinical studies demonstrated statistically significant improvements in efficacy in African-American patients. (Polvino Decl. ¶ 14.) Further, formal investigation of Envarsus XR in African-American patients who previously were on Prograf found that African-Americans were able to reduce their daily dose of tacrolimus after conversion to Envarsus XR and remained within therapeutic levels when tested one week later. (Bloom Decl. ¶ 13.)

As a result of FDA's decision to delay Envarsus XR's final approval, patients are being denied access to Envarsus XR, and its potential benefits. (*Id.* ¶ 16; Langone Decl. ¶ 17.) Depriving patients of access to potentially improved treatment options has broader impacts as well. Much of the cost of kidney transplant surgery in the United States, as well as the associated medical care, is borne by the federally funded Medicare program.[13]

H. Veloxis Will Suffer Irreparable Harm As A Result Of The FDA Decision

In addition to patient harm, FDA's decision delaying final approval of Envarsus XR also will have profound consequences for Veloxis and threaten its continued viability. (Polvino Decl. ¶¶ 23-34.) Envarsus XR is Veloxis's only product with commercial value. (*Id.* ¶ 23.) As such, the value of the company is closely tied to the immediate approval of Envarsus XR. (*Id*. ¶¶ 24, 33, 34.) For example, FDA's tentative approval decision resulted in Veloxis share prices falling approximately fifty percent, which represents a loss of more than $300 million of the company's market capitalization. (*Id.* ¶ 24.) The FDA decision also will cost Veloxis approximately $20 million in anticipated revenue between January 2015 and July 2016. (*Id*. ¶ 33.) Further, Envarsus XR's revenue is projected to grow steadily until it peaks in 2023, the year before Veloxis's patents expire. (*Id.*) Delaying Envarsus XR's release will shift that growth curve to the right, meaning that Envarsus XR's peak revenue in 2023 will be considerably lower than it would be if approved for sale immediately. (*Id*.)

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[13] Individuals with End-Stage Renal Disease ("ESRD"), defined as permanent kidney failure requiring dialysis or a kidney transplant, are eligible to receive Medicare benefits regardless of their age, provided certain conditions are met. *See* Centers for Medicare & Medicaid Services ("CMS"), *Medicare Coverage of Kidney Dialysis & Kidney Transplant Services*, *available at* www.medicare.gov/Pubs/pdf/10128.pdf. As reported by the United States Renal Data System, in fiscal year 2011, the Medicare program spent $34.3 billion for ESRD. *See* United States Renal Data System, *2013 Annual Data Report*, Ch. 11, *available at* www.usrds.org/2013/view/v2_11.aspx. Therapies that increase kidney transplant success rates may result in decreased costs to the Medicare program.

Based on Envarsus XR's clinical results and Veloxis's positive dialogue with FDA regarding approval, Veloxis established the commercial, regulatory, and quality infrastructure to support a January 2015 launch of Envarsus XR in the United States. (*Id.* ¶ 25.) To support these efforts, approximately twelve individuals have been hired over the last few months and twelve more have accepted offers to join the company contingent on the full approval of Envarsus XR. (*Id.* ¶ 26.) These costs were incurred entirely in anticipation of Envarsus XR's launch. (*Id.* ¶¶ 25-26.)

As a consequence of FDA's erroneous decision, Veloxis will be forced to terminate employees, reducing its current number of employees from forty-three to between five and twenty (*i.e.*, a reduction of 50-90%), and rescind any outstanding contingent offers. (*Id.* ¶¶ 26-27.) Such a sudden and drastic reduction to the Veloxis workforce will damage morale, reduce productivity, and disrupt research and development, marketing and other company efforts. (*Id.* ¶ 27.) Veloxis also will miss significant partnering and marketing opportunities in the United States and abroad. (*Id.* ¶ 29.)

Because of the irreparable financial harm imposed by FDA's erroneous decision, Veloxis also is likely to cancel important follow-on studies of Envarsus XR. (*Id.* ¶¶ 18-22.) These include a study focused on Envarsus XR's superior efficacy in African-American patients, a study of its reduced neurotoxicity and an additional three-way "switching" study to determine correct conversion doses among Envarsus XR, Astagraf XL, and Prograf. (*Id.* ¶ 19.)

ARGUMENT

The decision to grant injunctive relief rests within the discretion of the Court. *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 391, 126 S. Ct. 1837, 1839 (2006); *Bayer Healthcare, LLC v. FDA*, 942 F. Supp. 2d 17, 23 (D.D.C. 2013) ("An injunction is an equitable

remedy so its issuance falls within the sound discretion of the district court."). In the D.C. Circuit, a four-part test governs requests for a preliminary injunction: whether "(1) the plaintiff has a substantial likelihood of success on the merits; (2) the plaintiff would suffer irreparable injury were an injunction not granted; (3) an injunction would substantially injure other interested parties; and (4) the grant of an injunction would further the public interest." *Sottera, Inc. v. FDA*, 627 F.3d 891, 894 (D.C. Cir. 2010) (internal quotation marks omitted). A "sliding scale" approach is used to evaluate the preliminary injunction factors. *Tyndale House Publrs., Inc. v. Sebelius*, 904 F. Supp. 2d 106, 113 & n.6 (D.D.C. 2013) (Walton, J.). Here, each factor militates in favor of granting the requested preliminary injunction.

I. Veloxis is Likely to Succeed on the Merits

First, Astagraf XL was not entitled to a grant of exclusivity under the FDCA because its active ingredient, tacrolimus, is a pre-repeal antibiotic and the Astagraf XL NDA was pending at FDA prior to October 8, 2008. The fact that Astellas opted to withdraw its NDA for Astagraf XL in 2009 and refile it in 2012, without conducting any new studies upon which its exclusivity is based, cannot serve as a basis to avoid Congress's clear mandate.

Second, FDA's decision to apply Astagraf XL's exclusivity to Envarsus XR also ignores the plain language of the FDCA, which limits application of the exclusivity granted to one drug manufacturer to subsequent applicants who ***rely upon*** the clinical studies supporting approval of the drug awarded exclusivity. As the Envarsus XR NDA did not rely upon any study conducted to support the approval of Astagraf XL, or upon FDA's prior findings that Astagraf XL is safe and effective, FDA's application of Astagraf XL's exclusivity to Envarsus XR directly contravenes the FDCA's mandate.

Third, FDA has applied the exclusivity granted to Astagraf XL in an arbitrary and capricious manner, erroneously concluding that Envarsus XR and Astagraf XL share unspecified

"conditions of approval." In so ruling, FDA has ignored the significant clinical differences between the two drugs, the material differences in their package inserts, and more than 20 years of FDA's own precedent.

Pursuant to the APA, 5 U.S.C. § 706, a reviewing court must "hold unlawful and set aside agency action" that is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law" or "in excess of statutory jurisdiction [or] authority." *Id.* § 706(2)(A), (2)(C). FDA's granting of exclusivity to Astagraf XL and application of that exclusivity to the Envarsus XR NDA were in excess of FDA's statutory authority, and its application of Astagraf XL's exclusivity to Envarsus XR was arbitrary and capricious. For these reasons, Veloxis is likely to succeed on the merits of this action.

A. FDA Exceeded Its Statutory Authority In Granting Exclusivity to Astagraf XL

1. Astagraf XL Is Not Entitled to Exclusivity Under the Plain Language of Section 505(v) of the FDCA

To determine whether an agency has acted in excess of its statutory authority under the APA, the Court applies the two-step framework set out in *Chevron U.S.A. Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 104 S. Ct. 2778 (1984); *see also Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1067 (D.C. Cir. 1998); *Depomed, Inc. v. HHS*, No. 12-1592, 2014 WL 4457225, at *8 (D.D.C. Sept. 5, 2014). The first step in the *Chevron* analysis requires the Court to employ traditional tools of statutory construction to determine "whether 'Congress has directly spoken to the precise question at issue.'" *Mova Pharm.*, 140 F.3d at 1067 (quoting *Chevron*, 467 U.S. at 842, 104 S. Ct. at 2781); *see also Amalgamated Transit Union v. Skinner*, 894 F.2d 1362, 1368 (D.C. Cir. 1990) (quoting *Chevron*, 467 U.S. at 843 n.9, 104 S. Ct. at 2781 n.9). "Courts use traditional tools of statutory construction to determine whether Congress has unambiguously expressed its intent, including an examination of the statute's text, structure,

purpose, and legislative history." *Watson Labs*, 2012 WL 6968224, at *9 (internal citation and quotation omitted); *see also Amalgamated Transit Union*, 894 F.2d at 1368 (same).

If the Court determines that Congress has "directly spoken to the precise question at issue," "the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Mova Pharm.*, 140 F.3d at 1067 (quoting *Chevron*, 467 U.S. at 843, 104 S. Ct. at 2781-82) (internal quotation marks omitted). The Court only proceeds to Chevron's second step – where "'the question for the court is whether the agency's answer is based on a permissible construction of the statute'" – if the Court determines that the "'the statute is silent or ambiguous with respect to the specific issue.'" *Id.* (quoting *Chevron*, 467 U.S. at 843, 104 S. Ct. at 2782).

Here, Congress's intent is clear from the language of Section 505(v) and the structure and history of the FDCA. Tacrolimus, the active ingredient in both Prograf and Astagraf XL, is a pre-repeal antibiotic even though it is not intended for traditional antibiotic uses. *See* Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs, 65 Fed. Reg. 3,623, 3,627 (proposed Jan. 24, 2000). Prior to 2008, pre-repeal antibiotics were not eligible for certain Hatch-Waxman incentives, including three-year exclusivity. FDAMA, § 125(d)(1); *see also* FDA Section 507 Repeal Guidance.

In 2008, Congress amended the FDCA to provide additional incentives to spur research into new and innovative antibiotic therapies, in light of growing concerns about antibiotic resistance. *See* 154 Cong. Rec. 10171 (daily ed. Sept. 27, 2008) (statement of Rep. Sullivan). In particular, Congress provided that certain NDAs could be granted exclusivity even if they contained a pre-repeal antibiotic. 21 U.S.C. §§ 355(v)(1)(A), 355(v)(3)(B). However, Congress explicitly limited exclusivity rights under this provision to NDAs for drug products

submitted after October 8, 2008, the enactment date of the QI Act. *Id.* In other words, exclusivity does not attach to any drug product containing a pre-repeal antibiotic that was the subject of an NDA that had been approved or was pending at FDA prior to October 8, 2008. *See id.*

The Astagraf XL NDA initially was submitted in 2005 and, in fact, was pending at FDA prior to, during, and after the enactment of the QI Act on October 8, 2008. (Bragg Decl. Ex. E, encl. 3 at 4 n.4; *id*. Ex. K at 1, 7.) Accordingly, as a matter of law, Astagraf XL was not entitled to three-year exclusivity when the QI Act was passed. Where, as here, the plain language of the statute precludes FDA's interpretation, there is no need to proceed beyond *Chevron* step one analysis. Rather, the analysis begins and ends with the statutory language. *Depomed*, 2014 WL 4457225, at *9-12 (entering judgment in favor of drug manufacturer based upon *Chevron* step one analysis).

2. Withdrawal and Resubmission of the Astagraf XL NDA Does Not Overcome the Statutory Prohibition Established by Section 505(v)

It appears that FDA granted exclusivity to Astagraf XL on the basis that – even though it was the subject of a pending NDA at the time of the enactment of the QI Act – Astellas withdrew its NDA in 2009 and refiled it in 2012. The prohibitions of the QI Act, however, cannot be avoided through such manipulation of the regulatory process. FDA's grant of exclusivity to Astagraf XL was contrary to Congress's intent and inconsistent with the incentive structure created by Congress in the QI Act, and therefore in excess of FDA's statutory authority.

In enacting the QI Act, Congress was concerned with "strik[ing] the right balance between innovation and access." 153 Cong. Rec. 5630 (daily ed. May 7, 2007) (statement of Sen. Kennedy). Congress wanted to spur the development of new antibiotics for the public health, s*ee* 154 Cong. Rec. H10171 (daily ed. Sept. 27, 2008) (statement of Rep. Sullivan), while

at the same time, "prevent pharmaceutical manufacturers from abusing the process to extend the life of old active ingredient drugs," 153 Cong. Rec. S5823 (daily ed. May 9, 2007) (statement of Sen. Kennedy). The legislative history makes clear that, to achieve these twin goals, Congress only permitted the new exclusivity benefits to apply to new and innovative antibiotic therapies (*i.e.*, those that had not yet been developed to the point of a pending or approved application). *See* 21 U.S.C. § 355(v)(1)(B)(i).

Because Astagraf XL was subject to an NDA that was pending at FDA prior to October 8, 2008, it is precisely the type of "already developed" drug product that Congress explicitly exempted from the new exclusivity benefits pursuant to the QI Act. The fact that Astellas opted to withdraw its initial application for Astagraf XL in 2009 and resubmit a separate but related application in 2012 for the identical product does not change this analysis. To the contrary, although the subsequent application may have been assigned a new NDA number for administrative purposes, it must be treated as a continuation of the original NDA for exclusivity purposes. This is especially true where, as here, Astellas performed no new studies in support of its application between the time of withdrawal and resubmission of its NDA. Study 158 and Study 12-03 – which FDA cited in its Summary Review of the Astagraf XL NDA as the only clinical trials providing the basis for the drug's three-year exclusivity – were completed (and FDA's Summary Review suggests FDA had reviewed the studies) *before* Astellas withdrew its NDA in 2009. (Bragg Decl. Ex. K at 7.) Indeed, the Summary Review expressly references Astellas's withdrawn NDA as a "related NDA" to the 2012 Astagraf XL NDA. (*Id.*)[14]

[14] In other contexts, the FDCA highlights the relatedness between a withdrawn NDA and a subsequent application submitted by the same applicant for the same product. For example, under PDUFA, 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. 21 U.S.C. § 379h(a)(1)(C).

Treating the resubmission of the Astagraf NDA as anything other than a continuation of the original NDA for exclusivity purposes conflicts with the language, structure, and goals of the QI Act, and facilitates manipulative and anti-competitive behavior by sponsors of pre-repeal antibiotics, to the detriment of patients.[15] Doing so also fundamentally alters the incentive structure adopted by Congress by providing exclusivity to antibiotic products that already had been developed as of October 8, 2008 and thus were not considered by Congress to require additional incentives. "The FDA may not . . . change the incentive structure adopted by the Congress . . . ." *Ranbaxy Labs., Ltd. v. Leavitt*, 469 F.3d 120, 126 (D.C. Cir. 2006); *see also Teva Pharm. USA*, 595 F.3d at 1318 ("As Congress deliberately created the 180-day exclusivity bonus, the FDA cannot justify its interpretation by proudly claiming that it has eviscerated that bonus."). For all of these reasons, FDA's grant of exclusivity to Astagraf XL reflects an impermissible construction of the FDCA which is in excess of FDA's statutory authority and must be set aside under the APA. *See* 5 U.S.C. § 706(2)(C).

B. FDA Exceeded Its Statutory Authority in Applying Astagraf XL's Exclusivity to Envarsus XR

1. FDA's Decision Is Contrary To the Plain Language of the FDCA

Even if Astagraf XL is entitled to exclusivity, FDA's decision to apply that exclusivity to block immediate approval of Envarsus XR is based on a patently incorrect reading

[15] There is no evidence that Congress intended exclusivity for pre-repeal antibiotics to hinge on purely administrative actions that are solely within the control of, and thus subject to manipulation by, NDA applicants. To the contrary, the QI Act was specifically intended to "prevent pharmaceutical manufacturers from abusing the process to extend the life of old active ingredient drugs." 153 Cong. Rec. S5823 (daily ed. May 9, 2007) (statement of Sen. Kennedy). In a similar situation, the D.C. Circuit held that the availability of 180-day exclusivity did not hinge on an action solely within the control of an innovator drug company (delisting a patent from the FDA Orange Book), since this was subject to manipulation and inconsistent with the goals of the Hatch-Waxman Amendments. *See Teva Pharm. USA, Inc. v. Sebelius*, 595 F.3d 1303, 1317 (D.C. Cir. 2010).

of the relevant statutory language, which is inconsistent with Congressional intent. The three-year period of exclusivity granted to Astagraf XL under Section 505(c)(3)(E)(iii) does not, as a matter of law, apply to Envarsus XR because the Envarsus XR NDA does not reference Astagraf XL as a listed drug, rely on any Astagraf XL data or studies, or rely on FDA's findings of safety and effectiveness for Astagraf XL.[16]

Here, "'Congress has directly spoken to the precise question at issue.'" *Mova Pharm.*, 140 F.3d at 1067 (quoting *Chevron*, 467 U.S. at 842, 104 S. Ct. at 2781). The FDCA provides that if an NDA is approved and awarded three-year exclusivity based upon "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant," FDA may not approve a pending 505(b)(2) application "for the conditions of approval" of the first drug for a period of three years *if* the safety and effectiveness studies "*relied upon* by the [505(b)(2) applicant] for approval of the [505(b)(2)] were not conducted by or for [the 505(b)(2) 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) (emphasis added). This statutory language unambiguously requires an overlap in the relied upon studies to trigger the period of exclusivity. In the absence of such overlap, exclusivity is inapplicable as a matter of law.

[16] FDA's Tentative Approval letter also referred to Astagraf XL's exclusivity under Section 505(j)(5)(F)(iii) and did not specify which provision FDA believed applied to Envarsus XR. (Bragg Decl. Ex. C at 1-2.) As a matter of law, however, any exclusivity granted to Astagraf XL under Section 505(j)(5)(F)(iii) is irrelevant to Envarsus XR because that section only bars subsequent ANDAs. *See* 21 U.S.C. § 355(j)(5)(F)(iii) (referencing applications submitted under Section 505(j)). Envarsus XR was not eligible for approval as a 505(j) ANDA to Prograf or Astagraf XL due to its different dosage form, dosing regimen, and pharmacokinetic properties. *See* FDA 505(b)(2) Guidance at 5-6.

FDA's implementing regulation is faithful to the statutory language and confirms that reliance upon data essential to the approval of the first-in-time NDA is a necessary precondition to exclusivity. The regulation provides that:

> [If an NDA is approved based upon] reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant that were essential to approval of the [NDA], [FDA] will not make effective for a period of 3 years after the date of approval of the [NDA] the approval of a 505(b)(2) application . . . for the conditions of approval of the [NDA] . . . that ***relies on*** the information supporting the conditions of approval of an original new drug application.

21 C.F.R. § 314.108(b)(4)(iv) (2014) (emphasis added). The regulation's reliance requirement makes perfect sense in that Congress's clear intent was to incentivize drug manufacturers to conduct the time-consuming and expensive studies necessary to obtain FDA approval, yet make those same studies available to third parties desiring to enter the market with a competitive drug after a period of exclusivity.

It is undisputed that the Envarsus XR NDA did not rely upon any studies conducted to support the Astagraf XL NDA, rely upon FDA's prior findings of safety and effectiveness for Astagraf XL, or reference Astagraf XL as a listed drug. (Mc Guinness Decl. ¶¶ 26, 28.) Accordingly, as a matter of law, Astagraf XL's Section 505(c)(3)(E)(iii) exclusivity does not apply to the Envarsus XR NDA.

2. FDA's Decision Is Contrary To The Language, Structure, and Purpose of the Hatch-Waxman Amendments

The structure and purpose of the Hatch-Waxman Amendments further confirm that FDA's application of Astagraf XL's Section 505(c)(3)(E)(iii) exclusivity to the Envarsus XR NDA is contrary to Congressional intent. *See Amalgamated Transit Union*, 894 F.2d at 1368. The language of the Hatch-Waxman Amendments must be interpreted in light of the Amendments' structure and purpose. *See, e.g., Mova Pharm.,* 140 F.3d at 1067 ("[I]n

expounding a statute, we must not be guided by a single sentence or member of a sentence, but look to the provisions of the whole law, and to its object and policy.") (internal quotation marks omitted).[17]

The Hatch-Waxman Amendments created a streamlined approval procedure that significantly reduced the time and resources necessary to bring certain competing products to market by allowing them to rely upon the safety and effectiveness data generated for previously approved products. *See* 21 U.S.C. §§ 355(b)(2), 355(j). At the same time, to compensate companies for others' use of their proprietary data in this manner, and to maintain incentives for innovation, the Hatch-Waxman Amendments created, among other things, certain periods of non-patent exclusivity. *See* CDER FAQ.

Significantly, however, exclusivity is not intended to interfere with legitimate competition in the marketplace among innovative products that do not rely upon each other's data.[18] FDA has confirmed that the Hatch-Waxman Amendments establish a necessary relationship between (i) the "new clinical trials" that justify exclusivity, (ii) the "conditions of approval" based upon those studies, and (iii) the scope of the information relied upon by the

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[17] *See also* Letter from Steven K. Galson, Acting Dir., CDER, to Donald O. Beers, Arnold & Porter LLP et al., at 6 (Nov. 30, 2004) (FDA Docket No. 2004-P-0386) (FDA's interpretation of a specific Hatch-Waxman provision "looks not at these eight words in isolation but at the entire patent certification provision in context and at the Hatch-Waxman statutory scheme as a whole.") (Bragg Decl. Ex. L.)

[18] For this reason, exclusivity does not block approval of full NDAs submitted under Section 505(b)(1) of the FDCA, which do not rely upon any third-party data for approval. *See, e.g.*, CDER FAQ (explaining that "the new drug product exclusivity provisions of the Act [do not] provide any protection from the marketing of a duplicate version of the same drug product if the duplicate version is the subject of a full new drug application submitted under 505(b)(1) of the Act").

subsequent applicant.[19] For example, in response to citizen petitions, FDA has explained that "[w]hile [the] five- and three-year *exclusivity* periods [of Section 505(c)(3)(D)(ii)-(iv) and (j)(5)(D)(ii)-(iv)] are in effect, FDA may not accept or approve certain applications *that rely on the protected product for approval*." Letter from Janet Woodcock, Dir., CDER, to Katherine M. Sanzo, Morgan Lewis & Bockius, LLP et al., at 5 (Oct. 14, 2003) (FDA Docket Nos. 2001-P-0323, 2002-P-0447, and 2003-P-0408) (emphasis added in part) (Bragg Decl. Ex. N). Most recently, in 2013, FDA affirmed that "[a] 505(b)(2) applicant is subject to applicable periods of marketing exclusivity *granted to the listed drug relied upon* . . . ." Letter from Janet Woodcock to David B. Clissold, Hyman, Phelps, & McNamara P.C., at 4 (Sept. 18, 2003) (FDA Docket Nos. 2011-P-0869 and 2013-P-0995) (emphasis added) (Bragg Decl. Ex. O).

The language, structure, and purpose of the Hatch-Waxman Amendments all establish that Congress intended three-year marketing exclusivity under Section 505(c)(3)(E)(iii) to block approval of only those 505(b)(2) applications that rely upon the data supporting the approval of the drug with exclusivity. As the Envarsus XR NDA does not rely upon the clinical studies conducted by Astellas in connection with the Astagraf XL NDA, FDA's application of

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[19] *See* Letter from Keith O. Webber, Deputy Dir., Office of Pharm. Sci., CDER, to Kevin McKenna, Vice President, Regulatory Affairs, AstraZeneca, at 7-8 (Mar. 27, 2012) (FDA Docket No. 2011-P-0662) (discussing a related three-year exclusivity provision and explaining that "[t]he statute sets up a relationship between the 'new clinical investigations' that are 'essential to the approval of the [application],' and the scope of exclusivity. That is, if an applicant [receives] 3-year exclusivity for a change in the use of the drug product supported by new clinical investigations, the FDA may not approve an [application] *referencing that drug product* for the 'change approved in the supplement' during that 3-year exclusivity period.") (emphasis added) (Bragg Decl. Ex. M). In *AstraZeneca Pharm. LP v. FDA*, Judge Kollar-Kotelly upheld FDA's interpretation requiring reliance. 850 F. Supp. 2d 230, 235 (D.D.C. 2012). *See also Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996) (agreeing with FDA's interpretation that the scope of a related exclusivity provision was limited to the "proprietary research" undertaken to support approval of a particular indication).

Astagraf XL's exclusivity to Envarsus XR is contrary to the FDCA's plain language, in excess of the FDA's statutory authority, and in violation of the APA. *See* 5 U.S.C. § 706(2)(C). Veloxis therefore is entitled to a declaration and injunction requiring FDA to faithfully apply the statutory language by granting immediate final approval of the Envarsus XR NDA.

C. FDA's Decision is Arbitrary and Capricious

Even if FDA's interpretation of Section 505(c)(3)(E)(iii) is permissible (which it is not), FDA's application of Astagraf XL's exclusivity to Envarsus XR cannot stand because it is arbitrary and capricious. The APA's arbitrary and capricious standard requires the court to determine whether the agency has "'examine[d] the relevant data and articulate[d] a satisfactory explanation for its action including a rational connection between the facts found and the choice made.'" *Nat'l Fuel Gas Supply Corp. v. FERC*, 468 F.3d 831, 839 (D.C. Cir. 2006) (quoting *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43, 103 S. Ct. 2856, 2866 (1983)) (alteration in original). In so doing, the court must "consider whether the decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment." *State Farm*, 463 U.S. at 43, 103 S. Ct. 2856 at 2866-67 (citations omitted). An agency acts arbitrarily or capriciously if it "has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise." *Id.* Here, FDA's application of Astagraf XL's exclusivity to block approval of

Envarsus XR is arbitrary and capricious because it runs counter to the evidence before FDA and departs from longstanding FDA policy and precedent.[20]

1. Envarsus XR and Astagraf XL Do Not Share Conditions of Approval

The only reason FDA has provided for refusing to immediately approve Envarsus XR is the assertion that Envarsus XR and Astagraf XL "share conditions of approval." (Bragg Decl. Ex. C at 1-2.) Consistent with longstanding FDA precedent, however, because the two drugs have markedly different (i) dosage forms, (ii) dosing strengths, (iii) dosing regimens, and (iv) pharmacokinetic profiles, they cannot be considered to share conditions of approval.

(a) Different Dosage Forms

The statutory exclusivity granted to Astagraf XL is defined in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") as covering a "New Dosage Form." This FDA description of Astagraf XL's exclusivity is important because, as FDA previously has explained, "[e]xclusivities, including 3-year exclusivity, are published in the Orange Book *to put ANDA and 505(b)(2) applicants on notice regarding the scope and expiration dates of potential barriers to approval*." Letter from Keith O. Webber, Deputy Dir., Office of Pharm. Sci., CDER, to Kevin McKenna, Vice President, Regulatory Affairs,

[20] FDA also has failed to provide an adequate explanation for its decision to apply Astagraf XL's exclusivity to Envarsus XR. A "fundamental requirement of administrative law is that an agency set forth its reasons for decision; an agency's failure to do so constitutes arbitrary and capricious agency action." *Tourus Records, Inc. v. DEA*, 259 F.3d 731, 737 (D.C. Cir. 2001) (internal quotation marks omitted). "The agency's statement 'must be one of 'reasoning;' it must not be just a 'conclusion;' it must 'articulate a satisfactory explanation' for its action.'" *Butte Cnty., Cal. v. Hogen*, 613 F.3d 190, 194 (D.C. Cir. 2010) (quoting *Tourus Records*, 259 F.3d at 737). FDA's Tentative Approval letter asserts that Envarsus XR and Astagraf XL "share conditions of approval" but does not identify the purportedly shared conditions. Indeed, FDA has yet to articulate such conditions despite Veloxis's explicit request that FDA do so. FDA has offered only a "conclusion," not the "satisfactory explanation" the APA demands.

AstraZeneca, at 6 (Mar. 27, 2012) (FDA Docket No. 2011-P-0662) (Bragg Decl. Ex. M) (emphasis added). Given FDA's description, to be blocked by Astagraf XL's exclusivity, a subsequent product must share, at a minimum, Astagraf XL's unique dosage form. Envarsus XR, however, does not share even this most fundamental "condition of approval" as Astagraf XL is a *capsule* and Envarsus XR is a *tablet*.

FDA repeatedly has ruled that capsules and tablets are different "dosage forms" for regulatory purposes. Indeed, FDA has declined to treat tablets and capsules as presumptively interchangeable for the important reason that drugs dispensed through these different mediums may have different properties. *See, e.g.*, Letter from Janet Woodcock to Alan H. Kaplan, Kleinfeld, Kaplan & Becker et al. (Dec. 1, 2000) (FDA Docket Nos. 95-P-0262 and 96-P-0317) (Bragg Decl. Ex. P). Here, Astagraf XL's *capsule* and Envarsus XR's *tablet* are particularly distinct because Envarsus XR employs Veloxis's patented MeltDose technology, which improves the rate and extent that tacrolimus is absorbed. (Weinberg Decl. ¶ 22.) Envarsus XR and Astagraf XL thus do not share the "New Dosage Form" condition of approval cited in the Orange Book as the basis for Astagraf XL's exclusivity.

(b) Different Dosage Strengths

Envarsus XR is available in 0.75, 1.0, and 4.0 mg dosage strengths. (*Id.* ¶ 16.) In contrast, Astagraf XL is available in 0.5, 1.0, and 5.0 mg dosage strengths – the same strengths as Prograf, the twice-daily formulation of tacrolimus. (*Id.*) Given the overlapping dosage strengths of Astagraf XL and Prograf, medication errors have been reported in Europe, which resulted in serious adverse events, including kidney graft rejection. (*Id.*) In light of these medication errors, in October 2009, *FDA requested* that Veloxis develop Envarsus XR in different dosage strengths in order to help avoid such medication errors. (*Id.*) Veloxis agreed to

do so and developed Envarsus XR in 0.75, 1.0, and 4.0 mg dosage strengths. (*Id.*) The different dosage strengths prevent the drugs from sharing this "condition of approval."

(c) Different Dosing Regimens

The dosing regimens for Envarsus XR and Astagraf XL also differ in a number of significant respects. In particular, the FDA-approved labels for Envarsus XR and Astagraf XL reflect different starting doses, different target trough levels (blood levels used by physicians treating patients with tacrolimus to ensure appropriate dosing), and different timing for reducing ("stepping down") tacrolimus dosing after an initial period post-transplant. (*Id.* ¶ 35.) In addition, because Veloxis opted to conduct a clinical trial program to study and establish appropriate dosing for patients converting to Envarsus XR from once-daily Prograf, the Envarsus XR label contains conversion instructions to guide physicians. (*Id.* ¶¶ 34-35.) The Astagraf XL label contains no such instructions, leaving physicians to guess as to appropriate conversion doses, and leaving patients at risk of under dosing. (*Id.* ¶ 34; Bloom Decl. ¶ 12.) Each of these critical differences reflects differing "conditions of approval."

(d) Different Pharmacokinetic Profiles

As Dr. John Weinberg and Dr. Roy Bloom state in their declarations, Envarsus XR and Astagraf XL exhibit materially different pharmacokinetic profiles. (Weinberg Decl. ¶¶ 18-30; Bloom Decl. ¶ 6.) At the same dosage as Astagraf XL, Envarsus XR shows greater but slower absorption, and a flatter profile (*i.e.*, less significant "peaks" and "troughs"). (*Id.* ¶¶ 6-7.) Indeed, the pharmacokinetic profiles of Envarsus XR and Astagraf XL are so markedly different that a generic for one drug would not be suitable as a generic for the other because both the rate and extent of absorption of tacrolimus are significantly different for the two drugs. *Cf.* Envarsus XR Package Insert, Section 5.3 ("ENVARSUS XR is not interchangeable or substitutable with

tacrolimus immediate-release products or other tacrolimus extended-release products.") (Bragg Decl. Ex. C, encl. 1 at 5.) Given the marked differences in the drugs' pharmacokinetic profiles, Envarsus XR and Astagraf XL cannot be considered to share this "condition of approval."

2. FDA's Decision Departs From Long-Standing FDA Policy and Precedent

Although FDA has never identified the "conditions of approval" purportedly shared by Envarsus XR and Astagraf XL, Astellas's non-public September 12, 2014 letter to FDA argues that its exclusivity "encompass[es] the once daily formulation of tacrolimus indicated for the prophylaxis of organ rejection in transplant patients regardless of patient setting, and no application for those conditions can be approved until the expiration of the exclusivity period on July 19, 2016."[21] (*Id*. Ex. E, encl. 4 at 2.) More than twenty years of precedent, however, establishes that FDA has consistently approved 505(b)(2) applications for drugs that – like Envarsus XR and Astagraf XL – share active ingredients, indications, dosage forms, and other conditions of approval with drugs subject to statutory exclusivity, where the 505(b)(2) application does not rely upon data supporting approval of the drug with exclusivity.

For example, on August 1, 2000, FDA approved an NDA for Concerta® (extended-release methylphenidate tablets), a once-daily treatment for Attention Deficit

[21] Section 505(q)(1)(A) of the FDCA provides that FDA may not delay approval of a pending 505(b)(2) application because of any request to take action (such as a request to apply another product's three-year exclusivity) unless, *inter alia*, the request is made as a publicly filed "citizen petition." 21 U.S.C. § 355(q)(1)(A). Based on this requirement, FDA generally will refuse to consider information submitted by a drug manufacturer to its own NDA that could delay the approval of another application unless the information is filed as a citizen petition. *See* Letter from Nancy K. Hayes, Acting Dir., Office of Regulatory Policy, CDER, to Dennis Ahern, Sr. Dir., Regulatory Affairs, Teva Pharm. USA, at 2 (June 9, 2014) (FDA Docket No. 2013-P-1641) (Bragg Decl. Ex. Q). Here, however, FDA allowed Astellas to submit a request to delay approval of the Envarsus XR NDA via private correspondence rather than through a citizen petition, in violation of Section 505(q)(1)(A). In doing so, FDA violated both the letter and spirit of Section 505(q)(1)(A), and acted in a manner that was arbitrary, capricious, and contrary to law.

Hyperactivity Disorder ("ADHD"). (*Id*. Ex. R at 1.) Concerta was granted three-year exclusivity. (*Id*. Ex. S at 2.) Nevertheless, on April 3, 2001, FDA approved a 505(b)(2) application for Metadate CD® (20 mg extended-release methylphenidate capsules). (*Id*. Ex. T at 1.) Like 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. Also like the current situation, Concerta and Metadate CD are approved in different dosage forms (*i.e.*, extended-release tablets and extended-release capsules, respectively). As a result of this critical difference, Concerta's exclusivity did not block approval of Metadate CD.

Similarly, on February 28, 2000, FDA granted final approval to Androgel® 1%, a transdermal testosterone gel indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone ("Low T"). (*Id*. Ex. U at 1.) FDA also granted Androgel 1% three-year "new dosage form" exclusivity (covering 25 and 50 mg doses). (*Id*. Ex. V at 2.) Notwithstanding the exclusivity granted to Androgel 1%, on October 31, 2002, FDA granted final approval to Testim® 1%, another transdermal testosterone gel indicated for replacement therapy of testosterone, with a starting dose of 50 mg. (*Id*. Ex. W at 1.) The FDA Medical Officer's Clinical Review of Testim 1% expressly observed that "a similar topical testosterone gel for men was approved by the Division in February 2000" and that Testim 1% was "not [a new molecular entity], 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." (*Id*. Ex. X at 14.) The Testim 1% NDA, however, did not reference Androgel 1%, nor did it rely on any clinical studies performed in connection with the approval of Androgel 1%; rather, the applicant conducted its own studies. (*Id.*) As a result, notwithstanding the shared conditions of approval between the drugs, Androgel 1%'s exclusivity did not block final approval of Testim 1%.

Ten years later, FDA again granted overlapping exclusivity periods to multiple transdermal testosterone products. On November 23, 2010, FDA approved an NDA for Axiron®, a transdermal metered testosterone solution, to treat Low T (*Id*. Ex. Y at 1), and granted Axiron three-year exclusivity (*Id*. Ex. Z). Notwithstanding this exclusivity, on December 29, 2010, FDA approved a 505(b)(2) application for Fortesta®, a transdermal metered testosterone gel (*Id*. Ex. AA at 1), which also received three-year exclusivity (*Id*. Ex. AB at 1). And, on April 29, 2011, FDA approved a 505(b)(2) application for Androgel® 1.62%, another transdermal metered testosterone gel (Bragg Decl. Ex. AC at 1), which received its own three-year exclusivity (*Id*. Ex. AD at 1; *id*. Ex. AC.). The Fortesta and Androgel 1.62% 505(b)(2) applications did not rely upon data supporting approval of the prior testosterone transdermal products with exclusivity. (*Id*. Ex. AE at 1; *id*. Ex. AF at 1.) Presumably for this reason, FDA approved Fortesta and Androgel 1.62% during the periods of statutory exclusivity granted to Axiron and Fortesta, even though the drugs all share active ingredients and indications. Indeed, Androgel 1.62% was approved during Fortesta's statutory exclusivity period even though both drugs share the same dosage form (transdermal metered gel).

These examples confirm that, throughout the twenty years since the Hatch-Waxman Amendments were enacted, FDA repeatedly has approved 505(b)(2) applications for products that share a common active ingredient, indication, dosage form, and dosage frequency with a drug subject to exclusivity. FDA has done so because the later-in-time applications did not rely on data necessary to the approval of the drug with exclusivity. Indeed, Veloxis is not aware of a single instance in which FDA has applied exclusivity to block approval of a product with a different dosage form that did not reference or rely upon the drug with exclusivity.

The APA's requirement of reasoned decision-making "necessarily requires the agency to acknowledge and provide an adequate explanation for its departure from established precedent." *Dillmon v. NTSB*, 588 F.3d 1085, 1089-90 (D.C. Cir. 2009). Here, FDA has departed from its consistent practice of the past twenty years by applying exclusivity to Envarsus XR even though it does not rely upon Astagraf XL data, reply upon FDA's prior findings of safety and effectiveness for Astagraf XL, or reference Astagraf XL as a listed drug. FDA's failure to explain this departure renders its action arbitrary and capricious. *See Ramaprakash v. FAA*, 346 F.3d 1121, 1124 (D.C. Cir. 2003) ("[A]gency action is arbitrary and capricious if it departs from agency precedent without explanation."). For this additional reason, the Court must "hold unlawful and set aside" FDA's decision. 5 U.S.C. § 706(2)(A).

II. Veloxis Will Suffer Irreparable Harm In The Absence Of Preliminary Relief

Preliminary injunctive relief is appropriate where, as here, a plaintiff is likely to suffer harm for which there is no adequate compensatory or other relief. *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 28-29 (D.D.C. 1997) (where no compensatory action will abate economic harm, balance tips towards injunctive relief); *see also Chaplaincy of Full Gospel Churches v. England*, 454 F.3d 290, 297 (D.C. Cir. 2006) (holding that an irreparable harm is a harm that is "beyond remediation").

A. Veloxis Will Suffer Severe, Unrecoverable Economic Loss

Courts have found irreparable harm where a small company is prevented from selling, or will lose its market for, its only product or products. *See, e,g., Smoking Everywhere, Inc. v. FDA*, 680 F. Supp. 2d 62, 76-77 (D.D.C. 2010) (finding that FDA's decision to block small companies' importation of electronic cigarettes, which were their only product, threatened the companies' viability and caused irreparable harm) *aff'd sub nom. Sottera, Inc. v. FDA*, 627 F.3d 891, 898 (D.C. Cir. 2010); *CollaGenex*, 2003 WL 21697344, at *10-11 (small

pharmaceutical company with one primary product granted a preliminary injunction preventing larger, generic competitors from entering the market where the court found that the market for the company's only drug would have collapsed, threatening the company's continued viability).

Courts similarly have held that FDA's delay of final approval for a new drug may cause irreparable harm. For example, in *TorPharm*, FDA gave tentative approval to TorPharm's generic drug, delaying final approval until a competitor's period of exclusivity expired. 1997 WL 33472411, at *2. The court held that TorPharm would suffer an irretrievable monetary loss for which there is no remedy at law because the delay would cause it to be permanently disadvantaged in the market and it would lose an estimated $400 million in anticipated sales. *Id.* at *4. Accordingly, the court issued an injunction compelling FDA to immediately grant final approval to TorPharm's new drug. *Id*. at *1.

Here, similar to both *CollaGenex* and *TorPharm*, FDA's decision delaying the release of Envarsus XR until at least July 2016 will cause Veloxis irreparable harm given the severity of the consequences Veloxis will suffer. In particular:

- Envarsus XR is Veloxis's only revenue-generating product, one which it spent more than ten years and $200 million developing. (Polvino Decl. ¶ 23; Mc Guinness Decl. ¶ 5.)

- Based on Envarsus XR's strong clinical results and Veloxis's positive dialogue with FDA regarding approval, Veloxis established the commercial, regulatory, and quality infrastructure to support a January 2015 launch of Envarsus XR in the United States. (Polvino Decl. ¶ 25.)

- The FDA-imposed delay will deprive Veloxis of any revenue from the United States market until July 2016, including approximately $20 million in anticipated revenue during that period, and will cause Veloxis to have lower peak revenue during the years before expiration of Envarsus XR's patent protection. (*Id.* ¶ 33.)

- Veloxis may not have sufficient funds to sustain its operations until July 2016, the soonest Envarsus XR might be finally approved under FDA's current decision. (Polvino Decl. ¶ 27.)

Indeed, these harms to Veloxis threaten the company's viability in its current form. (Polvino Decl. ¶¶ 24, 34.) *See Wash. Metro. Area Transit Comm'n v. Holiday Tours, Inc.*, 559 F.2d 841, 843 (D.C. Cir. 1977) (finding irreparable harm where, absent a stay, the plaintiff would suffer "destruction in its current form"); *Smoking Everywhere*, 680 F. Supp. 2d at 76 (finding that loss of electronic cigarette sales "will deprive [companies] of needed revenue and thus threaten the continued viability of their respective enterprises"); *CollaGenex*, 2003 WL 21697344, at *9 ("CollaGenex has shown that it could suffer devastating losses that would affect its viability.").

The significance of this harm is compounded by the fact that Veloxis never will be able to recover money damages from FDA because "sovereign immunity shields the federal government and its agencies, like FDA, from suit." *Smoking Everywhere*, 680 F. Supp. 2d at 77 n.19 (citing *FDIC v. Meyer*, 510 U.S. 471, 475, 114 S. Ct. 996, 1000 (1994)). Courts in this District repeatedly have held that a plaintiff's inability to recover money damages is a factor that favors a finding of irreparable harm. *See, e.g.*, *Feinerman v. Bernardi*, 558 F. Supp. 2d 36, 51 (D.D.C. 2008) (Walton, J.) (internal citations omitted); *Smoking Everywhere*, 680 F. Supp. 2d at 77 n.19 (noting that even if "economic injury did not threaten plaintiffs' viability, it is still irreparable because plaintiffs cannot recover money damages against FDA").[22]

[22] Although this Court recently distanced itself from its *Feinerman* decision, it nevertheless confirmed that a party's inability to recover economic losses is "a factor" to be considered in determining whether the movant has shown irreparable harm. *Converdyn v. Moniz*, No. 14-1012, 2014 U.S. Dist. LEXIS 127838, at *32 (D.D.C. Sept. 12, 2014) (Walton, J.). As discussed above, this factor is particularly pertinent here given that a delayed launch may threaten the viability of Veloxis's business. (*See* Polvino Decl. ¶ 27 (explaining that Veloxis may not have sufficient funds to sustain its operations until July 2016).)

B. Veloxis Will Suffer Substantial Injuries Which Cannot Be Redressed Monetarily

Veloxis will be irreparably harmed for the additional reason that, absent preliminary relief, it will suffer harms that cannot be redressed monetarily. *First*, Veloxis likely will be forced to reduce its workforce by between fifty and ninety percent, and rescind offers of employment made in anticipation of Envarsus XR's launch. (Polvino Decl. ¶¶ 26-27.) Employee layoffs and the loss of personnel constitute irreparable harm. *See Express One Int'l, Inc. v. U.S. Postal Serv.*, 814 F. Supp. 87, 91 (D.D.C. 1992) (finding irreparable harm where, among other things, a company would have to lay off employees); *see also Hospira v. Burwell*, No. 14-02662, 2014 WL 4182398, at *4 (D. Md. Aug. 19, 2014) (finding irreparable harm where, among other things, FDA's approval of multiple generic drugs would cause a name-brand manufacturer to lay off part of its sales force). In *AstraZeneca LP v. Apotex, Inc.*, for example, the court held that "the damage caused by a loss in personnel and the impact this would have on the company are indeed significant and unquantifiable." 623 F. Supp. 2d 579, 612 (D.N.J. 2009), *aff'd*, 633 F.3d 1042 (Fed. Cir. 2010). Likewise here, the layoff of fifty to ninety percent of Veloxis's workforce will have the same deleterious effects. (Polvino Decl. ¶¶ 27-28.)

Second, absent injunctive relief, Veloxis likely will have to cancel promising clinical studies of Envarsus XR, another form of irreparable harm. In *AstraZeneca*, the impairment of research and development activities due to employee layoffs was a basis for the court's finding of irreparable harm. 623 F. Supp. 2d at 612. Similarly, in *Bayer Healthcare*, the court found that Bayer would suffer irreparable harm if FDA approved a generic version of its brand-name drug in part because competition would result in lost funding for research and development of new drugs. 942 F. Supp. 2d at 25. Similarly here, the FDA decision to delay final approval of Envarsus XR likely will cause Veloxis to cancel a study of Envarsus XR's

superior efficacy in African-American patients, a study of its reduced neurotoxicity, and a "switching" study to determine correct conversion doses. (Polvino Decl. ¶¶ 18-22.)

Third, Veloxis will suffer damage to its reputation and goodwill. *See, e.g.*, *Armour & Co. v. Freeman*, 304 F.2d 404, 406 (D.C. Cir. 1962) (holding that damage to a company's reputation caused by Department of Agriculture's requirements that company affix an "imitation ham" label to its product constituted irreparable harm); *Bayer Healthcare*, 942 F. Supp. 2d at 25 (finding irreparable harm from FDA approval of a generic drug because competition would result in loss of customer goodwill). Here, Veloxis's reputation in the market, and among doctors who had been anticipating the release of Envarsus XR as an innovative and beneficial new drug, will suffer harm as a result of the delay in FDA approval, employee terminations, and canceled clinical research. (Polvino Decl. ¶ 31.)

III. The Balance of Equities Is In Favor Of Veloxis

The balance of equities weighs in favor of Veloxis. In contrast to the significant harm Veloxis will suffer without injunctive relief, FDA will not be injured if ordered to grant final approval to Envarsus XR. FDA's agency action confirms its determination that Envarsus XR is safe and effective for its intended use. Veloxis only seeks review of FDA's decision regarding exclusivity, which is a normal and not disruptive part of the administrative process. *See CollaGenex*, 2003 WL 21697344, at *9.

Additionally, the harm to Veloxis in the absence of injunctive relief outweighs any harm to Astellas if Envarsus XR is approved. Astellas will not suffer a substantial injury for it is not entitled to exclusivity against Envarsus XR. *See American Therapeutics, Inc. v. Sullivan*, 755 F. Supp. 1, 1-2 (D.D.C. 1990) (finding that FDA's inadvertent issuance of final approval to a drug did not give pharmaceutical company vested right to market drug). Moreover, Astellas cannot be said to suffer serious harm simply because of the mere existence of

competition from Envarsus XR. *See Wash. Metro. Area Transit Comm'n*, 559 F.2d at 843 n.3 ("The mere existence of competition is not irreparable harm, in the absence of substantiation of severe economic impact.").

Finally, the harm to Veloxis as a small, single-drug company outweighs any economic harm to Astellas resulting from increased competition. In *CollaGenex*, the court found that the balance of harms weighed in favor of a small pharmaceutical company with a limited product line and significant investment in a drug because any harm to a larger company with more resources was "comparatively minimal." 2003 WL 21697344, at *9. The same conclusion is warranted here. Astellas is part of a global pharmaceutical company that, in the Americas alone, has nearly 3,000 employees and $2.9 billion in revenue.[23] In the United States, Astellas markets eleven drug products in the areas of cardiology, dermatology, immunology, infectious disease, oncology, and urology and boasts a "robust pipeline of products in clinical development."[24] Thus any harm to Astellas as a result of Envarsus XR's approval is far outweighed by the severe negative impact of the FDA decision to delay until 2016 the release of Veloxis's only product into the market.

IV. The Public Interest Strongly Favors Injunctive Relief

Finally, the public interest is best served by the immediate approval of Envarsus XR for several reasons. *First*, immediate approval of Envarsus XR will provide patients with numerous potential clinical benefits, including:

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[23] Astellas, https://www.astellas.us/about/profile/index.aspx (last visited Dec. 10, 2014). (Bragg Decl. Ex. AG at 2.)

[24] Astellas, https://www.astellas.us/therapeutic/product/index.aspx (last visited Dec. 10, 2014). (Bragg Decl. Ex. AH at 2-3); Astellas, https://www.astellas.us/therapeutic/rnd/index.aspx (last visited Dec. 10, 2014). (Bragg Decl. Ex. AI at 2).

- reduction in tacrolimus's severe or even debilitating side effects, such as tremors from neurotoxicity (Langone Decl. ¶¶ 11, 13-15, 18; Bloom Decl. ¶¶ 5, 7);
- fuller and faster absorptions, which may reduce early transplant rejections, incidences of delayed graft function, the length of hospital stays, and burdensome post-release testing (Polvino Decl. ¶¶ 7-10; Bloom Decl. ¶¶ 10-11);
- potentially significant benefits to African-American and other patient groups who have high unmet needs (Polvino Decl. ¶¶ 11-16; Bloom Decl. ¶¶ 8-9, 13, 16); and
- guidance to physicians who wish to convert patients from twice-daily Prograf (Weinberg Decl. ¶¶ 32, 34-35; Bloom Decl. ¶ 13).

Second, the public has a vital interest in having innovative new drugs come to market, and in encouraging pharmaceutical companies to invest in the development of innovative new drugs. *See* FDA 505(b)(2) Guidance at 3 (explaining that 505(b)(2) is "intended to encourage innovation in drug development"). Veloxis has invested substantially in the development of Envarsus XR, including undertaking a rigorous and expensive clinical testing program. (Mc Guinness Decl. ¶¶ 15-19.) As demonstrated by its orphan drug designation, Envarsus XR is different from, and indeed plausibly superior to, currently marketed tacrolimus therapies. (*Id.* ¶¶ 23-24.) The public has an interest in such innovative new drugs coming to market and in incentivizing companies, like Veloxis, to develop and sponsor them.

Third, "there is . . . a strong public interest in requiring an agency to act lawfully, consistent with its obligations under the APA, ..." *Bracco Diagnostics*, 963 F. Supp. at 30; *TorPharm*, 1997 WL 33472411, at *5 ("The public interest in . . . the correct application of the statute favors issuance of the injunction."). Here, the public interest favors injunctive relief correcting FDA's misapplication of the exclusivity provisions.

Fourth, the public has an important interest in increased competition in the drug industry. *TorPharm*, 1997 WL 33472411, at *5 (granting preliminary relief based in part on

public interest in competition among drug companies). Envarsus XR will present significant new competition for the currently marketed tacrolimus therapies.

CONCLUSION

For the reasons set forth above, Veloxis respectfully requests that the Court issue a preliminary injunction compelling FDA to grant final approval to Envarsus XR. A proposed order is attached.

Dated: December 17, 2014

Respectfully submitted,
/s/ Mitchell S. Ettinger

Jennifer L. Bragg (D.C. Bar No. 488946)
Mitchell S. Ettinger (D.C. Bar No. 415451)
Lauryn K. Fraas (D.C. Bar No. 984887)
Colin V. Ram (D.C. Bar No. 989848) *pro hac vice and admission pending*
SKADDEN, ARPS, SLATE, MEAGHER & FLOM LLP
1440 New York Avenue, N.W.
Washington, DC 20005
(202) 371-7000 (tel.)
(202) 393-5760 (fax)

Maya P. Florence (D.C. Bar No. 986139)
SKADDEN, ARPS, SLATE, MEAGHER & FLOM LLP
500 Boylston Street
Boston, MA 02116
(617) 573-4800 (tel.)
(617) 573-4822 (fax)

Attorneys for Plaintiff Veloxis Pharmaceuticals, Inc.

CERTIFICATE OF SERVICE

I hereby certify that on this date, the foregoing Motion and the accompanying Memorandum of Points and Authorities, declarations, and exhibits were filed and served electronically using the CM/ECF system to:

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

Attorney for Defendants

Dated: December 17, 2014

/s/ Mitchell S. Ettinger
MITCHELL S. ETTINGER (D.C. Bar No. 415451)

Attorney for Plaintiff Veloxis Pharmaceuticals, Inc.