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 SUMMARY JUDGMENT

Pursuant to Federal Rule of Civil Procedure 56 and the Court's Order (Dkt. 14) adopting the parties' Joint Proposed Scheduling Order (Dkt. 13), Plaintiff Veloxis Pharmaceuticals, Inc. ("Veloxis") moves the Court to find Defendant U.S. Food and Drug Administration's ("FDA") failure to grant immediate, full, and final approval to the New Drug Application filed by Veloxis for Envarsus XR™ to be "in excess of [its] statutory jurisdiction [or] authority," and "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law," 5 U.S.C. §§ 706(2)(A), (2)(C), and therefore to grant summary judgment in favor of Veloxis.

As set forth in the accompanying Memorandum of Points and Authorities, FDA's denial of immediate, full, and 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, 5 U.S.C. §§ 701 et seq.. Specifically, FDA's decision is erroneous as a matter of law for four independent reasons:

- *First*, according to the unambiguous statutory language of the Federal Food, Drug, and Cosmetic Act ("FDCA") and Congress's clear intent, as confirmed by thirty years of FDA's own precedent, any exclusivity granted to Astagraf XL 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 or upon FDA's prior findings that Astagraf XL is safe and effective.

- *Second*, under the plain language of the FDCA and FDA's own interpretation, the scope of Astagraf XL's exclusivity (if any) is limited to the scope of the "new clinical investigations" essential to its approval. Because Veloxis does not seek approval of Envarsus XR for the specific use studied in Astagraf XL's sole "new clinical investigation," Envarsus XR's full approval is not blocked by Astagraf XL's exclusivity.

- *Third*, under the FDCA, a later-in-time drug is blocked only to the extent it shares "conditions of approval" with a drug granted exclusivity. FDA arbitrarily and capriciously concluded that Envarsus XR and Astagraf XL share conditions of approval, ignoring the significant differences between the two drugs.

- *Fourth*, Envarsus XR is entitled to immediate final approval because Astagraf XL never was eligible for statutory exclusivity. For drug products like Astagraf XL, exclusivity is available only 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.

A Proposed Order is attached.

Dated: February 6, 2015

Respectfully submitted,
/s/ Mitchell S. Ettinger

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CERTIFICATE OF SERVICE

I hereby certify that on February 6, 2015, I caused a true and correct copy of the above-entitled Plaintiff's Motion for Summary Judgment and accompanying Memorandum of Points and Authorities, declaration, and exhibits, to be served via first-class mail and electronic mail to:

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Dated: February 6, 2015

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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)

[PROPOSED] ORDER GRANTING PLAINTIFF'S
MOTION FOR SUMMARY JUDGMENT

Upon consideration of the Motion for Summary Judgment filed by Plaintiff Veloxis Pharmaceuticals, Inc. ("Veloxis") and the memoranda in support thereof and in opposition thereto, it is hereby

ORDERED that Veloxis's Motion for Summary Judgment is **GRANTED**; and it is

FURTHER ORDERED that Defendant U.S. Food and Drug Administration immediately grant full and final approval to Veloxis's New Drug Application for Envarsus XR™.

SO ORDERED this __ day of _____, 2015.

_____
REGGIE B. WALTON
United States District Judge

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

VELOXIS PHARMACEUTICALS, INC.,	)	
	)	
	)	
Plaintiff,	)	
	)	
-v.-	)	Civil Action No. 14-cv-2126 (RBW)
	)	
	)	
UNITED STATES FOOD AND DRUG ADMINISTRATION, *et al.*,	)	HEARING REQUESTED
	)	
	)	
Defendants.	)	
	)	

MEMORANDUM OF POINTS AND AUTHORITIES
IN SUPPORT OF PLAINTIFF'S MOTION FOR SUMMARY JUDGMENT

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INTRODUCTION

Plaintiff Veloxis Pharmaceuticals, Inc. ("Veloxis") is a small, research-based pharmaceutical company seeking approval of its innovative drug product, Envarsus XR™. Envarsus XR is an extended-release tacrolimus tablet that reduces the potential for organ rejection in kidney transplant patients, a group with significant unmet medical needs. Veloxis's extensive clinical development program for Envarsus XR, undertaken with the advice and concurrence of the U.S. Food and Drug Administration ("FDA"), establishes that Envarsus XR is safe and effective and, in important respects, different from currently marketed tacrolimus drugs. These differences make Envarsus XR a meaningful new treatment option for kidney transplant patients and their physicians.

On December 28, 2013, following a decade of work and an investment of more than $200 million, Veloxis filed a New Drug Application ("NDA") with FDA seeking approval of Envarsus XR. FDA determined that Envarsus XR is safe and effective for its intended use. Nevertheless, FDA refuses to permit Veloxis to market Envarsus XR to the full population of kidney transplant patients for which it is safe and effective. FDA's action is based on a legally erroneous conclusion that the exclusivity granted to another drug, Astagraf XL®, blocks the immediate approval of Envarsus XR. FDA's decision emanates from a fundamentally flawed administrative process, and a series of *post hoc*, *ad hoc*, and arbitrary actions. FDA's action with regard to the Envarsus XR is inconsistent with the controlling statute and regulations as well as FDA's own precedent. Unless FDA's legally erroneous decision is reversed by this Court, many kidney transplant patients will be denied access to Envarsus XR until at least July 2016. Accordingly, Veloxis seeks declaratory and injunctive relief requiring FDA to comply with its statutory mandate and grant immediate, full, and final approval to the Envarsus XR NDA.

FDA's refusal to grant full and final approval to the Envarsus XR NDA is erroneous as a matter of law for four reasons:

- *First*, according to the unambiguous statutory language of the Federal Food, Drug, and Cosmetic Act ("FDCA") and Congress's clear intent – as confirmed by thirty years of FDA's own precedent – any exclusivity granted to Astagraf XL 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 or upon FDA's prior findings that Astagraf XL is safe and effective.

- *Second*, under the plain language of the FDCA and FDA's own interpretation, the scope of Astagraf XL's exclusivity (if any) is limited to the scope of the "new clinical investigations" essential to its approval. Because Veloxis does not seek approval of Envarsus XR for the specific use studied in Astagraf XL's sole "new clinical investigation," Envarsus XR's full approval is not blocked by Astagraf XL's exclusivity.

- *Third*, under the FDCA, a later-in-time drug is blocked only to the extent it shares "conditions of approval" with a drug granted exclusivity. FDA arbitrarily and capriciously concluded that Envarsus XR and Astagraf XL share conditions of approval, ignoring the significant differences between the two drugs.

- *Fourth*, Envarsus XR is entitled to immediate final approval because Astagraf XL never was eligible for statutory exclusivity. For drug products like Astagraf XL, exclusivity is available only 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.

For all these reasons, Veloxis respectfully moves this Court to find FDA's action to be "in excess of [its] statutory jurisdiction [or] authority," and "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law," 5 U.S.C. § 706(2)(A), (2)(C), and to grant summary judgment in favor of Veloxis.

STATEMENT OF FACTS

I. Statutory and Regulatory Background

A. Approval of Prescription Drugs

Under the FDCA, a new prescription drug may not be distributed in interstate commerce unless it has been approved by FDA. 21 U.S.C. § 355(a). Section 505 of the FDCA outlines three pathways for obtaining approval of a new drug. First, under Section 505(b)(1), a sponsor can submit a "full NDA." *Id.* § 355(b)(1). A full NDA must contain, *inter alia*, results from a battery of preclinical tests (laboratory and animal tests) and human clinical trials on the proposed drug product. *Id.* § 355(b)(1)(A); 21 C.F.R. § 314.50 (2014). FDA will not approve a full NDA unless the sponsor demonstrates by means of "adequate and well-controlled investigations" – usually extensive and expensive clinical trials – that the product is both safe and effective. 21 U.S.C. § 355(d); *see also Am. Bioscience, Inc. v. Thompson*, 269 F.3d 1077, 1079 (D.C. Cir. 2001). As a result, the process for obtaining approval of an innovative pharmaceutical product under Section 505(b)(1) is protracted, expensive and risk-laden. *Am. Bioscience*, 269 F.3d at 1079.

Second, 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).[1] The ANDA process allows the manufacturer to rely on FDA's prior findings that the previously approved drug is safe and effective, and to limit its clinical trials, if any, to relatively small bioequivalence studies. *Id.* Because of the limited

[1] A drug submitted for approval through an ANDA typically must have the same active ingredient, dosage form and strength, route of administration, labeling, quality, performance characteristics, and intended use as a previously approved drug. *See* 21 U.S.C. § 355(j); 21 C.F.R. § 314.92(a)(1) (2014).

testing and informational requirements for ANDAs, generic drugs can be brought to market more quickly and at less expense than innovative medicines.

Finally, under Section 505(b)(2), a sponsor may submit an application for a modification to a previously approved "listed drug" for which FDA 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 that the 505(b)(2) applicant does not own or for which it has not obtained a right of reference. This may include data from the previously approved drug, and must be coupled with data from new studies required to support the modifications to the previously approved drug. *Id.* In this way, the "Section 505(b)(2) NDA is a sort of hybrid of the other two pathways." *Takeda Pharm. U.S.A., Inc. v. Burwell*, No. 14-cv-1668 (KBJ), 2015 WL 252806, at *4 (D.D.C. Jan. 13, 2015). A 505(b)(2) application must identify the listed drug on which the applicant relies in seeking approval of its new drug product so that FDA may evaluate whether the application is impacted by any patent protection or statutory exclusivity. 21 C.F.R. § 314.54(a)(1)(iii) (2014).

B. Statutory Marketing Exclusivity

Congress created the 505(b)(2) and ANDA pathways as part of the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, also known as the "Hatch-Waxman Amendments." The Hatch-Waxman Amendments aimed to "'strik[e] a balance between [creating] incentives . . . for innovation,' on the one hand, and 'quickly getting lower-cost generic [and other competing] drugs to the market[,]' on the other." *Takeda Pharm.*, 2015 WL 252806, at *5 (second and fourth alteration and ellipsis in original) (quoting *Teva Pharm. Indus. Ltd. v. Crawford*, 410 F.3d 51, 54 (D.C. Cir. 2005)). To achieve these dual objectives, the expedited 505(b)(2) and ANDA approval pathways "permit sponsors to rely on what is already known about the previously approved drug, which allows for speedier

market entry than would be possible under the 505(b)(1) pathway and leads to increased competition." (FDA 00023.)[2] The Hatch-Waxman Amendments balance increased competition for approved drugs with rewards for the innovation and investment required to bring new drugs to market, in the form of periods of statutory marketing exclusivity and patent protection. (*Id*.)

Statutory exclusivity is intended to maintain incentives for companies to conduct time-consuming and costly clinical research, even in the absence of patent protection, 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. 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." *Id.*

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[2] Citations to the FDA Administrative Record in this case will appear as "FDA #."

[3] *See* Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,357 (Oct. 3, 1994).

C. Old Antibiotics

Although tacrolimus (the drug at issue here) is used as an immunosuppressant, it is considered an antibiotic drug. (FDA 00010.) 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. (FDA 00028.) 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. No. 105-115, § 125(d)(1), 111 Stat. 2296, 2325-27. 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 "old" 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. *See* 154 Cong. Rec. H10171 (daily ed. Sept. 27, 2008) (statement of Rep. Pallone). As part of the QI Program Supplemental Funding Act of 2008 ("QI Act"), Pub. L. No. 110-379, 122 Stat. 4075, Congress provided that an NDA for an old 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 incentives were unnecessary for drug products that already had been developed, Congress provided that such exclusivity could be granted only to old antibiotics that were the subject of new NDAs submitted to FDA after October 8, 2008. 21 U.S.C. §§ 355(v)(1)(B)(i), (3)(B). Congress thus did not authorize FDA to grant exclusivity to NDAs that were pending or approved on or before October 8, 2008.

II. Statement of Facts Derived from the Administrative Record

A. Immunosuppressant Therapies Prevent Rejection of Transplanted Kidneys

In 2013, there were 16,895 kidney transplants performed in the United States. (FDA 01627; FDA 01644.) 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. (FDA 00006.) Immunosuppressive drugs are used to decrease the body's immune response and thus prevent rejection of the transplanted organ, which can be fatal to the life-sustaining organ and the transplant recipient. (*Id.*) At the time of surgery, kidney transplant patients are referred to as *de novo* patients. (*Id.*) Immunosuppressive drugs generally are administered in combination with other drugs. (*Id.*) In particular, *de novo* patients frequently are dosed with an intensive level of immunosuppressive drugs – known as "induction" – from the time of transplant surgery until early after the surgery. (FDA 00006-7.)

Tacrolimus is a "narrow therapeutic index" drug, meaning that the active ingredient must be maintained in the patient's blood within a narrow range to avoid organ rejection, on the one hand, and potentially severe side effects, on the other. (FDA 00182-87.) As a result, the concentration and dosing of tacrolimus must be carefully managed and individually tailored for each transplant patient, and kidney transplant patients typically are required to undergo regular monitoring for months after receiving a new organ to establish the appropriate dosing regimen. (FDA 00007.) Once the appropriate regimen is established, patients are considered "maintenance," rather than *de novo* patients. (*Id.*) Maintenance patients remain on immunosuppressive therapy for the life of their transplanted kidney, but may replace one of the drugs in their immunosuppressive regimen with another drug for various reasons. This replacement process is known as "conversion." (FDA 00006; FDA 00008.)

Since 1994, a capsule version of tacrolimus has been marketed under the brand name Prograf® by Astellas Pharma US, Inc. ("Astellas") and its predecessor. (FDA 00009.) Prograf is no longer subject to any patent or exclusivity protection, and generic versions are available in the market. (FDA 00010, FDA 00016.) In 2013, FDA approved a new dosage form of tacrolimus – an extended-release capsule – also marketed by Astellas, under the brand name Astagraf XL. (FDA 00015.) Astagraf XL is approved for use in (1) *de novo* kidney transplant patients *with* induction, based upon the results of Astellas's Study 158, and (2) *de novo* kidney transplant patients *without* induction, based upon the results of Astellas's Study 12-03. (FDA 00015; FDA 00035) Astagraf XL is not approved for use in conversion patients. (FDA 00015-16.) Upon approval, Astagraf XL was granted three-year exclusivity, which FDA described with the notation "NDF" as pertaining to Astagraf XL's "new dosage form." (FDA 00016.)

Astellas initially submitted its NDA for Astagraf XL in 2005. (FDA 00010.) In 2007, FDA identified deficiencies in the NDA that Astellas would have to remedy in order to gain approval. (FDA 00011.) Under applicable FDA regulations, Astellas could have addressed these deficiencies without withdrawing its NDA. *See* 21 C.F.R. § 314.110(b) (2014). In 2009, however, Astellas chose to withdraw the Astagraf XL NDA. (FDA 00012.) In 2012, Astellas resubmitted the Astagraf XL NDA, but did not complete any new studies essential to its approval between withdrawing and resubmitting the NDA. (FDA 00015-16.)

B. History of the Envarsus XR NDA

Veloxis is a small specialty pharmaceutical company based in Edison, New Jersey engaged in the research and development of innovative drug products. (Compl. ¶ 16.) 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.* ¶ 45.) The clinical program for Envarsus XR spanned nearly 10 years and cost in excess of $200 million dollars. (*Id.* ¶ 3.) 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.* ¶¶ 3, 103; FDA 01629.)

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. (FDA 01629-30.) Veloxis repeatedly informed FDA that it would seek approval of Envarsus XR under Section 505(b)(2), and would reference only Prograf as the listed drug. (*See* FDA 01140 (noting that FDA "agreed with the 505(b)(2) route and provided advice on the Phase 1, Phase 2 and Phase 3 development").) 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"). (FDA 01629-30.) The SPA process permits a drug manufacturer to receive FDA feedback regarding the acceptability of a clinical trial design before beginning the trial. (FDA 01108-21.) Although securing an SPA adds time to the overall drug development process, it is designed to increase the predictability of regulatory review. FDA's agreement to the Study 3002 SPA reflected its conclusion that the design and planned analysis of Veloxis's proposed study would adequately address the objectives necessary to support the Envarsus XR NDA if the study outcomes were as expected. (FDA 01102.)

Veloxis's Phase III trial of Envarsus XR proved successful. On December 28, 2013, Veloxis submitted its NDA for Envarsus XR – an extended-release *tablet* form of tacrolimus – pursuant to Section 505(b)(2). (FDA 00016.) Based upon its Phase III clinical trials, Veloxis sought approval of Envarsus XR for (i) *de novo* kidney transplant patients *with* induction; and (ii) conversion patients. (*Id.*) Veloxis did not conduct studies in *de novo* kidney transplant patients *without* induction and thus did not seek approval of this use.

The Envarsus XR NDA identified and relied upon a single listed drug, Prograf, for the limited purpose of making use of pharmacology, clinical pharmacokinetic (*e.g.*, drug interaction studies), and pre-clinical animal toxicology data from studies conducted on Prograf. (*Id.*; Compl. ¶ 54.) By relying on this data, Veloxis avoided having to conduct duplicative testing on animals or human volunteers to establish what already was known about the basic safety and pharmacokinetics of tacrolimus. (FDA 00023; FDA 01946 ("It is wasteful and unnecessary to carry out studies to demonstrate what is already known about a drug.").) Veloxis relied upon no other listed drug in pursuing its NDA for Envarsus XR. (FDA 00016.) 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 prior findings of safety and effectiveness for Astagraf XL. (*Id.*) Rather, to establish the safety and effectiveness of its extended-release tablet product, Veloxis relied upon its own extensive clinical trials conducted on the proprietary Envarsus XR formulation pursuant to its own development program and the SPA agreement with FDA. (FDA 00016-17.)

Indeed, given the significant differences between Envarsus XR and Astagraf XL, it is unlikely that Veloxis could have relied upon Astagraf XL's data for approval. Envarsus XR was engineered using Veloxis's patented MeltDose® technology, which causes Envarsus XR to release tacrolimus in a slow and uniform manner. (FDA 01631-32.) This results in a markedly different pharmacokinetic profile than Astagraf XL. (*Id.*) At the same dose, Envarsus XR shows greater but slower absorption than Astagraf XL, and a flatter profile. (*Id.*; FDA 01645-77 (Decl. of Roy D. Bloom, M.D.) ¶ 6.) This means that patients taking Envarsus XR can achieve comparable blood levels of tacrolimus using approximately one-third lower dosage than if treated with Astagraf XL and experience more consistent blood levels throughout the 24-hour

dosing interval. (FDA 01631.) Longer absorption times and increased lower-limit concentrations of tacrolimus in a patient's blood may prevent levels from falling below the therapeutic range. (FDA 01645-77 ¶¶ 6-9.) It also may reduce the need for a patient to take additional doses of tacrolimus to maintain therapeutic levels (particularly patients, including 85% of African-American patients, who are rapid metabolizers of tacrolimus). (*Id.*)

FDA's deadline for acting on the Envarsus XR NDA was October 30, 2014.[4] 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. (FDA 01534-36.) 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." (FDA 01535.) 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.*)

Veloxis responded to FDA the next day. (FDA 01537-39.) 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 Information Request did not define the term "conditions of approval," Veloxis explained to FDA that Envarsus XR and Astagraf XL are substantially different products that do not share "conditions of approval" due to their different dosage forms, dosage strengths, dosing regimens, and pharmacokinetic profiles. (*Id.*)[5]

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[4] Under the Prescription Drug User Fee Act of 1992 ("PDUFA"), Pub. L. No. 102-571, 106 Stat. 4491, FDA is committed to meeting certain time standards for completing its review of NDAs.

[5] Veloxis emphasized Envarsus XR's and Astagraf XL's different dosage forms, in light of FDA's previous description of Astagraf XL's exclusivity as relating to its "New Dosage Form."

C. FDA's Non-Public Communications With Astellas

Although FDA first raised the exclusivity issue with Veloxis three days before FDA was required to act on the Envarsus XR NDA, unbeknownst to Veloxis, FDA began discussing the scope of Astagraf XL's exclusivity with Astellas months prior. (FDA 00018-19.) On September 12, 2014, Astellas sent a non-public letter to FDA as a "follow up to a discussion" that Astellas's Head of Global Regulatory Affairs apparently had with Dr. Renata Albrecht, the FDA division director who had reviewed and approved the Envarsus XR NDA in August 2014. (FDA 01417-19.) 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 recipients regardless of patient setting, and no application for those conditions can be approved until expiration of the exclusivity period on July 19, 2016." (FDA 01418.) Astellas specifically noted Veloxis's filing of the NDA for Envarsus XR and asked FDA whether it agreed with Astellas's view of the scope of Astagraf XL's exclusivity. (*Id.*) 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. Astellas's correspondence was intended to delay the approval of Envarsus XR. The FDCA provides that FDA may act on such a request only if it is filed as a Citizen Petition. *See* 21 U.S.C. § 355(q)(1)(A); *see also* 21 C.F.R. § 10.30 (2014). Although this requirement is intended to prevent precisely the type of eleventh-hour, non-public attempt to delay market competition that occurred here, FDA did not request or require Astellas to file its letter as a Citizen Petition.

D. FDA's Erroneous Decision

On October 30, 2014, FDA issued a "Tentative Approval" letter for Envarsus XR. The letter explained that FDA had found Envarsus XR to be eligible for approval under the FDCA, *i.e.*, safe and effective. (FDA 01544-84.) Nevertheless, FDA stated that it was delaying

final marketing approval of Envarsus XR until the expiration of Astagraf XL's exclusivity period because the drugs purportedly share "conditions of approval." (FDA 01544-45.) FDA did not identify the relevant conditions of approval. (*Id.*) The Administrative Record reveals that FDA issued its decision to withhold marketing approval of Envarsus XR notwithstanding the fact that it had not yet made the threshold determination regarding whether Astagraf XL was entitled to any exclusivity. (FDA 01540-43 (Memo from R. Albrecht to J. Sitlani (Oct. 30, 2014)) ("The Exclusivity Board has, however, become aware that an analysis under Section 505(v)(3)(B) . . . was not conducted as part of Astagraf XL's exclusivity determination. At this time, the Exclusivity Board is in the process of conducting such an assessment.").) In fact, FDA did not make the determination that Astagraf XL was entitled to exclusivity until January 8, 2015, *more than two months after it issued the Tentative Approval letter to Veloxis*. (FDA 01897-1902.)

After receiving the Tentative Approval letter, Veloxis engaged in a series of communications with FDA in which Veloxis sought information (unsuccessfully) about the basis for FDA's decision, including the identity of the purportedly overlapping "conditions of approval," and pointed out the factual and legal errors in FDA's still opaque decision. On November 6, 2014, Veloxis met with FDA. (FDA 01695-1725.) On November 14, 2014, in response to a request from FDA, Veloxis submitted a copy of the materials presented at the meeting, as well as additional data, information, and analysis regarding the implications of Astagraf XL's three-year exclusivity on the final approval of the Envarsus XR NDA. (FDA 01626-1738.)[6]

[6] Veloxis submitted additional materials in support of its Request for Final Approval on December 2 and 12, 2014. (FDA 01739-42; FDA 001759-61.)

On December 5, 2014, FDA contacted Veloxis to advise that, contrary to its October 30, 2014 Tentative Approval letter, it had determined that Astagraf XL's exclusivity did not completely preclude approval of Envarsus XR. (FDA 01748-50.) Rather, FDA advised that Envarsus XR could be immediately approved for a limited use if Veloxis amended the Envarsus XR label to restrict the NDA to patients being converted from immediate-release tacrolimus (*i.e.*, Prograf and its generics). (*Id.*) On December 8, 2014, Veloxis declined to revise its NDA, noting that FDA's proposal would artificially limit the patient population that would benefit from Envarsus XR and would be inconsistent with the requirements of the FDCA. (FDA 01751-58.) On December 12, 2014, FDA notified Veloxis that, although it had previously agreed to confirm or amend its Tentative Approval decision by no later than December 12, 2014, it would not be in a position to do so until January 12, 2015. (FDA 01762-66.)

On January 12, 2015, FDA issued a response to Veloxis's Request for Final Approval, in which it reaffirmed its prior decisions. (FDA 00001-4.) FDA stated that Veloxis could either: (i) seek full approval of the Envarsus XR NDA on or after the July 19, 2016 expiration of Astagraf XL's exclusivity period; or (ii) seek immediate final approval of Envarsus XR only for use by patients converting from immediate-release tacrolimus to Envarsus XR. (*Id.*) FDA's Response was accompanied by a 53-page "General Advice" letter that, for the first time, provided a rationale for FDA's decision, including identifying the purportedly overlapping conditions of approval and the "new" clinical investigations supporting Astagraf XL's exclusivity. (FDA 00005-57.) On January 21, 2015, Veloxis asked FDA to permit it to seek

approval in the conversion population, while pursuing full approval through this litigation. (Ettinger Decl. Ex. 1.)[7] FDA has not acted on this request.

ARGUMENT

Pursuant to the Administrative Procedure Act ("APA"), 5 U.S.C. § 706, a reviewing court must "hold unlawful and set aside agency action" that is "in excess of statutory jurisdiction [or] authority," or "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." *Id.* §§ 706(2)(A), (2)(C). Under Federal Rule of Civil Procedure 56, summary judgment generally is appropriate when the moving party "shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). However, "in a case involving review of final administrative action" under the APA, "the standard set forth in Rule 56 does not apply." *Takeda Pharm.*, 2015 WL 252806, at *13 (citing *ViroPharma, Inc. v. Hamburg*, 916 F. Supp. 2d 76, 79 (D.D.C. 2013)); *see also Cumberland Pharm. Inc., v. FDA*, 981 F. Supp. 2d 38, 47 (D.D.C. 2013) (Walton, J.). Instead, in an APA case, summary judgment "is the proper mechanism for deciding, as a matter of law, whether an agency action is supported by the administrative record and consistent with the APA standard of review." *Cumberland Pharm.*, 981 F. Supp. 2d at 47; *see also Am. Bioscience*, 269 F.3d at 1083-84. "[U]nder the APA, it is the role of the agency to resolve factual issues to arrive at a decision supported by the administrative record, whereas the function of the district court is to determine whether or not as a matter of law the evidence in the

[7] For the Court's convenience, difficult-to-access legal sources and other non-public documents relied upon by Veloxis in support of its Motion for Summary Judgment are attached as exhibits to the accompanying Transmittal Declaration of Mitchell S. Ettinger ("Ettinger Decl.").

administrative record permitted the agency to make the decision it did." *Cumberland Pharm.*, 981 F. Supp. 2d at 47 ((internal quotation marks omitted).

Here, FDA's decision is impermissible for four, independent reasons. *First*, FDA's decision to apply Astagraf XL's exclusivity to Envarsus XR 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 necessary for 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 mandate and thirty years of FDA's own precedent.

Second, as FDA acknowledges, Astagraf XL's exclusivity (if any) is limited to the scope of the "new clinical investigations" essential to its approval. Although FDA granted Astagraf XL exclusivity based upon two clinical studies, only one of those clinical investigations qualifies as "new" under the plain language of the FDCA and FDA's regulations. Because that clinical study did not include (i) *de novo* kidney transplant patients treated *with* induction, or (ii) conversion patients, Astagraf XL's exclusivity cannot block approval of Envarsus XR for these two uses – the only uses for which Veloxis seeks approval.

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 "conditions of approval." In so ruling, FDA has ignored the significant differences between the two drugs and their labeling.

Fourth, Envarsus XR should be fully and finally approved because Astagraf XL never was entitled to exclusivity. Astagraf XL's active ingredient, tacrolimus, is an old

antibiotic, and the Astagraf XL NDA was pending prior to October 8, 2008. Astellas's unilateral decision to withdraw its NDA in 2009 and refile it in 2012 does not permit Astellas to evade Congress's clear mandate that NDAs pending as of October 2008 do not qualify for exclusivity.

As explained below, FDA's grant of exclusivity to Astagraf XL and its application of that exclusivity to the Envarsus XR NDA were in excess of FDA's statutory authority and inconsistent with FDA's own regulations. FDA's application of Astagraf XL's exclusivity to Envarsus XR also was arbitrary and capricious. For these reasons, Veloxis is entitled to summary judgment.

I. FDA Exceeded Its Statutory Authority in Applying Astagraf XL's Exclusivity to Envarsus XR in the Absence of Reliance

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 Resources Defense 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-cv-1592 (KBJ), 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., Inc. v. Sebelius*, No. 12–1344 (ABJ), 2012 WL 6968224, at *9 (D.D.C. Oct. 22, 2012) (internal quotation marks omitted); *see also Amalgamated*, 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 842-43, 104 S. Ct. at 2781) (internal quotation marks omitted). Here, because the statute is unambiguous, the Court must give effect to Congress's intent by directing the immediate final approval of Envarsus XR.

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

FDA's decision to apply Astagraf XL's exclusivity to block immediate approval of Envarsus XR is based on a patently incorrect reading of the relevant statutory language. As a matter of law, the three-year period of exclusivity granted to Astagraf XL under Section 505(c)(3)(E)(iii) does not apply to Envarsus XR because the Envarsus XR NDA does not (i) reference Astagraf XL as a listed drug, (ii) rely on any Astagraf XL data or studies, or (iii) rely on FDA's findings of safety and effectiveness for Astagraf XL.

The plain language of the FDCA provides:

> If an application submitted under subsection (b) of this section for a drug . . . is approved . . . and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) of this section for the conditions of approval of [the approved drug] effective before the expiration of three years from the date of the approval of [the approved drug] if the [safety and effectiveness] investigations . . . ***relied upon*** by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

21 U.S.C. § 355(c)(3)(E)(iii) (emphasis added). This statutory language unambiguously requires an overlap between the "new clinical investigations" conducted to obtain exclusivity and those relied upon by the subsequent applicant to trigger exclusivity. In the absence of such overlap, exclusivity is inapplicable as a matter of law. Indeed, the importance of reliance in Section 505(c)(3)(E)(iii) is confirmed by FDA's implementing regulation, which provides that a

505(b)(2) application will be blocked by three-year exclusivity to the extent that it "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). FDA's own regulation thus recognizes that exclusivity arises from reliance by the second applicant on studies conducted by the first applicant to gain approval of its NDA.[8]

Notwithstanding this unambiguous statutory language and FDA's consistent regulation, FDA's decision in this case reads reliance out of the statute. FDA asserts that the statutory language – including the phrase "relied upon" – simply mirrors the language of Section 505(b)(2) and reflects Congress's intent to limit exclusivity to 505(b)(2) NDAs and not NDAs submitted pursuant to Section 505(b)(1).[9] This argument fails as a matter of textual construction. Had Congress simply intended to describe a 505(b)(2) application, as FDA suggests, it could have used the same phraseology that appears in other portions of Section 505 to do so. In this

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[8] On February 6, 2015, FDA published proposed regulations to implement Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, which amended provisions of the FDCA governing the approval of 505(b)(2) applications and ANDAs. The preamble to the proposed regulations again confirms the nexus between exclusivity and reliance on the listed drug. *See* Abbreviated New Drug Applications and 505(b)(2) Applications; Proposed Rule; 80 Fed. Reg. 6,802, 6,806 (Feb. 6, 2015) ("The timing of approval for a 505(b)(2) application and an ANDA (including a petitioned ANDA) is subject to the patent and marketing exclusivity protections accorded the listed drug(s) *relied upon* and the RLD, respectively.") (emphasis added).

[9] In arguing that reliance is not required, FDA highlights the preamble to its own 1989 *proposed rule* implementing the Hatch-Waxman Amendments, in which FDA *suggested* that exclusivity might block a 505(b)(2) application that did not refer to the drug with exclusivity as the listed drug. (FDA 00041 (citing 54 Fed. Reg. 28,872, 28,897 (July 10, 1989).) As FDA admits, however, in the 25 years since that Preamble it has not "refused to fully approve a 505(b)(2) application due to the 3-year exclusivity of another NDA on which the subsequent application did not rely." (FDA 00047.) Certainly the preamble to a proposed rule that FDA never has applied in practice cannot be sufficient to overcome the plain statutory language. To the contrary, FDA's consistent application of the statute throughout 25 years renders its decision here – premised on the application of a preamble to a proposed rule for the first and only time – arbitrary and capricious.

regard, Congress refers to an "application submitted under subsection (b)(2) of this section" in three places in Section 505;[10] in six other instances, Congress refers to a certification under subsection (b)(2)(A) of the section.[11] Using this same shorthand reference in Section 505(c)(3)(E)(iii) would have resulted in a far simpler formulation:

> If an application submitted under subsection (b) of this section for a drug . . . is approved . . . and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval ***of an application submitted under subsection (b)(2) of this section*** for the conditions of approval of such drug . . . effective before the expiration of three years from the date of the approval of [that drug].

But Congress did not use this language. Instead, Congress adopted language that requires a nexus between (i) the clinical studies conducted by the first applicant to obtain FDA approval and (ii) the clinical studies relied on by the subsequent applicant in seeking approval.

As Judge Jackson recently observed in *Takeda Pharmaceuticals*, "[t]he fact that the entire Section 505(b)(2) process concerns applications that rely, at least in part, on the safety and effectiveness find[ing]s of another drug, lends clear credence to [the] argument that reliance matters under this statutory scheme." *Takeda Pharm.*, 2015 WL 252806, at *24.[12] This Court, therefore, must give meaning to Congress's decision to emphasize the importance of reliance in the Hatch-Waxman exclusivity scheme by repeating the language from Section 505(b)(2) in

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[10] *See* 21 U.S.C. §§ 355(c)(3)(D)(i)(III), 355(q)(1)(A), and 355(q)(5)(A).

[11] *See* 21 U.S.C. §§ 355(c)(3), 355(c)(3)(A), 355(c)(3)(B), 355(c)(3)(C), 355(c)(3)(D)(i)(III), and 355(c)(3)(E)(ii).

[12] Although the *Takeda Pharmaceuticals* decision involved provisions of Section 505(b)(2) requiring that a 505(b)(2) applicant file certifications with respect to certain patents, Judge Jackson's statements regarding the structure and purpose of the Hatch-Waxman Amendments apply with equal force to Section 505(c)(3)(E)(iii). Moreover, it must be noted that in *Takeda Pharmaceuticals*, FDA espoused the view that reliance matters under the Hatch-Waxman statutory scheme. *See Takeda Pharm.*, 2015 WL 252806, at *24.

Section 505(c)(3)(E)(iii), and conclude that Section 505(c)(3)(E)(iii) unambiguously provides that a second-in-time 505(b)(2) application is blocked only to the extent it relies upon data supporting the approval of a drug with exclusivity. Because Envarsus XR does not rely on any clinical study conducted by Astellas in support of the Astagraf XL NDA, it cannot be subject to any exclusivity granted in connection with the approval of that drug. It is therefore entitled to immediate approval under the plain language of the statute.

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

The structure and purpose of the Hatch-Waxman Amendments further confirm that Section 505(c)(3)(E)(iii) exclusivity cannot block a subsequent 505(b)(2) application in the absence of reliance on the studies that serve as the basis for exclusivity. *See Amalgamated*, 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).[13]

"Congress intentionally designed [the] Hatch-Waxman [Amendments] to balance two important and potentially conflicting objectives: incentivizing investment in the innovation of new drugs, and encouraging the production of less-costly alternative drug products." *Takeda Pharm.*, 2015 WL 252806, at *25. "To ensure that *both* of these goals are achieved," *id.*,

[13] *See also* Letter from Steven K. Galson, Acting Dir., FDA Center for Drug Evaluation and Research ("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") (Ettinger Decl. Ex. 2.)

Congress created the streamlined 505(b)(2) process, which 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); (*see also* FDA 00023). 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* FDA 00023.)[14] "This *quid pro quo* arrangement is preserved" if Section 505(c)(3)(E)(iii) "is interpreted as it was written" – to provide that a 505(b)(2) application will be blocked where it has "relied upon" the findings of safety and efficacy for the drug enjoying exclusivity. *Takeda Pharm.*, 2015 WL 252806, at *25. It "is effectively undone" if a 505(b)(2) application is blocked by exclusivity granted to a drug upon which it does not rely (and from which it therefore receives no benefit). *Id.*; (*see also* FDA Cross-Motion for Summ. J. filed in *Takeda Pharm.* at 2, 10 (stressing significance of Hatch-Waxman's *quid pro quo* arrangements) (Ettinger Decl. Ex. 4)).

FDA's decision in this case upends the balance sought to be achieved by Congress. Here, Veloxis conducted its own studies and did not rely on the data generated by Astellas in establishing the safety and effectiveness of Astagraf XL. Notwithstanding the considerable investment made by Veloxis and the lack of reliance on the studies conducted by Astellas for Astagraf XL, FDA has blocked Envarsus XR from the market. Thus, contrary to the

[14] *See also* Letter from Steven K. Galson to David M. Fox, Hogan & Hartson, L.L.P., at 31 (Apr. 6, 2004) (FDA Docket No. 2003-P-0074) ("The Hatch-Waxman Amendments provided sponsors of innovator drugs with marketing exclusivity and patent listing provisions as a quid pro quo for the abbreviated approval mechanism for sponsors of generic drugs whereby generic drugs could rely on the agency's finding of safety and effectiveness for the innovator drug.") (Ettinger Decl. Ex. 3).

Hatch-Waxman Amendments' objectives, Veloxis reaps no reward for its own innovation and investment, while Astagraf XL is inappropriately shielded from competition against an innovative product that did not benefit in any way from Astagraf XL. By "completely unmoor[ing exclusivity] from the essential reliance underpinnings of the Section 505(b)(2) process," *Takeda Pharm.*, 2015 WL 252806, at *25, FDA has significantly – and impermissibly – modified the basic terms of the *quid pro quo* arrangement created by Congress. *See Ranbaxy Labs., Ltd. v. Leavitt*, 469 F.3d 120, 126 (D.C. Cir. 2006) ("The FDA may not . . . change the incentive structure adopted by the Congress . . . .").

The untenable nature of FDA's application of the statute is evident from the fact that an ANDA seeking approval of a generic version of Prograf and relying on the same Prograf data Veloxis cited in the Envarsus XR NDA would be approved immediately, whereas Envarsus XR is blocked from the marketplace for relying on that same data even though it conducted additional independent and costly studies and does not rely on any study associated with Astagraf XL. This absurd result demonstrates that the "relied upon" element necessarily requires overlap between the study for which exclusivity is granted and the data relied upon in the 505(b)(2) application.

Moreover, FDA's application of Astagraf XL's exclusivity to Envarsus XR leaves drug developers unable to navigate the 505(b)(2) pathway and thus dramatically undermines its viability. Under Congress's design, "a Section 505(b)(2) applicant has the discretion to select a reference drug, and to make that selection in relation to the scope of the materials the applicant desires to submit." *Takeda Pharm.*, 2015 WL 252806, at *21 (citing FDA Citizen Petition responses). In exercising this discretion, sponsors historically have understood that they will be blocked by exclusivity to the extent they rely upon data necessary to another drug's approval.

FDA's rejection of the reliance principle leaves drug developers unable to identify potentially applicable exclusivities and order their conduct accordingly. Untethering exclusivity from the reliance principle will lead rational drug developers to conclude that the only way to avoid being blocked by another drug's exclusivity is to conduct all their own research and pursue approval under Section 505(b)(1). This will result in unnecessary repetition of studies to generate data that already is known, waste research assets, and deter companies from investing in promising new drugs – outcomes Congress specifically sought to avoid through the Hatch-Waxman Amendments.[15]

In short, FDA's decision in this case results in myriad consequences that cannot be reconciled with the structure and purpose of the Hatch-Waxman Amendments. These incongruous outcomes demonstrate that FDA acted contrary to Congress's intent when it applied Astagraf XL's exclusivity to Envarsus XR in the absence of any reliance by Veloxis on clinical studies supporting the approval of Astagraf XL or on FDA's prior findings of safety and effectiveness for Astagraf XL.

C. Thirty Years of FDA Precedent Confirms That Exclusivity is Triggered Only Where There is Reliance on Data Necessary to Approval of the Blocking Drug

Section 505(c)(3)(E)(iii)'s reliance requirement is further confirmed by the fact that, throughout the thirty years since the Hatch-Waxman Amendments were enacted, FDA consistently has approved 505(b)(2) applications for drugs that – like Envarsus XR and Astagraf

[15] (*See* FDA 01771-1808 (Letter from J. Woodcock, CDER to K. Sanzo, Morgan Lewis & Bockius, LLP et al., at 14 (Oct. 14, 2003) (FDA Docket Nos. 2001-P- 0323, 2002-P-0447, and 2003-P-0408) ("In enacting the Hatch-Waxman Amendments, Congress authorized FDA to rely on information about the safe and effective use of an approved drug product to approve another drug with similar characteristics, because duplicative clinical testing to reestablish what has already been shown is wasteful, unnecessary, and may raise ethical issues.")).)

XL – share active ingredients and indications with drugs subject to statutory exclusivity, where the 505(b)(2) application does not rely upon data supporting approval of the drug with exclusivity. (*See* FDA 01639-41; FDA 01759-61.) Indeed, FDA concedes that "[a] search of the Agency's records *has not produced another instance where FDA refused to fully approve a 505(b)(2) application due to the 3-year exclusivity of another NDA on which the subsequent application did not rely*." (FDA 00047 (emphasis added).) As detailed below, this unbroken chain of agency conduct confirms that Section 505(c)(3)(E)(iii) is unambiguous, and that FDA's unprecedented action in this case is in excess of its statutory authority.

Veloxis's submissions to FDA have highlighted numerous examples in which FDA has approved 505(b)(2) applications in situations directly analogous to the Envarsus XR NDA. For instance, on August 1, 2000, FDA approved an NDA for Concerta® (extended-release methylphenidate tablets), a once-daily treatment for Attention Deficit Hyperactivity Disorder ("ADHD"). (FDA 02571-74.) Concerta was granted three-year exclusivity. (FDA 00050.) Nevertheless, on April 3, 2001, FDA approved a 505(b)(2) application for Metadate CD® (20 mg extended-release methylphenidate capsules). (FDA 02316-19.) 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. (FDA 02316-19; FDA 02571-74.) Also like the drugs in this case, Concerta and Metadate CD are approved in different dosage forms (*i.e.*, extended-release tablets and extended-release capsules, respectively). (*Id.*) Unlike this case, however, Concerta's exclusivity did not block approval of Metadate CD.

In another example, 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"). (FDA

02906-08.) FDA also granted Androgel 1% three-year "new dosage form" exclusivity (covering 25 and 50 mg doses). (FDA 00053.) 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. (FDA 00055; FDA 03231-32.) 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 a new route of administration." (FDA 03271.) 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. (FDA 03257-3308.) As a result, notwithstanding the shared conditions of approval between the drugs, Androgel 1%'s exclusivity did not block final approval of Testim 1%.[16]

In response to the precedent identified by Veloxis, FDA admits that it does not have contemporaneous documentation reflecting why the second-in-time products were not blocked by exclusivity in these instances. (FDA 00049 n.204.) In the case of Testim, FDA can offer no explanation, and suggests that the drug may have been approved in error. (FDA 00053.) In the other cases, FDA attempts to distinguish precedent by offering *post hoc* rationalizations,

[16] Veloxis's November 14, 2014 submission to FDA discussed another example involving Axiron®, Fortesta®, and Androgel® 1.62%, all transdermal metered testosterone products approved to treat Low T, which were granted overlapping periods of three-year exclusivity. (*See* FDA 001640.)

some of which actually support Veloxis's assertion that Envarsus XR does not share conditions of approval with Astagraf XL and therefore should not be blocked. (FDA 00050-51.)[17]

FDA also asserts that "in instances where the Agency has considered this situation" – *i.e.*, whether a 505(b)(2) application is blocked by the exclusivity of another NDA on which it does not rely – "it has applied considerations consistent with this interpretation of the scope of 3-year exclusivity." (FDA 00047.) The purported "precedent" that FDA cites, however, does not support this assertion. Instead, FDA's examples generally reflect internal FDA discussions regarding instances in which FDA did not actually make a final determination regarding reliance. (FDA 00047-49.) These internal discussions do not "represent the formal position of FDA," and do not bind FDA to the views expressed, 21 C.F.R. § 10.85(k); they are, at most, the regulatory equivalent of dicta.[18] Indeed, insofar as the examples FDA cites are not publicly available, they cannot serve to communicate FDA's position on reliance to drug developers or counter the publicly available precedents identified by Veloxis.[19]

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[17] As discussed in Section III.A below, FDA's attempt to distinguish the Concerta/Metadate CD precedent confirms that Envarsus XR and Astagraf XL do not share conditions of approval given their different pharmacokinetic profiles.

[18] For example, FDA asserts that it considered whether Conzip® would be blocked by exclusivity granted to Ryzolt® even though the products had different dosage forms and Conzip did not rely on Ryzolt for approval. (FDA 00048.) Ultimately, however, FDA did not need to make any determination regarding reliance because it determined that Conzip was not blocked because Ryzolt's exclusivity was limited to a specific titration schedule not shared by Conzip. (*Id.*)

[19] Nor do FDA's examples establish a clear FDA position on reliance. FDA suggests that it considered the approvability of Duoneb® in light of the exclusivity granted to Combivent®, even though Duoneb did not rely on Combivent. (FDA 00047-48.) Documents relating to the approval of Duoneb reveal that there was a difference of opinion within FDA about whether exclusivity could block approval in the absence of reliance; indeed, FDA officials previously informed the sponsor of Duoneb that Combivent's exclusivity only would apply if the Duoneb NDA *relied upon* Combivent data. (*See* Ettinger Decl. Ex. 5 (Jun. 17, 1997 Meeting Minutes).)

The only publicly available example FDA cites – its response to the Citizen Petition filed by Mutual regarding single-ingredient oral colchicine products – in fact confirms that a subsequent application will be blocked only to the extent it relies upon data supporting approval of a drug with exclusivity. FDA highlights that it determined that a subsequent 505(b)(2) applicant would not need to identify Colcrys® as a listed drug to be blocked by Colcrys's exclusivity. (FDA 00049-50.) FDA's Citizen Petition response, however, also stated that *the applicant would nevertheless need to include information in its label about a lower dose regimen evaluated in Mutual's clinical trial for Colcrys*. (FDA 02216-18.) It was for this reason – because applicants would be required to include labeling language that *relied upon* Colcrys's clinical trial data – that subsequent applicants would be blocked by Colcrys's 3-year exclusivity, even if they did not explicitly reference Colcrys as a listed drug. (*Id.*)

In the end, although FDA approves approximately forty drugs per year via the 505(b)(2) pathway, neither FDA nor Veloxis can identify a single instance in which FDA has applied exclusivity to block approval of a product that did not reference or rely upon the drug with exclusivity. To the contrary, Veloxis has identified several examples where FDA approved such a drug during another sponsor's exclusivity period. This administrative precedent – in contrast to the arguments FDA now advances to justify its legally erroneous decision – is consistent with Congress's unambiguous intent as evidenced by the statute's plain language, FDA's implementing regulation, and the structure and purpose of the Hatch-Waxman Amendments.[20] It is undisputed that the Envarsus XR NDA did not rely upon any studies

[20] FDA's precedent also highlights the arbitrary and capricious nature of its action in this case. 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). FDA's departure *(cont'd)*

conducted to support the Astagraf XL NDA, did not rely upon FDA's prior findings of safety and effectiveness for Astagraf XL, or reference Astagraf XL as a listed drug. Accordingly, as a matter of law, any exclusivity granted to Astagraf XL under Section 505(c)(3)(E)(iii) cannot serve to block the final approval of Envarsus XR.

II. FDA Exceeded Its Statutory Authority In Determining That the Scope of Astagraf XL's Exclusivity Blocks Approval of Envarsus XR in De Novo Kidney Transplant Patients

As both FDA and the courts have recognized, the language and structure of the Hatch-Waxman Amendments create a necessary relationship between (i) the "new clinical investigations" that justify Section 505(c)(3)(E)(iii) exclusivity, (ii) the "conditions of approval" based upon those studies, and (iii) the scope of the information relied upon by the subsequent applicant. *See AstraZeneca Pharm. LP v. FDA*, 850 F. Supp. 2d 230, 235 (D.D.C. 2012).[21] Indeed, FDA acknowledges this necessary relationship, asserting that it "interprets the scope of exclusivity to be related to the scope of the underlying new clinical investigations that were essential to the approval." (FDA 00026.) Based upon this principle, FDA now acknowledges that, because Astellas did not conduct an adequate, well-controlled trial in conversion kidney transplant patients, any exclusivity granted to Astagraf XL cannot block Envarsus XR's approval for use in this population. (FDA 00043-46.)[22]

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from its consistent practice of the past thirty years without explanation renders its action arbitrary and capricious and in violation of the APA.

[21] As FDA notes, while the *AstraZeneca* decision considered three-year exclusivity in the context of an approved supplement and subsequent ANDAs, the same rule applies to an approved NDA and subsequent 505(b)(2) application. (*See* FDA 00026 at n.110.)

[22] This conclusion is contrary to the October 30, 2014 Tentative Approval letter, which determined that Astagraf XL's exclusivity blocked approval of Envarsus XR for all indications. (FDA 01544-84.) Notwithstanding FDA's conclusion that Envarsus XR in fact is entitled to immediate final approval for the conversion population, FDA has not permitted *(cont'd)*

Veloxis agrees. There is no dispute, therefore, that Envarsus XR must be finally approved for use in conversion kidney transplant patients. As a matter of law, however, Envarsus XR also must be approved immediately for use in *de novo* kidney transplant patients *with* induction (*i.e.*, dosed intensively in combination with other immunosuppressive therapies during and immediately after transplant surgery). Section 505(c)(3)(E)(iii) provides that a drug is entitled to exclusivity only to the extent it is approved based upon "new clinical investigations." 21 U.S.C § 355(c)(3)(E)(iii). The Astagraf XL NDA sought approval of Astagraf XL based upon two studies: (i) Study 158 – which studied Astagraf XL in *de novo* kidney transplant patients *with* induction, and (ii) Study 12-03 – which studied Astagraf XL in *de novo* kidney transplant patients *without* induction. (FDA 00035.) As discussed below, Study 158 does not qualify as a "new" clinical investigation; only Study 12-03 qualifies as such. Because Study 12-03 addressed only *de novo* kidney transplant patients treated *without* induction – a use for which Veloxis is not seeking approval – Astagraf XL's exclusivity cannot block the full and immediate approval of Envarsus XR for use in *de novo* kidney transplant patients *with* induction.

A. Study 158 Does Not Qualify As a "New Clinical Investigation" Under the Plain Language of the FDCA and FDA's Regulation

Under the plain language of the FDCA and FDA's regulations, Study 158 does not qualify as a "new clinical investigation." FDA's regulations define a "new clinical investigation" as "an investigation in humans *the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product*

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Veloxis to proceed on a dual track whereby it receives that final approval while seeking the Court's review of FDA's refusal to approve Envarsus XR for the *de novo* population *with* induction.

for any indication or of safety for a new patient population . . . ." 21 C.F.R. § 314.108(a) (2014) (emphasis added).[23] Although FDA asserts that Astagraf XL received exclusivity based upon both Study 158 and Study 12-03 (FDA 00044), FDA also admits that Study 158 previously was submitted to and relied upon by FDA in connection with a supplemental new drug application for Prograf. As such, Astagraf XL is not entitled to exclusivity based upon Study 158.

Study 158 included three arms: (i) once-daily Astagraf XL, (ii) twice-daily Prograf, and (iii) twice-daily Neoral® (cyclosporine). (FDA 00035.)[24] In 2006, Astellas submitted the full results of Study 158, including all three arms, to FDA in support of a supplemental NDA (sNDA) for Prograf. (FDA 01520.) The sNDA sought approval of a new use for Prograf in combination with another drug, mycophenolate mofetil (MMF) in kidney transplant patients, and the results of Study 158 were relied upon by FDA to demonstrate substantial evidence of effectiveness for this new use. (FDA 00411 (FDA Astagraf XL Clinical Review) (noting that Study 158 "was also one of the 2 studies that provided support for the approval of Prograf use with MMF in kidney transplant recipients").) Upon approval of the efficacy supplement in 2009, new dosing instructions were added to the Prograf label to describe

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[23] Under *Auer v. Robbins*, FDA's application of its own regulation is not controlling if it is "plainly erroneous or inconsistent with the regulation." *Auer v. Robbins*, 519 U.S. 452, 461, 117 S. Ct. 905, 911 (1997) (quotations and citations omitted); *see also Christensen v. Harris Cnty.*, 529 U.S. 576, 588, 120 S. Ct. 1655, 1663 (2000) ("*Auer* deference is warranted only when the language of the regulation is ambiguous.")

[24] An "arm," also known as a "treatment group," is a "group or subgroup of participants in a clinical trial that receives specific interventions, or no intervention, according to the study protocol." *See* U.S. Nat'l Insts. Of Health, Glossary of Common Site Terms, www.clinicaltrials.gov/ct2/about-studies/glossary (last visited Feb. 5, 2015). A clinical investigation typically contains two or more "arms" to compare various dosages of a particular drug and/or test the study drug against a placebo or active control (*i.e.*, another drug intended for the same use). *See* 21 C.F.R. § 314.126 (2014).

this new use with MMF. (FDA 01520.) In addition, the Prograf label specifically includes safety and efficacy data from Study 158. (*Id.*)

When Astellas sought exclusivity for Astagraf XL three years later, it acknowledged that Study 158 was submitted to FDA in support of the Prograf sNDA. (FDA 01515-22.) And, in considering whether to grant exclusivity to Astagraf XL, FDA recognized that Study 158 previously was relied upon to support the efficacy of Prograf. (FDA 01086 (Astagraf XL Exclusivity Summary) (stating that "[Study 158] . . . has three arms. One of the arms was used to support approval of another NDA.").) Notwithstanding the fact that Study 158 was relied upon by FDA to demonstrate substantial evidence of Prograf's effectiveness, FDA has concluded that both Study 12-03 and Study 158 are "new clinical investigations" supporting Astagraf XL's exclusivity. (FDA 00044.) FDA does not explain, however, how Study 158 can qualify as a "new" investigation in light of its significant role in supporting the approval of Prograf.

In its request for Astagraf XL exclusivity, Astellas argued that Study 158 should qualify as a "new clinical investigation" because "FDA did not include data from [one of its arms] the Advagraf versus Neoral analysis . . . in the Prograf label [and] it is assumed FDA would not have needed to directly rely on the Advagraf arm data to demonstrate the effectiveness of Prograf for use in kidney transplant patients." (FDA 01520.)[25] This argument is flawed as a matter of law. The plain language of Section 505(c)(3)(E)(iii) provides exclusivity for a "new clinical investigation," not for separate "study arms." In this regard, an "investigation" includes

[25] Astagraf XL is marketed in Europe under the name Advagraf, and was referred to as such in the Astagraf XL NDA.

all its arms, which are conducted under a single investigative protocol.[26] Moreover, when Congress intends to recognize the distinction between a clinical investigation and an "arm" of a study, it does so. *See* 42 U.S.C. § 282(j)(3)(I)(iii) (requiring public reporting of adverse event information from "each arm" of a clinical investigation). In this instance, Congress chose to base exclusivity on the status of the "investigation" as a whole, and FDA's regulation is consistent in this regard.

FDA's decision to treat Study 158 as a new clinical investigation also is factually flawed. In this regard, the Prograf sNDA review package explicitly confirms that data *from all three arms of Study 158* were considered in connection with FDA's approval. (*See, e.g.*, Prograf sNDA Statistical Review and Evaluation, at 14 ("One year efficacy failure (first occurrence of BCAR, graft loss, death or loss to follow-up) was 14% (30/214), 15.1% (32/212) and 17.0% (36/212) in [Astagraf XL]/MMF, Prograf/MMF and Neoral/MMF groups.") (Ettinger Decl. Ex. 6).) In any event, the "results of" Study 158 unquestionably were submitted to and "relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product" – Prograf. 21 C.F.R. § 314.108(a) (2014). Accordingly, Study 158 is not a "new" clinical investigation entitled to exclusivity under the plain language of Section 505(c)(3)(E)(iii) or FDA's regulations.

B. Envarsus XR is Not Blocked by Exclusivity Granted to Astagraf XL Based Upon Study 12-03

As Study 158 does not qualify as a "new clinical investigation," the scope of Astagraf XL's exclusivity must be limited to the subject matter of Study 12-03, which

[26] *See generally* U.S. Nat'l Insts. Of Health, Glossary of Common Site Terms, www.clinicaltrials.gov/ct2/about-studies/glossary (last visited Feb. 5, 2015).

investigated the use of Astagraf XL in *de novo* kidney transplant patients *without* induction.[27] Veloxis, however, *does not* seek approval of Envarsus XR for use in *de novo* kidney transplant patients *without* induction. Rather, Veloxis only seeks approval of Envarsus XR for use in (i) *de novo* patients *with* induction and (ii) conversion patients. (FDA 01547.) Because Study 12-03 did not study Astagraf XL for either of these uses, the proper scope of Astagraf XL exclusivity, to the extent it exists, cannot block the full and immediate approval of Envarsus XR. For the same reason that FDA would permit Envarsus XR to be approved for immediate use in conversion patients (FDA 00043-46), it likewise should permit approval for use in *de novo* patients *with* induction. FDA's contrary conclusion is "plainly erroneous," "inconsistent with [FDA's] regulation," *Auer*, 519 U.S. at 461, 117 S. Ct. at 911, and in excess of FDA's statutory authority.

III. FDA's Conclusion That Envarsus XR and Astagraf XL Share Conditions of Approval is Arbitrary and Capricious

FDA's application of Astagraf XL's exclusivity to Envarsus XR cannot stand for the additional reason that 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

[27] The Astagraf XL labeling reflects the results of this study by specifying a separate dosing regimen for this particular patient population. (FDA 00321-24.) In particular, according to the Astagraf XL label, both the starting doses and target trough levels are different for patients *without* induction compared to patients *with* induction. (*Id.*)

and whether there has been a clear error of judgment.'" *State Farm*, 463 U.S. at 43, 103 S. Ct. at 2866-67 (citation 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*. at 43, 103 S. Ct. at 2867. 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.

Section 505(c)(3)(E)(iii) provides – and FDA does not dispute – that a 505(b)(2) application will be blocked by exclusivity granted to another NDA only to the extent the applications share "conditions of approval." 21 U.S.C. § 355(c)(3)(E)(iii). Although neither the FDCA nor FDA's regulations define the phrase "conditions of approval," FDA asserts that "the relevant conditions of approval for exclusivity purposes are those changes for which the new clinical investigations were essential." (FDA 00025-26.) According to FDA, "the change in Astagraf XL for which new clinical investigations were needed was the change to a *once-daily, [extended-release] version of tacrolimus*." (FDA 00036 (emphasis added); *see also* FDA 00019 (stating that Astagraf XL's exclusivity covers its "[extended-release] dosage form and its once-daily dosing regimen").) Thus, FDA has adopted the unprecedented position that Astagraf XL's exclusivity is broadly scoped to cover any and all once daily versions of tacrolimus for *de novo* kidney transplant patients – *even those it did not study or obtain approval for* – irrespective of other salient approval characteristics. This decision defies logic.

Simply put, FDA's broad grant of exclusivity to Astagraf XL is arbitrary and capricious. FDA cherry picks from among Astagraf XL's "conditions of approval," emphasizing

those that fit FDA's theory – extended-release formulation and once-daily dosing – and rejecting others as "not . . . clinically meaningful," (FDA 00036), even while acknowledging that differences need not be clinically meaningful to be significant for exclusivity purposes (FDA 00034 n.145). Despite FDA's efforts to downplay the distinctions between Envarsus XR and Astagraf XL, the drugs have markedly different (i) pharmacokinetic profiles, (ii) dosage forms, (iii) dosing strengths, and (iv) dosing regimens. These differing conditions of approval preclude Astagraf XL's exclusivity from blocking approval of Envarsus XR.

A. Envarsus XR and Astagraf XL Have Different Pharmacokinetic Profiles As a Result of Envarsus XR's Proprietary MeltDose Technology

Envarsus XR was engineered using Veloxis's patented MeltDose technology, which results in the slow and uniform release of tacrolimus over time. (FDA 01631-32.) As a result, the pharmacokinetic profiles for Envarsus XR and Astagraf XL exhibit material differences in the rate and extent of absorption of tacrolimus. (*Id.*; FDA 01645-77 (Bloom Decl. ¶ 6).) Indeed, these differences are so markedly different that a generic for one drug would not be suitable as a generic for the other. (*Cf.* FDA 01551 (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.").)

Although FDA dismisses these differences as not clinically meaningful (FDA 00036), FDA's own argument serves to highlight the clear significance of pharmacokinetic differences. In attempting to distinguish the Concerta/Metadate CD precedent cited by Veloxis (discussed above), FDA suggests that Concerta did not block Metadate CD because Concerta received exclusivity for its "specific [pharmacokinetic] profile that results from its proprietary drug release mechanism" (FDA 00049-50.), while Metadate CD "had a different [pharmacokinetic] profile that was associated with a different drug release mechanism, and a

clinical study that was essential for the approval of Metadate CD was designed to demonstrate the safety and efficacy of the specific [pharmacokinetic] profile for Metadate CD" (FDA 00050-51).[28]

As with Concerta and Metadate CD, Envarsus XR has a different specific pharmacokinetic profile than Astagraf XL. (FDA 01631-32; FDA 01645-77 (Bloom Decl.) ¶ 6.) Indeed, this difference in pharmacokinetic profile led FDA to require Veloxis to demonstrate the safety and efficacy of the specific pharmacokinetic profile for Envarsus XR, just as it did with Metadate CD. FDA's claim now that "the clinical significance of the different tacrolimus [pharmacokinetic] profiles of Envarsus XR and Astagraf XL (and Prograf) has not been established," or that those differences are irrelevant for exclusivity purposes (FDA 00037), is nothing more than an arbitrary and capricious rationalization to justify its departure from thirty years of precedent.

B. Envarsus XR and Astagraf XL Have 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." (FDA 01094, 01096, 01098, 01100.) FDA is responsible for making entries in the Orange Book and has exclusive domain to select the appropriate designation to describe the exclusivity it grants. FDA previously has explained that "[e]xclusivities, including

[28] Even this explanation rings hollow because Concerta and Metadate CD had the same novel pharmacokinetic characteristics. (*See* FDA 02557 (stating "Like Concerta, Metadate CD is intended to partly mimic immediate release administration by providing an initial bolus in the morning (by dissolution of IR beads that comprise 30% of the dose), and then providing ongoing coverage over the rest of the day (by delayed and sustained dissolution of ER beads that comprise 70% of the dose.").) FDA's *post hoc* explanation that the pharmacokinetic profiles were meaningfully different cannot be squared with the administrative record of its review of the Metadate CD NDA.

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, AstraZeneca, at 6 (Mar. 27, 2012) (FDA Docket No. 2011-P-0662) (Ettinger Decl. Ex. 7) (emphasis added).) Given FDA's description of Astagraf XL's exclusivity, a subsequent product must, at a minimum, share Astagraf XL's dosage form to be blocked by its exclusivity. Envarsus XR and Astagraf XL, however, do not share a dosage form as Astagraf XL is an extended-release *capsule* and Envarsus XR is an extended-release *tablet*.

FDA repeatedly has ruled that capsules and tablets are different "dosage forms" for regulatory purposes. (*See, e.g.*, Letter from Janet Woodcock to Alan H. Kaplan, Kleinfeld, Kaplan & Becker et al., at 2 (Dec. 1, 2000) (FDA Docket Nos. 95-P-0262 and 96-P-0317) (Ettinger Decl. Ex. 8).) In contravention of this history, FDA now attempts to gloss over this meaningful difference by asserting that the drugs are both "once-daily, ER [extended release] dosage forms of tacrolimus." (FDA 00038.) This characterization of "dosage form," however, is inconsistent with FDA's own publications, which provide that a "dosage form is the physical form in which a drug is produced and dispensed, such as a tablet, a capsule, or an injectable." *See* U.S. Food & Drug Admin., Drugs@FDA Glossary of Terms, www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm (Ettinger Decl. Ex. 9). That the general description "once-daily, extended-release" is not itself a "dosage form" is confirmed by the numerous "extended-release" dosage forms listed in FDA's Orange Book, including extended-release tablets, extended-release capsules, extended-release films, extended-release

suspensions, extended-release inserts, and extended-release powders. (Ettinger Decl. Ex. 10 (Orange Book Appendix C).)[29]

Under FDA's new, expanded interpretation, any extended-release version of tacrolimus would be blocked by Astagraf XL's exclusivity even though Astellas only studied and obtained approval for an extended-release capsule. FDA maintains that "Astellas did not obtain approval of Astagraf XL in conversion patients and thus its exclusivity cannot extend to block approval for this population." (FDA 00043.) The same rule should apply in the case of dosage forms: Astellas also did not obtain approval of an extended-release *tablet* dosage form and thus its exclusivity cannot extend to block this dosage form.

C. Envarsus XR and Astagraf XL Have Different Dosage Strengths and Different Dosing Regimens

In addition to having different dosage forms and resulting differences in pharmacokinetic profiles, Envarsus XR and Astagraf XL are available in different dosage strengths and have different dosing regimens. Envarsus XR is available in 0.75, 1.0, and 4.0 mg dosage strengths (FDA 00016), while Astagraf XL is available in 0.5, 1.0, and 5.0 mg dosage strengths (FDA 00010).[30] As reflected in the FDA-approved labels for Envarsus XR and

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[29] Had FDA actually intended to grant Astagraf XL exclusivity for its "once-daily, extended-release" formulation, it could have selected any of a number of other codes better suited to that scope of exclusivity, including "once daily dosing," "once-a-day dosing regimen," and "change in dosing interval to once-daily administration." (*See* FDA 01973 (Orange Book, Patent & Exclusivity Abbreviations).) FDA's selection of the exclusivity code "New Dosage Form" suggests that, contrary to the arguments FDA now asserts to justify its erroneous decision, Astagraf XL in fact received exclusivity for its extended-release *capsule* dosage form.

[30] Astagraf XL is available in the same dosage strengths as Prograf. As a result, medication errors have been reported in Europe, which resulted in serious adverse events, including kidney graft rejection. (FDA 01635-36.) In light of these medication errors, in October 2009, FDA requested that Veloxis develop Envarsus XR in different dosage strengths in *(cont'd)*

Astagraf XL, the drugs also have 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 tacrolimus dosing after an initial period post-transplant. (FDA 00321-24; FDA 01547-49; FDA 001634-35.)

FDA's dismissal of these differing "conditions of approval" as "not clinically meaningful," (FDA 00036; FDA 00040), is irrelevant as a matter of law. Under the plain language of Section 505(c)(3)(E)(iii), a second-in-time product is not blocked by another product's exclusivity unless the products share "conditions of approval." The statute does not include any requirement that differences in "conditions of approval" be clinically meaningful to prevent exclusivity from applying. In light of the myriad differences between Envarsus XR and Astagraf XL, FDA's *ad hoc* cherry picking of relevant "conditions of approval" is arbitrary, capricious, and cannot survive scrutiny.

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

Finally, Envarsus XR's approval cannot be blocked for the separate, independent reason that, under Section 505(v) of the FDCA, Astagraf XL was never entitled to exclusivity because it is an old antibiotic and the Astagraf XL NDA was pending prior to October 8, 2008.

A. Astagraf XL Does Not Qualify for Exclusivity Under Section 505(v)

Tacrolimus is an old antibiotic. (FDA 00010.) Prior to 2008, old antibiotics were not eligible for certain Hatch-Waxman incentives, including three-year exclusivity. FDAMA,

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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.*)

§ 125(d)(1).[31] In 2008, Congress amended the FDCA to provide additional incentives to spur research into new and innovative antibiotic therapies. *See* 154 Cong. Rec. H10171 (daily ed. Sept. 27, 2008) (statement of Rep. Pallone). In particular, Congress provided that certain NDAs could be granted exclusivity even if they contained an old 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 that were not pending as of the date of the QI Act – those *submitted after October 8, 2008*. *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. (FDA 00010-12.) Accordingly, as a matter of law, Astagraf XL was not entitled to three-year exclusivity under the plain language of the QI Act when it was enacted.

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

FDA's sole basis for granting exclusivity to Astagraf XL is that Astellas withdrew its NDA in 2009 and resubmitted it in 2012. (FDA 00031-33.) The prohibitions of the QI Act, however, cannot be evaded through such manipulation of the regulatory process. In enacting the QI Act, Congress was concerned with "strik[ing] the right balance between innovation and access." 153 Cong. Rec. S5630 (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. Pallone), 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

[31] *See also* U.S. Food & Drug Admin, *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.

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 purportedly "new" application in 2012 for the identical product does not change this analysis.[32] Astellas's "new" NDA was a continuation of the previously submitted NDA: it pertained to the exact same product, was based on the same exact Phase III studies previously submitted to or requested by FDA, and relied upon FDA's prior reviews and observations regarding deficiencies.[33]

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 rewards manipulative and anti-competitive behavior by sponsors of old antibiotics, to the detriment of patients. There is no evidence that Congress intended

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[32] The Administrative Record in this case reflects that FDA viewed Astellas's resubmitted NDA as a continuation of its withdrawn NDA. FDA initially directed Astellas to "[r]etain the [prior] NDA number for the resubmitted application," and specifically instructed Astellas to address the deficiencies identified in the prior review in the resubmitted NDA. (FDA 00874.)

[33] Although FDA notes that Astellas submitted various "new" data and information as part of the resubmitted Astagraf XL NDA, there is no question that Study 158 and Study 12-03 – the only studies FDA cites as providing the basis for Astagraf XL's three-year exclusivity – both were completed *before* Astellas withdrew its NDA in 2009. (FDA 00011.)

exclusivity for old antibiotics to hinge on purely administrative actions that are solely within the control of and subject to manipulation by NDA applicants. To the contrary, the QI Act specifically was 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).[34] FDA's willingness to afford exclusivity to the Astagraf NDA 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. *See Ranbaxy Labs.*, 469 F.3d at 126 (FDA may not alter the incentive structure designed by Congress).

For all 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).

CONCLUSION

For the reasons set forth above, Veloxis respectfully requests that the Court grant summary judgment in favor of Veloxis and grant relief set forth in Veloxis's Complaint for Declaratory and Injunctive Relief.

Dated: February 6, 2015

Respectfully submitted,
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[34] 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, 1317-18 (D.C. Cir. 2010).

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