IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

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

REPLY IN SUPPORT OF DEFENDANTS' MOTION TO DISMISS, OR IN THE ALTERNATIVE, FOR SUMMARY JUDGMENT

The Hatch-Waxman Amendments strike the proper balance envisioned by Congress between two competing purposes: (1) providing incentive for innovation in drug development, and (2) accelerating through an abbreviated approval pathway the availability of lower-cost drugs to consumers. The Amendments provide incentive for pharmaceutical innovation by conferring various periods of exclusivity to protect qualified drug products approved under 21 U.S.C. § 355(b) from competition. Dissatisfied with the careful balance established by Congress, Veloxis Pharmaceuticals, Inc. ("Veloxis") asks this Court to strip its competitor, Astellas Pharm US, Inc. ("Astellas") of the three-year exclusivity FDA properly granted to it. As each of Veloxis' four arguments is unsupported by the administrative record and fails as a matter of law, the Court must dismiss Veloxis' lawsuit, or alternatively, deny Veloxis' summary judgment motion and grant summary judgment for the Federal Defendants.

ARGUMENT

Disappointed with the highly deferential legal standards that govern review of agency action under the Administrative Procedure Act ("APA"), Veloxis attempts to tell a tale of agency impropriety. Nothing could be further from the truth:

- Despite Veloxis' insinuations to the contrary, FDA was under no obligation to make Veloxis aware of any of its communications with Astellas regarding Astagraf's exclusivity, and it did not engage in any improper communication.[1] As documented in the administrative record, FDA's communications with both Astellas and Veloxis reflect a regulator's interest in gathering pertinent information to make an informed decision involving a complex regulatory scheme. Such is the design of the drug approval process: Congress requires sponsors to submit applications and data to FDA, and tasks FDA with evaluating sponsors' submissions to make drug approval determinations. *See generally* 21 U.S.C. § 355; 21 C.F.R. Part 314. There were no ulterior motives, and Veloxis has not pointed to any legal missteps by FDA in this process (other than an off-hand reference to 21 U.S.C. § 355(q) that is entirely misplaced). [2]

- FDA did everything it could to consider Veloxis' requests related to the Envarsus XR ("Envarsus") NDA on an expedited timeline. For example, after receiving FDA's tentative approval letter on October 30, 2014, Veloxis contacted FDA and requested a meeting. The agency honored that request and over 20 FDA employees from various agency components met with representatives from Veloxis six days later, on November 6, 2014. AR at FDA 01588–91. After this meeting, Veloxis continued to administratively engage FDA in order to have the agency consider new information related to the Envarsus NDA. Veloxis submitted additional information to FDA on four occasions after November 6, 2014: November 14, December 2, December 8, and December 12, 2014. AR at FDA 01623–1742; FDA01751–61. Understanding that Veloxis was anxious to have the agency consider this new information as expeditiously as possible, FDA worked overtime to ensure that Veloxis' request remained a priority.

---

[1] Veloxis' use of the term "ex parte" to describe FDA's communication with Astellas is misplaced. In a legal sense, "ex parte" refers to communication with only one party in an adversarial proceeding between two parties. EX PARTE, Black's Law Dictionary (10th ed. 2014) (online edition). But Veloxis and Astellas are not parties to an adversarial proceeding before FDA, and thus the agency's decision to communicate with an entity it regulates is *not* "ex parte," and certainly not improper in any event. Moreover, the communication has been made part of the administrative record in this case.

[2] As noted in Federal Defendants' opening brief, Veloxis' reference to 555(q) (21 U.S.C. § 355(q)) is a red herring. *See* Defendants' Memorandum of Points and Authorities In Support of Their Motion to Dismiss, Or In The Alternative, For Summary Judgment And Opposition to Plaintiff's Summary Judgment Motion ("Defs.' Br.") at 12 n. 7. Further, Veloxis has failed to establish that the agency acted improperly under this section of the FDCA (or any other).

- Veloxis (prematurely) filed this lawsuit because, at least in part, it claims that "FDA has never explained what conditions of approval it believes [Envarsus and Astagraf] share." Pl.'s Comp. ¶ 59. FDA answered that question, as promised to Veloxis, on January 12, 2015, just one month after Veloxis' December 12, 2014 submission. In its well-reasoned 50+ page decision (attached to Defendants' opening brief as Exhibit A), FDA explained why Envarsus could not, with its current labeling, be approved before July 19, 2016. AR at FDA 00001–57. As it did on December 5, 2014 when the agency first communicated that Envarsus could be approved for the conversion use, *see* AR at FDA 1748–50, FDA encouraged Veloxis to submit revised labeling for Envarsus that would enable FDA to approve, and Veloxis to legally market, Envarsus in the U.S. immediately. AR at FDA 00001–57. To date, Veloxis has not submitted such labeling, demonstrating a business decision to favor this litigation over immediate entry into the U.S. market. Accordingly, any harm that Veloxis may now allege is purely self-inflicted.[3]

- Veloxis' Reply reads as though time stood still on October 30, 2014, ignoring the administrative process— that Veloxis itself requested—to have FDA reevaluate the October 30, 2014 tentative approval decision. *See, e.g.,* Memorandum of Points and Authorities In Support of Its Motion for Summary Judgment And Opposition to Defendants' Motion to Dismiss, Or In The Alternative, For Summary Judgment ("Pl.'s Reply") at 2. FDA's January 12, 2015 decision—which came at the end of this administrative process—is entitled to deference. *Serono Labs., Inc. v. Shalala,* 158 F.3d 1313, 1325 (D.C. Cir. 1998); *see also* Defs.' Br. at 22 n. 11.

- Veloxis chose to instigate this litigation on December 16, 2014, despite FDA's assurance that the agency would issue its decision by January 12, 2015. Veloxis cannot now complain that FDA had the Complaint and Motion for Preliminary Injunction when the agency was drafting its January 12, 2015 decision. Further, it is entirely within Veloxis' control whether and when it submits a labeling amendment to obtain approval for the conversion use.

I. RELIANCE IS NOT REQUIRED FOR A LATER-IN-TIME APPLICANT TO BE BLOCKED BY THREE-YEAR EXCLUSIVITY UNDER 21 U.S.C. § 355(c)(3)(E)(iii)

A. Under *Chevron,* FDA's interpretation of the statute must be upheld

As explained in the Federal Defendants' opening brief, to be eligible for three-year exclusivity under 21 U.S.C. § 355(c)(3)(E)(iii), an application must: (1) be a 505(b)(1) or 505(b)(2) NDA; (2) have been approved after the Hatch-Waxman Amendments (in 1984); (3) be for a drug that contains a previously-approved active ingredient (including any ester or salt of the

[3] *See infra* p. 23.

active ingredient); and (4) contain at least one new clinical study (that is not a bioavailability study) that is essential to approval of the application. Defs.' Br. at 32. If three-year exclusivity attaches to an application, FDA may not subsequently approve a 505(b)(2) application for the "conditions of approval" for which exclusivity was granted for a period of three years. Nowhere in the relevant statutory provision does it require that the blocked application rely upon FDA's findings of safety and effectiveness for the protected application in order for it to be blocked by that application's exclusivity-protected conditions of approval. Under *Chevron* step one, the Court can thus rule in favor of the Federal Defendants as the statutory text is clear.

Veloxis also advocates for the Court to dispose of this matter under *Chevron* step one; however, it has a vastly different reading of the statutory text. Pl.'s Reply at 5. It claims that three-year exclusivity can block a subsequent 505(b)(2) application only if the 505(b)(2) application "relies upon data from studies essential to the approval of a drug with exclusivity." Pl.'s Reply at 5. The problem with Veloxis' argument is the colossal leap required to reach its conclusion that the words of the three-year exclusivity provision protect an application approved earlier in time only if the competitor relied upon such application. While Veloxis makes several conclusory statements that the "plain language" supports its position, *see* Pl's Br. at 18–20, it never actually walks through its statutory language analysis. It is far from "plain" how Congress' mere use of the phrase "relied upon" in the statutory provision, regardless of the context of that phrase, "unambiguously requires an overlap," Pls. Br. at 18, between the conditions of approval for which three-year exclusivity is granted and the FDA findings of safety and effectiveness referenced in a 505(b)(2) application.

Moreover, as the Federal Defendants explained in the opening brief, the phrase "relied upon" is used only to define a 505(b)(2) application, as is plain from the statutory text:

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

21 U.S.C. § 355(c)(3)(E)(iii) (emphasis added). Similarly, the language bolded above appears in the statute's definition of a 505(b)(2) NDA:

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

21 U.S.C. § 355(b)(2) (emphasis added). Juxtaposing these two statutory provisions, it is obvious that the bolded text—in which the phrase "relied upon" appears—is simply the longhand way to describe a 505(b)(2) application. *IBP, Inc. v. Alvarez*, 546 U.S. 21, 34 (2005) ("the normal rule of statutory interpretation [is] that identical words used in different parts of the same statute are generally presumed to have the same meaning"). While there are perhaps less cumbersome ways that Congress could have referenced a 505(b)(2) application in 21 U.S.C. § 355(c)(3)(E)(iii), as Veloxis suggests, Congress did not. But whether Congress *could* have used different language to describe a 505(b)(2) application is not the relevant inquiry under *Chevron* step one, which only requires an analysis of "whether Congress has directly spoken to the precise question at issue." *Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S.

837, 842 (1984). The simple fact remains that Congress chose the words that it did, and FDA and this Court must give meaning to those words. *Conn. Nat'l Bank v. Germain*, 503 U.S. 249, 253-54 (1992) ("We have stated time and again that courts must presume that a legislature says in a statute what it means and means in a statute what it says there."). Veloxis' reliance argument thus fails at *Chevron* step one.[4]

The Federal Defendants have set forth sufficient support for the Court to uphold FDA's position on *Chevron* step one; however, should the Court disagree and proceed to *Chevron* step two, FDA's position should also be upheld. FDA explained in the preamble to the 1989 Proposed Rule that exclusivity is not dependent upon the drug product listed in a 505(b)(2) application: "when exclusivity attaches to . . . an innovative change in an already approved drug, the . . . effective date of approval of . . . 505(b)(2) applications for a drug with that . . . innovative change will be delayed until the innovator's exclusivity has expired . . . *regardless of the specific listed drug product to which the . . . 505(b)(2) application refers*." ANDA Regulations 54 Fed. Reg. 28,872, 28,897 (July 10, 1989) (emphasis added). The agency's position is further explained in FDA's well-considered January 12, 2015 decision. The agency's reasonable interpretation of the three-year exclusivity provision thus warrants deference, and

[4] Veloxis claims that FDA's regulation, 21 C.F.R. § 314.108(b)(4)(iv), "includes a reliance requirement." Pl's. Reply at 6–7. But this "reliance requirement" is not applicable here; as FDA explained in its January 12, 2015 decision, 21 C.F.R. §314.108(b)(4)(iv) refers to reliance only in the context of abbreviated new drug applications ("ANDAs") approved under 21 U.S.C. § 355(j)(2)(C). *see* AR at FDA 00027, n. 112. Similarly, Veloxis points to two citizen petition responses and *Astrazeneca Pharms. LP v. FDA*, 850 F. Supp. 2d 230, 235 (D.D.C. 2012), which contain statements such as, "while . . . exclusivity periods are in effect, FDA may not accept or approve certain applications that rely on the protected product for approval." *See* Pl.'s Reply at 6, n.4. Statements like these do not support Veloxis' position, because while they discuss *a* way in which a 505(b)(2) application can be blocked, they do not describe *the only* way in which a 505(b)(2) application can be blocked, and certainly do not preclude FDA from concluding that a 505(b)(2) NDA is also blocked from approval, in whole or part, by the exclusivity of a drug that it did not rely upon—an interpretation supported by the statutory language and clearly contemplated by the preamble statements. AR at FDA 00042.

should be upheld. *See* Defs.' Br. at 37–38; *Barnhart v. Walton*, 535 U.S. 212, 222 (2002); *United States v. Mead Corp.*, 533 U.S. 218, 227–28 (2001); *Mylan Labs., Inc. v. Thompson*, 389 F.3d 1272, 1279–80 (D.C. Cir. 2004).

B. FDA's reading of the statute is consistent with the purpose of the Hatch–Waxman Amendments

A recurring refrain in Veloxis' Reply is that FDA's reading of the statute is inconsistent with the legislative history and the purposes of the Hatch-Waxman amendments. Pl.'s Reply at 4, 8, 10, 21. This is simply untrue. As explained in the Federal Defendants' opening brief, the Hatch-Waxman Amendments serve two purposes: (1) to provide an incentive for innovation in drug development, and (2) to accelerate through an abbreviated approval pathway the availability of lower-cost drugs to consumers. Defs.' Br. at 3. Three–year exclusivity is one way the Hatch–Waxman Amendments encourage drug manufacturers to continue seeking innovations with already-approved active ingredients. *Id.* at 4–5. Under Veloxis' one-sided interpretation, three-year exclusivity would be rendered virtually meaningless, thereby disrupting the careful balance Congress intended between incentivizing innovation and fostering greater access to lower-cost drugs. FDA's interpretation, on the other hand, maintains the balance Congress established and does not elevate one goal over the other, as Veloxis would have the Court do here.

C. This is not a patent case

Veloxis tries to force a square peg into a round hole by inappropriately drawing on patent certification case law. While both patents and exclusivity are forms of intellectual property protection and are sometimes discussed together for the sake of convenience,[5] patents and

[5] *See, e.g.*, ANDA & 505(b)(2) Proposed Rule, 80 Fed. Reg. 6,082, 6,806 (Feb. 6, 2015) (to be codified at 21 C.F.R. pts 314 & 320).

exclusivity are not the same and are subject to distinct statutory provisions in the NDA approval context.

Patents are granted by the patent and trademark office ("PTO") and can encompass a range of claims and technological advances. In the Hatch-Waxman context, new drug applications are required to include a list of patents that claim the drug product, drug substance, or an approved method of use, and 505(b)(2) applications are required to include certifications to patents that claim the listed drugs, or approved uses for those drugs that they reference. *See* 21 U.S.C. § 355(b)(1) ("The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug . . . or which claims a method of using such drug"); 21 U.S.C. §§ 355(b)(2) – 355(b)(2)(A) ("[a]n application . . . for a drug for which the investigations . . . relied upon by the applicant for approval of the application were not conducted by or for the applicant . . . shall also include . . . a certification . . . with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug"). Thus, the patent provisions expressly link the requirements for patent certification to the drug relied upon for approval.

Exclusivity, on the other hand, is a prohibition on FDA approving (or, in some cases, accepting for review) certain competing applications, and it attaches to a drug upon final approval in accordance with the relevant statutory exclusivity provision. *See, e.g.*, 21 U.S.C. § 355(c)(3)(E)(ii), (j)(5)(F)(ii) (five-year new chemical entity exclusivity); 21 U.S.C. § 355(c)(3)(E)(iii), (j)(5)(F)(iii) (three-year exclusivity for new clinical investigation(s) essential to approval). Exclusivity was part of the balance created by the Hatch-Waxman Amendments; the Hatch-Waxman Amendments incentivize certain types of innovation (by, among other things,

delaying competition through exclusivity) while promoting competition through the creation of abbreviated approval pathways.

The statutory provision at issue in *Takeda Pharms., U.S.A., Inc. v. Burwell*, 2015 U.S. Dist. LEXIS 5908, *16-17 (D.D.C. Jan. 13, 2015), the recent District Court opinion Veloxis cites at length, relates to patent certification, not exclusivity. The patent certification provision at issue in *Takeda Pharms*, 21 U.S.C. § 355(b)(2)(A), unlike the exclusivity provision at issue in this case, expressly ties the need for such certification to the "drug for which . . . investigations [that were relied on in the 505(b)(2) application for approval] were conducted." *See* 21 U.S.C. 355(b)(2)(A). In contrast, the three-year exclusivity provision at issue here, 21 U.S.C. § 355(c)(3)(E)(iii), prohibits the agency from approving a 505(b)(2) application for the "conditions of approval" for which new clinical investigations were essential to the approval of the earlier-approved application.

The differences between patent-related provisions of the FDCA and the exclusivity provisions are an important backdrop for Veloxis' cherry-picked statements, such as Judge Jackson's statement that "reliance matters." *Takeda Pharms., U.S.A., Inc. v. Burwell*, 2015 LEXIS 5908, at *95. Reliance does matter—for patent certification cases, not for three-year exclusivity determinations under 21 U.S.C. § 355(c)(3)(E)(iii). Because patent certification has nothing to do with this case, Veloxis' attempts to import patent certification law here must fail.

D. FDA's long-standing position is that reliance is not a prerequisite for being blocked by three-year exclusivity

Veloxis wrongly claims that "thirty years of FDA's own precedent" favors Veloxis' view of the statute. Pl.'s Reply at 1. To the contrary, FDA's position here is consistent with FDA's longstanding position. At the outset, the agency has noted that this situation does not arise often because it requires a particular series of events, and because of "rational decision-making by

knowledgeable industry actors." Defs.' Br. at 37; AR at FDA00046. Moreover, Veloxis conveniently overlooks the examples that FDA highlighted in the January 12, 2015 decision where the agency has expressly articulated its view. FDA 00047–48. For example, in the case of Duoneb in 1997, FDA concluded that it likely would not be able to fully approve the drug until Combivent's exclusivity expired, even though Duoneb did not rely on FDA's findings of safety and effectiveness for Combivent in its 505(b)(2) application. Defs.' Br. at 34 n.17; FDA 00048; FDA 02181 ("a full approval would likely not be possible now, due to pertinent exclusivity for Combivent"); *see generally* FDA 02153-02182.

More recently, in May 2010, FDA considered the same issue here (*i.e.*, whether a 505(b)(2) NDA can be blocked by the exclusivity of another NDA even if there is no reliance on FDA's findings of safety and effectiveness for that NDA) for potentially-competing tramadol hydrochloride extended release products. Cipher, a later-in-time applicant, referenced in its 505(b)(2) application FDA's finding of safety and effectiveness for the first tramadol hydrochloride extended-release product, Ultram ER. AR at FDA 02186. Although Cipher did not reference or rely upon FDA's findings of safety and effectiveness for Ryzolt, FDA clearly stated that Cipher's product nonetheless could be blocked by Ryzolt's exclusivity-protected conditions of approval under 21 U.S.C. § 355(c)(3)(E)(iii). AR at FDA 00048; FDA 02184 ("Thus, the three-year exclusivity granted to Ryzolt will delay approval of the Cipher extended-release tramadol product if Cipher is seeking the same conditions of approval as are protected for Ryzolt."); *see generally* FDA 02183–88. This is entirely consistent with the position that FDA has taken here.

Finally, the Federal Defendants have explained that FDA's review of precedent, including the Metadate CD/Concerta and Testosterone examples, provides no indication that

FDA has abandoned its position on reliance. Defs.' Br. at 34–37; *see also* AR at FDA 00046–57. With respect to Metadate CD and Concerta in particular, Veloxis' assertions that the only plausible reason why Metadate CD was approved despite Concerta's exclusivity is because Metadate CD did not rely on FDA's findings of safety and effectiveness for Concerta is false. Pl.'s. Reply at 11–12. But Veloxis incorrectly focuses on the similarities between the two products rather than conducting the analysis the statute commands—that is, first analyzing the change in Concerta for which new clinical studies were essential, and then determining whether Metadate sought (and obtained) approval for those exclusivity-protected conditions of approval. *See infra* p. 17–21; Defs.' Br. at 24–31; AR at FDA 00025. As the administrative record makes clear, Concerta conducted new clinical studies that were essential to approval of a product with its unique PK profile, and Metadate was not blocked because it had a different PK profile. FDA's conclusion in the Metadate CD/Concerta example is consistent with FDA's conclusion here: because the conversion use is not protected by exclusivity, Envarsus can be approved for this use before Astagraf's exclusivity expires. AR at FDA 00043–46.[6]

II. FDA PROPERLY CONCLUDED THAT STUDY 158 IS A NEW CLINICAL INVESTIGATION WITHIN THE MEANING OF THE STATUTE AND THE AGENCY'S REGULATIONS

Veloxis asserts that because Study 158 had been previously submitted to FDA in support of a Prograf sNDA, that study cannot be a "new clinical investigation" that supports Astagraf's approval. Pl.'s Reply at 13–14. While conceding that it did not raise this issue in its November 14, 2014 submission to FDA, or its subsequent submissions to the agency on December 2, 8, or 12, Veloxis claims that it only learned the complete basis for FDA's decision, including which

[6] Veloxis also refers to Testim in its Reply brief. Pl.'s Reply at 12. Federal Defendants already addressed Testim in their opening brief and January 12, 2015 decision. Defs.' Br. at 36, AR at FDA 00051–53; FDA 00055–56. FDA also addressed other examples in its decisional letter. *See* AR at FDA 00046–49.

studies FDA believed constituted "new clinical investigations," via FDA's January 12, 2015 decision. Pl.'s Reply at 14, n 8; AR at FDA 01626–1742; FDA 01751–61. This assertion is belied by the declaration Plaintiff filed with this Court on December 17, 2014. *See* Bragg Decl. ¶ 6 (Dkt. No. 7–4):

> On November 7, 2014, I filed a Freedom of Information Act ("FOIA") request seeking FDA's Summary Basis of Approval for the Astagraf XL NDA as well as any communications from Astellas Pharma US, Inc. ("Astellas") to FDA regarding the scope of Astagraf XL's exclusivity. Attached hereto as Exhibit E is a true and correct copy of a cover letter and accompanying materials that Veloxis received from FDA on November 17, 2014, in response to Veloxis's FOIA request. The accompanying materials are: Enclosure 1: FDA Exclusivity Summary for Astagraf XL . . .

As is plain from the attachments to that declaration, Veloxis had, as of November 17, 2014, the Astagraf Exclusivity Summary, *see* AR at FDA 01082–1089, which identified Study 158 as one of the new clinical investigations essential to Astagraf's approval.[7]

Notwithstanding this fact, Veloxis' submissions to FDA, as well as its complaint, are devoid of any mention of Study 158 or Veloxis' current contentions that Study 158 fails to meet FDA's definition of a "new clinical investigation." *See Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 554–55 (2007); *Ciralsky v. CIA*, 355 F.3d 661, 668–70 (D.C. Cir. 2004) ("a sufficient complaint 'contains a short and plain statement of the claim showing that the pleader is entitled to relief' enough 'to give a defendant fair notice of the claims against him.'") (quoting Fed. R.

[7] Veloxis tries to make much of the fact that the Agency did not check "yes" or "no" in response to the question on the Astagraf Exclusivity Summary regarding whether the investigation "has been relied on by the agency to demonstrate the effectiveness of a previously approved drug product." Pl.'s Reply at 15, n. 10. However, as Veloxis acknowledges, FDA instead noted that Study 158 has three arms and one of the arms was used to *support* approval of another NDA. AR at FDA 01087. Veloxis also ignores the fact that FDA listed Study 158 when asked to identify each "new" investigation essential to the approval of Astagraf. AR at FDA 01087. Veloxis' attempts to cherry-pick statements from the Astagraf exclusivity summary are unavailing and do not demonstrate that Study 158 fails to qualify as a "new clinical investigation" under FDA's regulations. AR at FDA 01082-01089, 02068-02082; 21 C.F.R.§ 314.08(a).

Civ. P. 8(a)). Should the Court consider this new argument despite Veloxis' failure to raise it before the agency or file an amended complaint, the result nonetheless would not differ. This claim still fails as a matter of law based on the existing administrative record in this case for three independent reasons.

First, contrary to Veloxis' assertions, FDA reasonably concluded that Study 158 is a "new clinical investigation" within the meaning of 21 U.S.C. § 355(c)(3)(E)(iii) as interpreted in 21 C.F.R. § 314.108(a) because it was not used to demonstrate "substantial evidence of effectiveness" for Prograf for any indication or of safety for a new patient population. The statutory term "new clinical investigation," *see supra* p. 3, is defined in FDA's implementing regulation, 21 C.F.R. § 314.108(a):

> New clinical investigation means an investigation in humans the results of which have not been relied on by FDA to demonstrate *substantial evidence of effectiveness* of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product. For purposes of this section, data from a clinical investigation previously submitted for use in the comprehensive evaluation of the safety of a drug product but not to support the effectiveness of the drug product would be considered new.

(emphasis added). Thus, a "new clinical investigation" is not limited to an investigation that has not been previously submitted to FDA in support of an application or that FDA has never previously reviewed or included in product labeling. Among other bases, a clinical investigation may be determined to be "new" for exclusivity purposes if FDA has not previously relied on that investigation to "demonstrate substantial evidence of effectiveness or of safety in a new patient population." *Id.* In this case, although FDA previously reviewed certain data from Study 158 in connection with the Prograf NDA, and added a description of certain study information to the Prograf labeling, FDA did not rely on Study 158 to demonstrate *substantial evidence of*

effectiveness for Prograf or otherwise rely on it. Therefore it is "new" within the meaning of 21 U.S.C. § 355(c)(3)(E)(iii) and 21 C.F.R. § 314.108(a) for purposes of three-year exclusivity for Astagraf.

Try as it might, Veloxis has failed to show that FDA relied on Study 158 to demonstrate *substantial evidence of effectiveness* for Prograf or otherwise relied on it such that it was ineligible for consideration as a "new clinical investigation" for Astagraf. *E.g.*, Pl.'s Reply at 14 ("Astellas previously submitted the results of Study 158 in seeking an expansion of the Prograf label"); Pl.'s Reply at 14 ("FDA relied on those results in approving the label change"); Pl.'s Reply at 15 ("FDA relied upon at least two arms"); Pl.'s Reply at 16 ("FDA reviewed the data from all three arms of Study 158 in connection with its approval"). The conclusion that Study 158 is a new clinical investigation is further supported by the administrative record. *See also*, AR at FDA 01086 (Astagraf Exclusivity Summary stating that one of the arms was used to *support* approval of another NDA); AR at FDA 02073 (Astagraf Exclusivity Summary attachments noting that the *Prograf label was updated to include* this Prograf data in kidney patients). These documents do not reflect any FDA conclusion that Study 158 was relied on by FDA to demonstrate *substantial evidence of effectiveness* of a previously approved drug (Prograf) for any indication or of safety for a new patient population.

In fact, FDA only approved the Prograf sNDA in 2009 *after* another study (the Symphony-Elite trial) was submitted. It was the Symphony-Elite trial that demonstrated substantial evidence of effectiveness and safety for Prograf when combined with another immunosuppressant drug, mycophenolate mofetil ("MMF"), and established the recommended safe and effective dosing regimen for Prograf/MMF. AR at FDA 00191 (Table 1, Summary of Initial Oral Dosage Recommendations and Observed Whole Blood Trough Concentrations in

Adults). The Symphony-Elite trial and Study 158 included different dosing regimens, the latter of which was not the recommended regimen.[8] AR at FDA 00191 (*compare* Table 1 and Table 1 footnote (a) referring to dosing regimen in second smaller trial (Study 158)). Specific information on Study 158 comparing Prograf/MMF and a control group was ultimately included in the Prograf labeling to inform practitioners that more people died on the Prograf/MMF arm of Study 158 than did in the control arm of that study. AR at FDA 00221–00222 (*e.g.*, Tables 20: Incidence of BPAR, Graft Loss, Death or Loss to Follow-up at 12 Months in Study 2; Table 21: Tacrolimus Whole Blood Concentrations (Study 2); Table 22: MMF Dose Over Time in the Prograf/MMF group (Study 2)); *see also generally* AR at FDA 00188-00230. Because of this "imbalance in mortality," FDA *did not* and *could not* rely on Study 158 to demonstrate substantial evidence of effectiveness for Prograf because the safety of the dosing regimen had not been established in that study. AR at FDA 00221. In other words, Study 158 established no safe dosing regimen which could be evaluated for substantial evidence of effectiveness. Because Study 158 did *not* "demonstrate substantial evidence of effectiveness," for Prograf, FDA properly concluded it was a "new clinical investigation" under 21 C.F.R. § 314.108(a) when it considered it in conjunction with the Astagraf NDA.

Second, Study 158 had three arms: one for Astagraf with MMF ("Astagraf/MMF"), one for Prograf with MMF ("Prograf/MMF"), and an active control (which here was Neoral, a previously-approved drug product) with MMF ("control/MMF"). AR at FDA 00420; FDA 02073. By design, Study 158's main objective was: (1) to compare safety and efficacy of

[8] *See also, e.g.*, AR at FDA 00188-00230 (referencing Symphony-Elite trial as Study 1 and Study 158 as Study 2); FDA 00392 (referencing Study 158, in the context of January 19, 2007 Approvable Letter for Astagraf, and stating that Study 158 data "do not provide sufficient evidence of safety and efficacy to support an alternative dose of MMF" and noting that "an acceptable regimen of MMF dosing with tacrolimus in kidney transplantation was subsequently approved May 19, 2009, and is reflected in the approved Prograf[] labeling"); FDA 00428.

Prograf/MMF and control/MMF in *de novo* kidney transplant recipients; and, (2) to compare safety and efficacy of Astagraf/MMF and control/MMF in *de novo* kidney transplant recipients. AR at FDA 02073. A "clinical investigation" means "any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects." 21 C.F.R. § 314.108(a). Study 158 consisted of "two experiments," in which two different drugs (Prograf and Astagraf) were measured against the active control, and were "administered or dispensed to, or used on, human subjects." *Id.* Essentially, then, Study 158 included two clinical investigations each of which could independently qualify as a "new clinical investigation" under 21 C.F.R. § 314.08(a). This is supported by Prograf labeling. AR at FDA 000219-222. Accordingly, although Study 158 was submitted to support the Prograf sNDA, the data related to Astagraf were not included in the updated Prograf label because FDA did not rely on them to demonstrate the effectiveness of Prograf for use in kidney transplant patients. *Id.* Hence, on this basis, too, FDA considered Study 158 a "new clinical investigation" that could support Astagraf's three-year exclusivity.

Third, the extra-record March 14, 2007, FDA Statistical Review for the Prograf sNDA that Veloxis points to does not support its assertions.[9] Veloxis states that the Prograf sNDA Statistical Review shows FDA reviewed data "from all three arms of Study 158 in connection with its approval," which Veloxis acknowledges is consistent with good scientific practice. Pl.'s Reply at 16 (emphasis omitted). But Veloxis' conclusory statement conveniently ignores the

[9] The Federal Defendants maintain that Veloxis' introduction of the new argument and extra-record material is improper, *see infra* p. 11–13 & Defs.' Br. at 16–17 n. 9; 25 n. 13. Nonetheless, the Agency is addressing Veloxis' argument here in light of the expedited briefing schedule and Veloxis' unwillingness to alter that schedule to allow the parties time to review the administrative record in light of Veloxis' new basis for review. Veloxis has concurrently with its Reply, filed a Motion to Supplement the Administrative Record with two extra-record documents. The Federal Defendants intend to oppose that motion in a separate filing.

Statistical Review's Conclusions and Recommendations section, which makes no mention of the Astagraf and active control comparison. The Statistical Review also states "[a]ppropriate doses of MMF to be given with Prograf in *de novo* kidney transplantation cannot be accurately assessed from these data since a safe and effective MMF dose was not assessed." Plaintiff's Memorandum of Points & Authorities in Support of its Motion for Summary Judgment ("Pl's Br.") Ex. 6 at 25. This conclusion is consistent with the fact that Study 158 as a whole *was not* and *could not have been* relied on by FDA to demonstrate substantial evidence of effectiveness for Prograf because the safety of the dosing regimen had not been established in that study. Moreover, Veloxis has cherry-picked one of three publicly-available statistical reviews in an attempt to skew the facts.[10] The August 20, 2007 Prograf sNDA Statistical Review—which Veloxis did *not* attach to its summary judgment motion—expressly refers to the Agency's action on March 14, 2007, in which FDA declined to approve the Prograf supplement because "a safe and effective dosage regimen of MMF as an adjunct therapy with Prograf [had] not been established in [Study 158]." The May 15, 2009 Statistical Review primarily describes the Symphony-Elite trial, which is what led FDA to approve the Prograf sNDA. Thus, the extra-record statistical review that Veloxis cites does not demonstrate that Study 158 was not a "new clinical investigation" under 21 C.F.R. § 314.08(a).

The Agency's conclusion here is supported by the administrative record and FDA's interpretation of its regulation and the regulatory scheme; it is therefore entitled to "substantial deference." *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994) ("This broad deference is all the more warranted when, as here, the regulation concerns 'a complex and highly technical

[10] All three statistical reviews for the Prograf sNDA are contained in the same .pdf document on FDA's website. *See http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/050708Orig1s027_StatR.pdf.*

regulatory program. . .'") (quoting *Pauley* v. *BethEnergy Mines, Inc.*, 501 U.S. 680, 697 (1991). FDA's position is also supported by the preamble statement that "an applicant is not limited to recently conducted clinical investigations; a clinical investigation that provides a "new" basis for drug approval can qualify for exclusivity." Abbreviated New Drug Applications; Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338 at 50,359 (Oct. 3, 1994) (Final Rule).

For all these reasons, Veloxis' arguments concerning Study 158 do not alter FDA's exclusivity determination for Astagraf, and Veloxis' claim therefore fails as a matter of law.[11]

III. ENVARSUS AND ASTAGRAF SHARE EXCLUSIVITY-PROTECTED CONDITIONS OF APPROVAL

The parties in this case agree that exclusivity is governed by "conditions of approval," which is determined by the "new clinical investigations" essential to that approval. Pl.'s Br. at 29, 35 (citing 21 U.S.C. § 355(c)(3)(E)(iii); Defs.' Br. at 25. Veloxis concedes that the term "conditions of approval" is not defined in either the FDCA or its implementing regulations, Pl.'s Br. at 35, and does not assert that its meaning is plain, implicitly conceding that "conditions of approval" is appropriately analyzed under *Chevron* Step Two.

The agency has explained that the scope of three-year exclusivity covers "the innovative change" that is supported by new clinical investigations. AR at FDA 00025. Courts have upheld this position. *E.g., Zeneca Inc. v. Shalala*, No. CIV.A. WMN–99–307, 1999 WL 728104, at *12 (D. Md. Aug. 11, 1999) *aff'd*, 213 F.3d 161 (4th Cir. 2000) ("The exclusivity extends only to the 'change approved in the supplement.'"). Because the three-year exclusivity analysis hinges on the conditions of approval for which new clinical investigations were essential, a 505(b)(2)

[11] Because Veloxis has failed to demonstrate that Astagraf's exclusivity was not properly based on Study 158, the agency need not address its argument regarding the proper scope of Astagraf's exclusivity based on Study 12-03 alone. The Federal Defendants included a short analysis on this point in their opening brief. Defs.' Br. at 27.

application can differ in certain respects from the previously-approved product protected by exclusivity and nonetheless be blocked. Defs.' Br. at 6; AR at FDA 00026. Conversely, a 505(b)(2) application can be the same as a previously-approved product in many respects and not be blocked if it does not share those conditions of approval for which exclusivity was granted. *E.g.*, AR at FDA 00049–51 (explaining this situation in the context of Metadate CD and Concerta); FDA 02297–904.

While Veloxis does not dispute FDA's approach to the "conditions of approval" analysis (nor does it offer an alternative that is plausible under the statute[12]), it disagrees with how FDA has applied this analysis to the facts of this case, arguing once again that because Envarsus and Astagraf are different in a number of respects, Astagraf's exclusivity should not block Envarsus' approval. FDA agrees that for non-exclusivity protected conditions of approval, *i.e.*, those conditions of approval for which new clinical investigations were *not* essential, Envarsus is not blocked, regardless of whether it is the same as or different from Astagraf in those aspects. Hence, the agency has determined that Veloxis could immediately be approved for the conversion use if it submits a labeling amendment to its 505(b)(2) application. AR at FDA 00001–57. The other differences Veloxis asserts (pharmacokinetic ("PK") profile, dosage form, dosage strength, and dosing regimen) are irrelevant for the exclusivity analysis in this case because Veloxis seeks approval for Envarsus for an exclusivity-protected condition of Astagraf's approval. *See* Defs.' Br. at 29–31.

[12] As noted in the Federal Defendants' opening brief, Veloxis' "conditions of approval" analysis would render 21 U.S.C. § 355(c)(3)(E)(iii) superfluous because three-year exclusivity would only block approval of ANDAs. *See* Defs.' Br. at 29. Although Veloxis contends on reply that it is not claiming that only duplicates would be blocked under 21 U.S.C. § 355(c)(3)(E)(iii), it has failed to explain how anything more than just duplicates could be blocked under its interpretation. Pl.'s. Reply at 19. It certainly has not demonstrated that FDA's interpretation of "conditions of approval" is unreasonable, in violation of the APA, or undeserving of *Chevron* deference. *Mylan Labs.*, 389 F.3d at 1279.

In addition to rehashing the differences between the two products while ignoring the exclusivity-protected conditions of approval that Envarsus and Astagraf share (*i.e.*, their once-daily, extended release dosage forms for prophylaxis of organ rejection in *de novo* kidney transplant patients), Veloxis' principal argument concerns the timing of FDA's analysis. But Veloxis' discontent on this point would be more appropriately directed at Congress for creating a statutory scheme for three-year exclusivity that is based on shared exclusivity-protected conditions of approval. 21 U.S.C. § 355(c)(3)(E)(iii); Defs.' Br. at 24–25; Pl.'s. Br. at 29, 35. To determine whether two products *share* such conditions of approval, the agency necessarily has to wait until a second, potentially-competing drug application with the same conditions of approval as an already-approved drug for which that sponsor has conducted new clinical investigations essential to its approval (*i.e.*, the exclusivity-protected conditions of approval) nears approval. Defs.' Br. at 2, 25; AR at FDA 00025. That FDA's analysis regarding whether two drugs share exclusivity-protected conditions of approval necessarily occurs *after* the agency's grant of exclusivity for the first drug *does not* render the agency's exclusivity analysis "post hoc" in the legal sense. *Serono Labs., Inc. v. Shalala*, 158 F.3d at 1325 ("'The post hoc rationalization' rule is not a time barrier which freezes an agency's exercise of its judgment after an initial decision has been made and bars it from further articulation of its reasoning. It is a rule directed at reviewing courts which forbids judges to uphold agency action on the basis of rationales offered by anyone other than the proper decisionmakers.'") (quoting *Local 814, Int'l Bhd. of Teamsters v. NLRB*, 546 F.2d 989, 992 (D.C. Cir. 1976)). There is no question here that the appropriate FDA decisionmakers engaged in that analysis and determined that Envarsus is

blocked by Astagraf's exclusivity because the two drugs share at least one exclusivity-protected condition of approval. Defs.' Br. at 30; AR at FDA 00001–57.[13]

As Veloxis notes, this analysis is "far from so simple." Pl.'s Reply at 20. The Federal Defendants agree. *See* AR at FDA 00006 (noting that the agency's decision in this case "involved the intersection of complex legal, regulatory, policy, scientific, and technical issues."). And that is why FDA's determinations on such matters are afforded deference. *Thomas Jefferson Univ. v. Shalala*, 512 U.S. at 512 ("[t]his broad deference is all the more warranted when . . . the regulation concerns 'a complex and highly technical regulatory program,' in which the identification and classification of relevant 'criteria necessarily require significant expertise and entail the exercise of judgment grounded in policy concerns.'") (quoting *Pauley v. BethEnergy Mines, Inc.*, 501 U.S. 680, 697 (1991)). Courts must "review scientific judgments of the agency 'not as the chemist, biologist, or statistician that [they] are qualified neither by training nor experience to be, but as a reviewing court exercising [its] narrowly defined duty of holding agencies to certain minimal standards of rationality.'" Troy Corp. v. Browner, 120 F.3d 277, 283 (D.C. Cir. 1997) (quoting Ethyl Corp. v. EPA, 541 F.2d 1, 36 (D.C. Cir. 1976)); Int'l Fabricare Inst. V. EPA, 972 F.2d 384, 389 (D.C. Cir. 1992) ("The rationale for deference is particularly strong when [the agency] is evaluating scientific data within its technical expertise.").

Finally, Veloxis alludes to "important consequences for drug development" as a further reason why the Court should overturn FDA's reasonable interpretation of an undefined statutory term. Under FDA's approach, a 505(b)(2) applicant who avails itself of the abbreviated pathway

[13] Veloxis also intimates that FDA's January 12, 2015 decision is "post-hoc." Pl.'s Reply at 19. It is not, nor is it undeserving of deference because of its timing. *See infra* p. 3 (citing *Serono Labs., Inc.*, 158 F.3d at 1325); Defs.' Br. at 22 n. 11 (same).

bears some uncertainty when it engages in the drug development process because another entity may obtain approval for a similar product faster, and therefore be eligible for a potentially blocking exclusivity. One way to mitigate this risk is to file a 505(b)(1) NDA; such applications are not blocked by three-year exclusivity under 21 U.S.C. § 355(c)(3)(E)(iii). Defs.' Br. at 32. Under Veloxis' view, however, the risk should fall not on the later-in-time applicant but instead on the earlier-approved NDA applicant who conducted the new clinical studies that earned it exclusivity. AR at FDA 00026. Of course, because Envarsus is a later-in-time application, Veloxis urges this Court to place all of the uncertainty in the drug approval process on the earlier-approved applicants who would (under Veloxis' interpretation) risk having their exclusivity rendered considerably less valuable by the premature approval of a competing 505(b)(2) application. *Id.* This approach would significantly reduce the incentive to conduct new clinical studies and disturb the careful balance Congress created with the Hatch-Waxman amendments. Defs.' Br. at 3–6; FDA 00026–28. Moreover, the agency—not Veloxis—is in the best position to weigh competing policy goals.

In sum, FDA's reasonable interpretation that exclusivity protects "conditions of approval" for which new clinical investigations were essential is deserving of deference under *Chevron* step two. Applying this analysis to the facts here, the only logical conclusion is that Envarsus is blocked by Astagraf because, like Astagraf, Envarsus is also a once-daily, extended release dosage form for use in *de novo* kidney transplant patients for the prophylaxis of organ rejection.

IV. FDA PROPERLY GRANTED ASTAGRAF EXCLUSIVITY UNDER 21 U.S.C. § 355(v)

Veloxis urges on reply that this Court should set aside the plain meaning of 21 U.S.C. § 355(v) in favor of the legislative history. This approach runs afoul of the basic principle of

statutory interpretation requiring Courts to begin (and end) their analysis with the unambiguous words of a statute. *E.g., Conn. Nat'l Bank*, 503 U.S. at 253-54. This is especially true where, as here, Congress spoke clearly when it made Old Antibiotics eligible for Hatch-Waxman exclusivity based on the date an application was submitted. 21 U.S.C. § 355(v)(1)(B) ("an application . . . submitted . . . *after* the date of the enactment of [the QI Act] in which the drug that is the subject of the application contains [an Old Antibiotic]"); Defs.' Br. at 6–7; 22–23. But even under *Chevron* step two, as Veloxis urges, the Federal Defendants have outlined a number of reasons why the agency's reading of the statute is reasonable. Defs.' Br. at 23–24.[14] As explained in the Federal Defendants' opening brief, Astagraf's eligibility for exclusivity under 21 U.S.C. § 355(v) is clear on the face of the statutory text; in the alternative, Veloxis has not advanced any valid basis to overturn FDA's reasonable interpretation of the statute, which hinges on the date an application is submitted regardless of any applications that were previously withdrawn; and Veloxis has failed to demonstrate that Astellas was ineligible for exclusivity under either 21 U.S.C. § 355(c) or 355(v). *See id*.

V. VELOXIS' SELF-INFLICTED HARM DOES NOT WARRANT INJUNCTIVE RELIEF

Veloxis asks this Court to overlook its failure to allege harm in this case, or in the alternative, focus on the harms it asserted in its November 6, November 14, and December 8, 2014 submissions to FDA. Pl.'s Reply at 25. Of course, the harms stated in these submissions pre-date the agency's January 12, 2015 decision in which it provided Veloxis the opportunity to submit revised labeling that would enable FDA to grant immediate final approval to Envarsus for

[14] Veloxis also encourages FDA and the Court to draw conclusions about Astellas' reasoning for withdrawing its application. Pl.'s Reply at 24. But FDA's regulation does not require a sponsor to provide such rationale to FDA, and "[a] decision to withdraw the application is without prejudice to refiling." 21 C.F.R. § 314.65.

the conversion use and not be blocked by Astagraf's exclusivity. *Id.* To date, Veloxis has declined to submit such labeling to the agency. Given that it remains, to date, in Veloxis' control when Envarsus will be available to the American public, any harm it may allege *today* is necessarily self-inflicted, and therefore cannot support Veloxis' claims for injunctive relief. *Pennsylvania v. New Jersey*, 426 U.S. 660, 664 (1976) (per curiam) (litigant cannot "be heard to complain about damage inflicted by its own hand"); *Safari Club Int'l v. Salazar*, 852 F. Supp. 2d 102, 123 (D.D.C. 2012) (no irreparable harm when plaintiffs could avoid harm); *Lee v. Christian Coal. of Am.*, 160 F. Supp. 2d 14, 33 (D.D.C. 2001) ("the irreparable harm criterion" is not satisfied "when the alleged harm is self-inflicted") (citations omitted).

CONCLUSION

Veloxis chose to submit Envarsus as a 505(b)(2) application rather than a stand-alone NDA. It now attempts to blame FDA for the consequences of that decision. FDA cannot be faulted for faithfully implementing the statutory scheme Congress designed, which permits three-year exclusivity for Old Antibiotic drugs in certain cases. Accordingly, the Court should grant the Federal Defendants' Motion to Dismiss, Or in the Alternative, for Summary Judgment, and deny Veloxis' summary judgment motion.

Respectfully submitted,

Of Counsel:

WILLIAM B. SCHULTZ
General Counsel

ELIZABETH H. DICKINSON
Associate General Counsel
Food and Drug Division

PERHAM GORJI
Deputy Chief Counsel, Litigation

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

BENJAMIN C. MIZER
Acting Assistant Attorney General

JONATHAN F. OLIN
Acting Assistant Attorney General

MICHAEL S. BLUME
Director

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