

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206406Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2016 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER NAME OF APPLICANT/NDA HOLDER Veloxis Pharmaceuticals A/S	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) Envarsus			
ACTIVE INGREDIENT(S) Tacrolimus		STRENGTH(S) 0.75, 1, and 4 mg	
DOSAGE FORM Oral tablet			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 7,994,214		b. Issue Date of Patent 08/09/2011	
		c. Expiration Date of Patent 08/30/2024	
d. Name of Patent Owner Veloxis Pharmaceuticals A/S		Address (of Patent Owner) Bøge Allé 5, 2th	
		City/State Hørsholm, Denmark	
		ZIP Code 2970	FAX Number (if available) +45-3613-0319
		Telephone Number +45-70333300	E-Mail Address (if available) patents@veloxis.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Jay P. Lessler		Address (of agent or representative named in 1.e.) The Chrysler Building, 405 Lexington Avenue	
		City/State New York, N.Y.	
		ZIP Code 10174-0208	FAX Number (if available) (917)332-3773
		Telephone Number (212)885-5176	E-Mail Address (if available) jlessler@blankrome.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No 			
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No 			

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☒ No

2.6 Does the patent claim only an intermediate? ☐ Yes ☒ No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

3.2 Does the patent claim only an intermediate? ☐ Yes ☒ No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

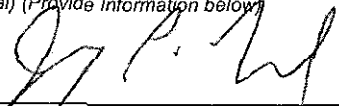
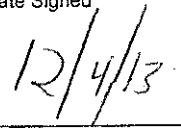
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification	
6.1 <i>The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.</i> Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.	
6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below) 	Date Signed 
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Check applicable box and provide information below.	
☐ NDA Applicant/Holder ☐ Patent Owner	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official ☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Jay P. Lessler	
Address The Chrysler Building, 405 Lexington Avenue	City/State New York, N.Y.
ZIP Code 10174-0208	Telephone Number (212)885-5176
FAX Number (if available) (917)332-3773	E-Mail Address (if available) jlessler@blankrome.com
This section applies only to requirements of the Paperwork Reduction Act of 1995. *DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.* The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to: Department of Health and Human Services Food and Drug Administration Office of Chief Information Officer Paperwork Reduction Act (PRA) Staff PRAStaff@fda.hhs.gov <i>"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."</i>	

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1. GENERAL			
a. United States Patent Number 8,486,993		b. Issue Date of Patent 07/16/2013	
		c. Expiration Date of Patent 08/30/2024	
d. Name of Patent Owner Veloxis Pharmaceuticals A/S		Address (of Patent Owner) Bøge Allé 5, 2th	
		City/State Hørsholm, Denmark	
		ZIP Code 2970	FAX Number (if available) +45-3613-0319
		Telephone Number +45-70333300	E-Mail Address (if available) patents@veloxis.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Jay P. Lessler		Address (of agent or representative named in 1.e.) The Chrysler Building, 405 Lexington Avenue	
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		ZIP Code 10174-0208	FAX Number (if available) (917)332-3773
		Telephone Number (212)885-5176	E-Mail Address (if available) jlessler@blankrome.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No			
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No			

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.	
2. Drug Substance (Active Ingredient)	
2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes ☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes ☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes ☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.	
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	
☐ Yes ☒ No	
2.6 Does the patent claim only an intermediate?	
☐ Yes ☒ No	
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	
☐ Yes ☐ No	
3. Drug Product (Composition/Formulation)	
3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	
☒ Yes ☐ No	
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4. Method of Use	
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4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	
☒ Yes ☐ No	
4.2 Patent Claim Number(s) (as listed in the patent) 7 and 8	4.2 Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
☒ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) Prophylaxis of organ rejection
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For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	
☐ Yes	

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

12/4/13

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Check applicable box and provide information below.

☐ NDA Applicant/Holder

☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

☐ Patent Owner

☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Jay P. Lessler

Address

The Chrysler Building, 405 Lexington Avenue

City/State

New York, N.Y.

ZIP Code

10174-0208

Telephone Number

(212)885-5176

FAX Number (if available)

(917)332-3773

E-Mail Address (if available)

jlessler@blankrome.com

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Food and Drug Administration
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Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2016 See OMB Statement on Page 3.	
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1. GENERAL			
a. United States Patent Number 8,586,084		b. Issue Date of Patent 11/19/2013	c. Expiration Date of Patent 8/30/2024
d. Name of Patent Owner Veloxis Pharmaceuticals A/S		Address (of Patent Owner) Bøge Allé 5, 2th	
		City/State Hørsholm, Denmark	
		ZIP Code 2970	FAX Number (if available) +45-3613-0319
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e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Jay P. Lessler		Address (of agent or representative named in 1.e.) The Chrysler Building, 405 Lexington Avenue	
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		Telephone Number (212)885-5176	E-Mail Address (if available) jlessler@blankrome.com
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4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

4.2 Patent Claim Number(s) (as listed in the patent) 1, 2, and 4-17 Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No

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5. No Relevant Patents

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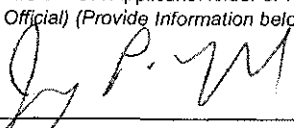
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		c. Expiration Date of Patent 08/30/2024	
d. Name of Patent Owner Veloxis Pharmaceuticals A/S		Address (of Patent Owner) Bøge Allé 5, 2th	
		City/State Hørsholm, Denmark	
		ZIP Code 2970	FAX Number (if available) +45-3613-0319
		Telephone Number +45-70333300	E-Mail Address (if available) patents@veloxis.com
		e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Jay P. Lessler	
		FAX Number (if available) (917)332-3773 E-Mail Address (if available) jlessler@blankrome.com	
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		☐ Yes ☒ No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		☐ Yes ☐ No	

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☒ No

2.6 Does the patent claim only an intermediate? ☐ Yes ☒ No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? ☒ Yes ☐ No

3.2 Does the patent claim only an intermediate? ☐ Yes ☒ No

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4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

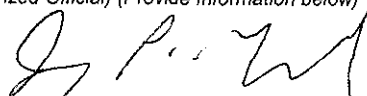
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

12/4/13

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder

☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

☐ Patent Owner

☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Jay P. Lessler

Address

The Chrysler Building, 405 Lexington Avenue

City/State

New York, N.Y.

ZIP Code

10174-0208

Telephone Number

(212)885-5176

FAX Number (if available)

(917)332-3773

E-Mail Address (if available)

jlessler@blankrome.com

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRASaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2016 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER NAME OF APPLICANT/NDA HOLDER Veloxis Pharmaceuticals A/S	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) Envarsus			
ACTIVE INGREDIENT(S) Tacrolimus		STRENGTH(S) 0.75, 1, and 4 mg	
DOSAGE FORM Oral tablet			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 8,617,599		b. Issue Date of Patent 12/31/2013	
		c. Expiration Date of Patent 08/30/2024	
d. Name of Patent Owner Veloxis Pharmaceuticals A/S		Address (of Patent Owner) Bøge Allé 5, 2th	
		City/State Hørsholm, Denmark	
		ZIP Code 2970	FAX Number (if available) +45-3613-0319
		Telephone Number +45-70333300	E-Mail Address (if available) patents@veloxis.com
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Jay P. Lessler		Address (of agent or representative named in 1.e.) The Chrysler Building, 405 Lexington Avenue	
		City/State New York, N.Y.	
		ZIP Code 10174-0208	FAX Number (if available) (917)332-3773
		Telephone Number (212)885-5176	E-Mail Address (if available) jlessler@blankrome.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		☐ Yes ☒ No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		☐ Yes ☐ No	

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2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No

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2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☒ No

2.6 Does the patent claim only an intermediate? ☐ Yes ☒ No

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4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☒ No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

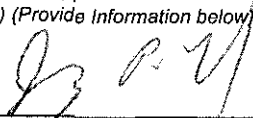
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)

Date Signed



12/13/13

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder

☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

☐ Patent Owner

☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Jay P. Lessler

Address

The Chrysler Building, 405 Lexington Avenue

City/State

New York, N.Y.

ZIP Code

10174-0208

Telephone Number

(212)885-5176

FAX Number (if available)

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E-Mail Address (if available)

jlessler@blankrome.com

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRASaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

Date Submitted: 12/28/2013
Date Received: 12/30/2013

Veloxis Pharmaceuticals
1.3. Administrative Information

Tacrolimus extended-release tablets

DEBARMENT CERTIFICATION

Veloxis Pharmaceuticals hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Ron Guido

Digitally signed by Ron Guido
DN: dc=local, dc=veloxis, ou=Veloxis, ou=Users,
ou=Internal, ou=US, cn=Ron Guido,
email=rguido@veloxis.com
Date: 2013.11.15 07:05:27 -05'00'

Ronald Guido

Senior Vice-President, Quality and
Regulatory Affairs

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 206406	NDA Supplement # NA	If NDA, Efficacy Supplement Type: NA
Proprietary Name: Envarsus XR Established/Proper Name: tacrolimus Dosage Form: extended-release tablets, 0.75mg, 1mg, 4mg		Applicant: Veloxis Pharmaceuticals, Inc. Agent for Applicant (if applicable): NA
RPM: Lois Almoza		Division: Division of Transplant and Ophthalmology Products
<u>NDAs and NDA Efficacy Supplements:</u> NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (For additional information regarding 505(b)(2)s, please refer to http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/RegulatoryAffairsTeam/ucm027499.htm) <u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): NDA 050708 - Prograf® (tacrolimus) Capsules 0.5mg, 1 mg and 5 mg Provide a brief explanation of how this product is different from the listed drug. This application provides for a new extended-release formulation. ☐ This application does not rely upon a listed drug. ☐ This application relies on literature. ☐ This application relies on a final OTC monograph. ☒ This application relies on (explain) The applicant relies on Bioavailability (BA) studies and they also conducted their own efficacy and safety trials. <u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u> <u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u> ☒ No changes ☐ Updated Date of check: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.		
❖ Actions - Proposed action - User Fee Goal Date is August 12, 2015 - Previous actions (<i>specify type and date for each action taken</i>)		☒ AP – 7/10/15 ☐ TA ☐ CR TA – 10/30/14

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain <u>N/A</u>	☐ Received N/A
❖ Application Characteristics ³	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rolling Review ☒ Orphan drug designation ☐ Breakthrough Therapy designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC ☐ Submitted in response to a Pediatric Written Request REMS: ☐ MedGuide ☐ Communication Plan ☐ ETASU ☐ MedGuide w/o REMS ☐ REMS not required Comments:	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	☐ Yes ☐ No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Exclusivity	
Is approval of this application blocked by any type of exclusivity? NOTE: The October 30, 2014, Tentative Approval letter stated the following: As noted in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), the listed drug product Astagraf XL (NDA 204096), with which you share conditions of approval for which new clinical studies were essential, is subject to a period of exclusivity protection under sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the Act. Therefore, final approval of your application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be effective until that product's exclusivity period has expired. Please see Pages 1 through 3 of the July 10, 2015, Clinical Review for the Regulatory History of this application, including issues pertaining to Exclusivity.	☒ No ☐ Yes
NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.	☒ No ☐ Yes If yes, NDA/BLA # _____ and date exclusivity expires: _____ Prograf is approved for kidney transplantation but does not have Orphan Exclusivity in this indication.
(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) Note: refer to history under first bullet in this section	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)	☒ No ☐ Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)

Version: 12/09/2013

its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	X
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) TA – 10/30/14 AP – 7/10/15

⁴ Fill in blanks with dates of reviews, letters, etc.

Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	X Included labeling dated 7/7/15
- Original applicant-proposed labeling dated 12/28/2013 - Labeling submitted with 6/12/15 Class 1 resubmission	X Included
Example of class labeling, if applicable	NDA 204096/Astagraf XL
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☒ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	X Included labeling dated 7/2/15
Original applicant-proposed labeling dated 12/28/2013	X Included
Example of class labeling, if applicable	NDA 204096/Astagraf XL
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
Most-recent draft labeling	X Included Container labels dated 9/26/14 Container ^(b) ₍₄₎ overwrap dated 10/9/14 Carton label dated 10/16/14
❖ Proprietary Name	Proprietary Name Request Granted Acceptable on 4/18/14 Re-review for Class 1 Resubmission after a Tentative Approval action is not necessary
- Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) 04/18/14 - Review(s) Review finalized on 03/14/14 - Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.	
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☐ RPM ☒ DMEPA 8/26/14, 10/02/14 & 10/07/14 ☒ DMPP/PLT (DRISK) 10/08/14 ☒ OPDP (DDMAC) 10/09/14 & 10/15/14 ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	

Administrative Reviews (e.g., RPM Filing Review ⁵ /Memo of Filing Meeting) (indicate date of each review)	RPM Filing Review 3/12/14
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment Form signed 7/10/15	☐ Not a (b)(2) X Included 7/10/15
❖ NDAs only: Exclusivity Summary (signed by Division Director) <i>Note: Exclusivity Summary to be finalized at a later date.</i>	X Not Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
○ If yes, Center Director's Exception for Review memo (indicate date)	
○ If yes, OC clearance for approval (indicate date of clearance communication)	☐ Not an AP action
❖ Pediatrics (approvals only)	N/A - Orphan drug designation granted for the active moiety for the indication prophylaxis of organ rejection in patients receiving allogeneic kidney transplant.
• Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: <u>Orphan Drug Designation letter dated December 20, 2013 from the Office of Orphan Products Development in the December 30, 2013, submission</u>	
• Pediatric Page/Record (approvals only, must be reviewed by PERC before finalized)	
	☒ Not Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (include certification)	☒ Verified, statement is acceptable
❖ Outgoing communications (letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)	X Included
❖ Internal memoranda, telecons, etc.	X Included
❖ Minutes of Meetings	
• Regulatory Briefing (indicate date of mtg)	☒ No mtg
• If not the first review cycle, any end-of-review meeting (indicate date of mtg)	☐ N/A Type C meeting held on 3/11/15 after Tentative Approval was granted on 10/30/14
• Pre-NDA/BLA meeting (indicate date of mtg)	☐ No mtg Two separate meetings were held on 8/07/13, one with DTOP and one with ONDQA.
• EOP2 meeting (indicate date of mtg)	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (indicate dates of mtgs)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (do not include transcript)	

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

Decisional and Summary Memos

❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	X 10/30/14 & 7/10/15
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	X 10/15/14
PMR/PMC Development Templates (<i>indicate total number</i>)	X 5 Templates
Clinical Information⁶	
❖ Clinical Reviews	
Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	9/25/14 & 7/10/15 reviews signed by Director and Deputy Director for Safety
Clinical review(s) (<i>indicate date for each review</i>)	9/25/14 & 7/10/15
Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	X Page 26 of 10/30/14 Division Director Review and Page 29 of Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ Not applicable
❖ Risk Management - REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) - REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) - Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	X Included in the Action Package are the OSI Clinical inspection review summary dated 9/25/14 & 3 OSI letters to investigators regarding site inspections (7/22/14 letter to Suphamai Bunnapradist, M.D.; 9/19/14 letter to Klemens Budde, M.D.; and 9/22/14 letter to Kazimierz Ciechanowski, M.D.)

⁶ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology ☐ None	
✓ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	Division Director signed primary review dated 7/24/14
Clinical Microbiology Review(s) (indicate date for each review)	Clinical Microbiologist signed primary review dated 7/23/14 and signed review noted on 6/18/15
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	☒ None
Statistical Team Leader Review(s) (indicate date for each review)	Team Leader signed primary reviews dated 9/24/14 and 7/10/15
Statistical Review(s) (indicate date for each review)	Statistical Reviewer signed primary reviews dated 9/24/14 and 7/10/15
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☒ None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	Primary review signed on 9/25/14 by Pharmacometrics Team Leader and OCP Team Leader; Addendums to 9/25/14 primary review signed on 10/16/14 and 7/9/15 by Pharmacometrics Team Leader & OCP Team leader; OCP Team Leader review signed by OCP Team Leader on 6/25/15
Clinical Pharmacology review(s) (indicate date for each review)	Primary review signed on 9/24/14 by Pharmacometrics Reviewer and OCP Reviewer; Addendum to 9/25/14 primary review signed on 10/15/14 by Pharmacometrics Reviewer and OCP Reviewer; Addendum to 9/25/14 primary review signed by Pharmacometrics Reviewer on 7/9/15
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	☒ None

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	☒ None
• Supervisory Review(s) <i>(indicate date for each review)</i>	Secondary Review signed on 10/29/14 by Team Leader; Primary reviews signed on 9/24/14 and 10/30/14 by Team Leader; Labeling review signed on 6/30/15 by Team Leader
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	Labeling review signed on 6/30/15 by Reviewer; Primary reviews signed on 9/24/14 and 10/30/14 by Reviewer
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	☒ None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	☒ None requested

Product Quality ☐ None	
✓ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	☒ None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	Biopharmaceutics review addendum signed on 10/16/14 by Biopharmaceutics Team Leader; Product Quality review signed by Branch Chief on 10/29/14; Biopharmaceutics review signed by Biopharmaceutics Team Leader on 6/25/15; Product Quality review signed on 7/1/15 by Acting Quality Assessment Lead and Acting Branch Chief
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	Biopharmaceutics review addendum signed on 10/16/14 by Biopharmaceutics reviewer; Product Quality reviews signed by Product Quality reviewer and Senior Product Quality reviewer on 10/28/14 and 9/25/14; Biopharmaceutics review signed by Biopharmaceutics reviewer on 6/25/15
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	Included in Product Quality Microbiology Assessment review signed by reviewer and team leader on 1/13/2014
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	Page 103 of September 25, 2014, Product Quality review
☐ Review & FONSI <i>(indicate date of review)</i>	
☐ Review & Environmental Impact Statement <i>(indicate date of each review)</i>	

❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) (date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites ⁷)	Date completed: September 01, 2014 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation (check box only, do not include documents)	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review) ☒ NA, as noted in Page 8 of 113 September 25, 2014, Product Quality review

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

From: Almoza, Lois
Sent: Monday, July 06, 2015 3:09 PM
To: Ron Guido (rgu@Veloxis.com)
Cc: Willard, Diana M
Subject: Class 1 Resubmission - NDA 206406/ Envarsus XR(tacrolimus extended-release tablets) 0.75 mg, 1 mg, 4 mg/Veloxis Pharmaceuticals, Inc

Good Afternoon,

Please see attached the recommended revisions to the Package Insert, section 2, Dosage and Administration, 2.1 Administration Instructions. If you have any questions, please do not hesitate to contact me.

Thank you,
Lois

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6241
Silver Spring, MD 20993
Phone: 240-402-5146 Fax: 301-796-9881

2 DOSAGE AND ADMINISTRATION

2.1 Administration Instructions

- Take ENVARSUS XR on an empty stomach at the same time of the day, preferably in the morning (to ensure consistent and maximum possible drug exposure) [see *Clinical Pharmacology (12.3)*].
- Swallow ENVARSUS XR whole with fluid (preferably water); do not chew, divide, or crush the tablets.
-
- If a dose is missed, take it as soon as possible within 15 hours after missing the dose; beyond the 15-hour time frame, wait until the usual scheduled time to take the next regular daily dose. Do not double the next dose.
- Avoid eating grapefruit or drinking grapefruit juice or alcoholic beverage while taking ENVARSUS XR [see *Drug Interactions (7.2)*].
- African-American patients, compared to Caucasian patients, may need to be titrated to higher ENVARSUS XR dosages to attain comparable trough concentrations [see *Use in Specific Populations (8.8)* and *Clinical Pharmacology (12.3)*].

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/s/

LOIS A ALMOZA
07/06/2015

From: Almoza, Lois

Sent: Monday, June 29, 2015 3:01 PM

To: Bill Polvino (wjp@veloxis.com); (b) (4)

Cc: Willard, Diana M

Subject: Proposed CMC PMCs - NDA 206406/ Envarsus XR(tacrolimus extended-release tablets) 0.75 mg, 1 mg, 4 mg/Veloxis Pharmaceuticals, Inc

Good Afternoon,

Please see the proposed CMC PMCs below and let me know if you are in agreement. In addition to sending your response via e-mail, please also submit your response to the application on file.

PMC#1: Develop and validate a regulatory X-Ray Powder Diffraction (XRPD) test, with a limit of detection of not more than (b) (4), for determination of crystalline tacrolimus content in tacrolimus extended-release tablets. Revise 3.2.P.5 Drug Product Specification accordingly. Submit a supplemental NDA to add the XRPD testing facility.

Add XRPD testing to the on-going drug product stability protocol (first three commercial batches of each strength or next three consecutive commercial batches of each strength and annual stability commitment batches).

The following timelines are proposed for **PMC#1**:

Final Protocol Submission: 09/2015

Study/Trial Completion: 04/2016

Final Report Submission: 07/2016

Interim Report: 01/2016

PMC#2: Develop and validate an X-Ray Powder Diffraction (XRPD) test, with a limit of detection of not more than (b) (4)

[REDACTED]

Add XRPD testing to tacrolimus (b) (4) stability protocol.

The following timelines are proposed for **PMC#2:**

Final Protocol Submission:	09/2015
Study/Trial Completion:	04/2016
Final Report Submission:	07/2016
Interim Report:	01/2016

PMC#3: Evaluate the crystalline content of available legacy batches of tacrolimus (b) (4) and of drug product stability batches by XRPD.

The following timelines are proposed for **PMC#3:**

Final Protocol Submission:	09/2015
Study/Trial Completion:	04/2016
Final Report Submission:	07/2016

Interim Report: 01/2016

PMC#4: Evaluate conditions that might be expected to promote crystallization of tacrolimus in (b) (4) tablets, including:

1. Any relationship between (b) (4) and crystalline Tacrolimus content in tacrolimus extended-release tablets.
2. The (b) (4) stability of tacrolimus in (b) (4) tablets under accelerated and stress conditions.

The following timelines are proposed for **PMC#4:**

Final Protocol Submission:	10/2015
Study/Trial Completion:	10/2016
Final Report Submission:	01/2017
Interim Report:	04/2016

PMC#5: Evaluate the effect of MeltDose manufacturing process parameters on crystalline content of (b) (4) tablets.

The following timelines are proposed for **PMC#5:**

Final Protocol Submission: 10/2015

Study/Trial Completion: 10/2016

Final Report Submission: 01/2017

Interim Report: 04/2016

Thank you,

Lois

Lois Almoza, M.S.

Regulatory Health Project Manager

Division of Transplant and Ophthalmology Products

Office of Antimicrobial Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue

Building 22, Room 6241

Silver Spring, MD 20993

Phone: 240-402-5146

Fax: 301-796-9881

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/s/

LOIS A ALMOZA
06/29/2015

MEMORANDUM

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

DATE: June 25, 2015

TO: NDA 206406

FROM: Lois Almoza, M.S.
Regulatory Health Project Manager

SUBJECT: Verbal Information Request

APPLICATION/DRUG: tacrolimus extended-release tablets

Veloxis Pharmaceuticals, LLC submitted an Amendment: Draft Labeling – Conversion Patients submission, received on June 12, 2015.

During the review process, a concern was raised based on the material submitted. On June 25, 2015, the Agency notified the Applicant that the electronic submission received did not contain a recent version of their Medguide or carton and container labels. Veloxis will submit a general correspondence to the application on file to formally inform the Agency exactly which Medguide and carton and container they would like the Agency to consider for Approval. Over the phone Veloxis stated the Division could consider the Medguide submitted on October 29, 2014 for approval.

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/s/

LOIS A ALMOZA
06/25/2015



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION TRANSMITTAL SHEET

DATE: June 25, 2015

To: Dr. Bill Polvino, President & Chief Executive Officer	From: Lois Almoza, M.S., Regulatory Health Project Manager
Company: Veloxis Pharmaceuticals, Inc.	Division of Transplant and Ophthalmology Products
Phone Number: 732-321-3202	Phone Number: 301-796-1600
Email: wjp@veloxis.com	Email: lois.almoza@fda.hhs.gov

Subject: NDA 206406/Envarsus XR (tacrolimus extended-release tablets), 0.75 mg, 1.0 mg and 4.0 mg/Veloxis Pharmaceuticals, Inc.

Total no. of pages including cover: 26

Document to be mailed: ☐ YES ☒ NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-796-1600. Thank you.

Dear Dr. Polvino:

Please refer to your June 12, 2015, resubmission, received June 12, 2015, 2013, to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Envarsus XR (tacrolimus extended-release tablets), 0.75 mg, 1 mg and 4 mg.

We are providing recommended revisions to the Package Insert and Medication Guide. Attached please find a copy of the proposed Package Insert and Medication Guide for your review. If you have any questions, please do not hesitate to contact us.

We are providing the above information by email for your convenience. Contact me at 301-796-1600 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LOIS A ALMOZA
06/25/2015

From: Almoza, Lois

Sent: Tuesday, June 23, 2015 9:21 AM

To: Bill Polvino (wjp@veloxis.com); (b) (4)

Cc: Willard, Diana M

Subject: NDA 206406/ Envarsus XR(tacrolimus extended-release tablets) 0.75 mg, 1 mg, 4 mg/Veloxis Pharmaceuticals, Inc

Good Morning,

In follow-up to my phone call, please submit to the application on file a request for proprietary name review for the Class 1 resubmission received, June 12, 2015 as soon as possible.

Thank you,

Lois

Lois Almoza, M.S.

Regulatory Health Project Manager

Division of Transplant and Ophthalmology Products

Office of Antimicrobial Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue

Building 22, Room 6241

Silver Spring, MD 20993

Phone: 240-402-5146

Fax: 301-796-9881

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/s/

LOIS A ALMOZA
06/23/2015



NDA 206406

**ACKNOWLEDGE -
CLASS 1 COMPLETE RESPONSE**

Veloxis Pharmaceuticals, Inc.
Attention: William Polvino, MD
Chief Executive Officer
499 Thornall Street
3rd Floor
Edison, NJ 08837

Dear Dr. Polvino:

We acknowledge receipt on August 12, 2015, of your August 12, 2015, resubmission to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Envarsus XR (tacrolimus extended-release tablets), 0.75 mg, 1 mg and 4 mg.

We consider this resubmission a complete, class 1 response to our action letter. Therefore, the user fee goal date is August 12, 2015.

If you have any questions, call me, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LOIS A ALMOZA
06/19/2015

MEMORANDUM

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

DATE: June 18, 2015

TO: NDA 206406

FROM: Lois Almoza, M.S.
Regulatory Health Project Manager

SUBJECT: Verbal Information Request

APPLICATION/DRUG: tacrolimus extended-release tablets

Veloxis Pharmaceuticals, LLC submitted an Amendment: Draft Labeling – Conversion Patients submission, received on June 12, 2015.

During the review process, a concern was raised based on the material submitted. On June 18, 2015, the Agency notified the Applicant that the electronic submission received was incomplete. Under the 1.14 Labeling module, the Proposed Labeling Text – Redline (Word) submission was empty. All other draft labeling submitted and received on June 12, 2015, was able to be viewed. The Applicant agreed to resubmit the Proposed Labeling Text – Redline (Word) immediately.

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/s/

LOIS A ALMOZA
06/18/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

William Polvino, MD
Chief Executive Officer
Michelle Mc Guinness
Vice President, Global Regulatory & Quality Assurance
Veloxis Pharmaceuticals, Inc.
499 Thornall Street
3rd Floor
Edison, NJ 08837

Dear Dr. Polvino and Ms. Mc Guinness,

This letter responds to your letters dated January 20, 2015 and April 13, 2015, regarding your tentatively approved new drug application (NDA) for Envarsus XR (NDA 206406). In your letters, you explain that Veloxis seeks

(b) (4)

Specifically, you propose that:

(b) (4)

First and foremost, CDER does not provide legal advice on litigation strategy nor would it be appropriate to do so. As a procedural matter,

(b) (4)

(b) (4)

Sincerely,

Edward M. Cox, MD, MPH
Director
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

EDWARD M COX
05/26/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

April 29, 2015

William Polvino, MD
Chief Executive Officer
Veloxis Pharmaceuticals, Inc.
499 Thornall Street, 3rd Floor
Edison, New Jersey 08837

Dear Dr. Polvino,

On behalf of Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER), I acknowledge your letter of April 13, 2015, regarding NDA 206406 for Envarsus XR.

Dr. Woodcock is working with CDER's Division of Transplant and Ophthalmology Products and others to carefully consider your letter.

Sincerely,

Jay Sitlani

Senior Regulatory Counsel
Office of Regulatory Policy, CDER

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/s/

LOIS A ALMOZA
05/12/2015



NDA 206406

MEETING MINUTES

Veloxis Pharmaceuticals, Inc.

Attention: Ms. Michelle A. McGuinness

VP Global Regulatory Affairs & Quality Assurance

499 Thornall Street

3rd Floor

Edison, NJ 08837

Dear Ms. McGuinness:

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

We also refer to the meeting between representatives of your firm and the FDA on March 11, 2015. The purpose of the meeting was to discuss the contents of proposed labeling for use of Envarsus XR in conversion patients only.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting.

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

Sincerely,

{See appended electronic signature page}

Renata Albrecht, MD

Director

Division of Transplant and Ophthalmology

Products

Office of Antimicrobial Products

Office of New Drugs

Center for Drug Evaluation and Research

Enclosure:

Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Other

Meeting Date and Time: March 11, 2015 from 3:00PM – 4:00PM (EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: 206406
Product Name: Envarsus XR (tacrolimus extended-release tablets), 0.75 mg, 1 mg, and 4 mg
Indication: prophylaxis of organ rejection in kidney transplant patients
Applicant Name: Veloxis Pharmaceuticals, Inc.

Meeting Chair: Renata Albrecht, MD
Meeting Recorder: Lois Almoza, MS

FDA ATTENDEES

Renata Albrecht, MD	Director, Division of Transplant and Ophthalmology Products (DTOP)
Ozlem Belen, MD, MPH	Deputy Director for Safety, DTOP
Marc Cavaillé-Coll, MD, PhD	Clinical Reviewer, DTOP
Ergun Velidedeoglu, MD	Clinical Reviewer, DTOP
Shukal Bala, PhD	Clinical Microbiology/Immunology Reviewer, Division of Anti-Infective Products (DAIP)
Gerlie Gieser, PhD	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology IV (DCPIV)
Yan Wang, PhD	Statistical Team Leader
Hongling Zhou, PhD	Statistical Reviewer, OB/DBIV
Diana Willard	Chief, Project Management Staff, DTOP
Judit Milstein	Chief, Project Management Staff, DTOP
Lois Almoza, MS	Regulatory Health Project Manager, DTOP

VELOXIS PHARMACEUTICALS, INC. ATTENDEES

Bill Polvino, MD	President and Chief Executive Officer
Vicenza Nigro	Vice President (VP) of Medical Affairs
Michelle McGuinness	VP Global Regulatory Affairs & Quality Assurance

VELOXIS PHARMACEUTICALS, INC. CONSULTANTS

Jennifer Bragg
Scott Lassman

Skadden, Arps, Slate, Meager & Flom LLP
Kleinfeld, Kaplan, & Becker LLP

BACKGROUND

The cover letter of a February 13, 2015, submission, received February 18, 2015, from Veloxis Pharmaceuticals, Inc. (Veloxis) requested a Type A meeting for NDA 206406 to, "... discuss our stalled product development program for NDA 206405 (*sic*) Envarsus XR™ (tacrolimus extended-release tablets) 0.75 mg, 1.0 mg and 4.0 mg." Veloxis' submission included the following as a brief statement of the purpose and objectives of the meeting:

(a) understand the basis for the Agency's refusal to allow conversion patients access to Envarsus XR where FDA agrees no exclusivity blocks the product's approval for this indication; and (b) explore and rapidly agree upon the administrative pathway to enable immediate approval in conversion patients while concurrently enabling Veloxis to resolve its dispute with the Agency over the *de novo* indication through the ongoing litigation.

The Agency's March 4, 2015 Meeting Granted letter stated:

We also refer to your February 13, 2015, correspondence, received February 18, 2015, requesting a Type A meeting because you believe that your product development for Envarsus XR in conversion patients is currently stalled. We disagree that your development program for Envarsus XR in conversion patients is stalled because you have the option of submitting a Class 1 resubmission containing revised labeling for that use at any time. Therefore, we are granting you a Type C meeting on March 11, 2015, to discuss the contents of proposed labeling for the conversion use. This date is within the timeframe of a Type A meeting.

Veloxis agreed to the proposed March 11, 2015, meeting date on March 5, 2015 and submitted the Meeting Package on March 10, 2015.

INTRODUCTION

The following introductory statements were made by FDA:

Good afternoon and welcome to the FDA. I am Lois Almoza, the Regulatory Health Project Manager for NDA 206406/Envarsus XR (tacrolimus extended-release tablets).

The purpose of this meeting is to discuss the content of Veloxis' proposed labeling for conversion patients only, and our meeting today will be limited to that topic. As stated in the Meeting Granted letter issued March 4, 2015, we note that FDA does not provide advice regarding litigation strategy and a meeting with representatives of the Center for Drug Evaluation and Research is not an appropriate forum for seeking advice about how to maintain a pending lawsuit. As this is a scientific discussion, FDA's counsel is not present at this meeting.

We received your briefing package containing the proposed labeling yesterday (Tuesday,

March 10, 2015). The Division will listen to your proposed labeling changes and provide preliminary comments. However, we may not be able to answer all questions at this meeting and we cannot provide today any final decisions pertaining to your proposed revised labeling.

Following introductions of meeting attendees, the meeting was turned over to Veloxis.

DISCUSSION

The questions submitted in the March 10, 2015, Meeting Package are provided in **bold font**. And the discussion during the March 11, 2015, meeting is presented in regular font.

1. Would the Agency provide comment to the proposed labeling provided as background to this meeting?

Meeting Discussion:

Veloxis presented its slides (Attachment 1) in order. Veloxis also included proposed revised labeling (Attachment 2) in the Meeting Package dated March 10, 2015.

Veloxis provided a proposed revision to section 1 Indications and Usage (slide 4) reflecting conversion of kidney transplant patients from immediate release preparations of tacrolimus to Envarsus XR only. The Agency acknowledged the revision was reasonable and noted that the final decision would be made after formal submission of the labeling and discussions by the review team.

Veloxis subsequently presented section (b) (4) (slide 5). The Agency acknowledged the deletion of that section, and asked for clarification, including the statement regarding dosing (b) (4)

Veloxis presented section 2.3 Conversion from Tacrolimus Immediate-Release Formulation (slide 6) and section 6.1 Adverse Reactions - Clinical Studies Experience (slide 7). The Agency acknowledged the changes appeared reasonable, and requested presentation of adverse events overall and for the conversion population only in both tabular and narrative format for the Division's consideration.

Veloxis presented section 8.5 Geriatric Use (slide 8), clarifying the patient counts were adjusted to reflect conversion only, as well as section 12.3, Pharmacokinetics (slide 9). To avoid confusion, the Agency requested Veloxis to refer to Phase 3 Study 3001 in the labeling as the "Conversion Study" rather than "Study 1."

The Agency stated the review team would discuss how to best describe data regarding the 0.14 mg/kg/day and 0.17 mg/kg/day in the labeling.

Consistent with the recommendations during the December 5, 2014, meeting, Veloxis proposed to delete (b) (4)

2. If Veloxis were to amend its NDA to pursue the conversion-only approach:

a. When can Veloxis expect final Agency feedback on labelling, if not today?

Meeting Discussion:

Veloxis asked the question above and the Agency replied with the following:

The Agency can provide preliminary scientific input but does not intend to make any final decisions at this meeting. The proposed labeling would need to be submitted to the NDA as a Class 1 resubmission for Agency review before a final decision on conversion labeling for Envarsus XR can be made.

b. What would be the steps and timing for final approval of conversion-only NDA?

Meeting Discussion:

Veloxis asked the question above and the Agency replied with the following:

Per PDUFA agreements, the goal date for an action on a Class 1 resubmission is two months from the date of receipt. The Agency intends to review revised labeling promptly consistent with its review priorities upon receipt of a formal submission of a Class 1 resubmission to the application. The Agency will be available for dialog with Veloxis regarding proposed conversion labeling during this two month period.

c. What would be the subsequent steps and timing for final approval of tentatively approved labeling (i.e., to include de novo following expiry of Astagraf XL exclusivity)?

Meeting Discussion:

The Agency asked Veloxis if there is a timeframe for when Veloxis will make a decision on their course of action – either when they will submit a Class 1 resubmission, or alternatively when they will make a decision not to send a resubmission. Veloxis stated they would let the Agency know their decision by the end of the March and Veloxis acknowledged that the next decision and steps are up to Veloxis, and specifically used the expression that the ball is in Veloxis' court.

d. Could the Agency confirm the date of expiry of Astagraf XL exclusivity as July 19, 2016 and specify whether or not any extensions may occur?

Meeting Discussion:

The Agency replied that as was stated in the introductory comments to this meeting, as well as in the March 4, 2015, Meeting Granted letter, this meeting is limited to discussion of the contents of proposed labeling for the conversion use. This question is outside the scope of this meeting.

3. **What administrative pathway can be agreed upon to allow for immediate approval and patient access in the conversion setting** [REDACTED] ^{(b) (4)}
[REDACTED] **that is the subject of the current Tentative Approval letter?**

Meeting Discussion:

Regarding this question, the Agency responded that a reply was already provided to this question in the March 4, 2015, Meeting Granted letter which stated, “We also note your reference to your January 21, 2015 letter and intend to respond to that letter separately.”

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/s/

RENATA ALBRECHT
03/26/2015

Center Director Decisional Briefing

Date: December 3, 2014

Topic: Does 3-Year Exclusivity for Astagraf XL, a Once-Daily, Extended-Release Dosage Form of Tacrolimus, Block Final Approval of Envarsus XR?

CDER Staff Contact: Jay Sitlani

CDER Executive Operations Staff Contact: Chris Bechtel

Attendees

CDER OCD: Janet Woodcock, Bob Temple
OTS/OCP: Phil Colangelo, John Lazor, Gerlie Gieser,
ORP: Jay Sitlani, Carol Bennett, Nancy Hayes, Nisha Shah, Melissa Matles
OCC: Liz Dickinson, Kim Dettelbach, Mustafa Unlu, Sonal Vaid, Sonia Nath, Nancy Boocker, Amanda Edmonds
OND: John Jenkins
OAP: John Farley, Jacquelyn Smith
DTOP: Renata Albrecht, Marc Cavaille-Coll, Ozlem Belen, Ergun Velidedeoglu
OCOMM: Kim Rawlings
OGD: Kristin Davis, Kendra Stewart, Katherine Uhl

Agenda

(See attached slides)

- Approval of Astagraf XL & Envarsus XR: Discussion of Product Characteristics, Clinical Studies Essential to Approval
- Scope of Astagraf XL's 3-Year Exclusivity
- Discussion of Options: Policy Concerns & Legal/Regulatory Risks

Issue

The scope of 3-year exclusivity for Astagraf XL: Does Astagraf XL's exclusivity block the final approval of Envarsus XR?

Options

Option 1 -- *Status quo -- Envarsus XR remains tentatively approved.*

Option 2 – Approve Envarsus XR for use in the conversion (or stable) kidney transplant population only (assuming Veloxis agrees to this approach).

Option 3 --- Approve Envarsus XR without any changes to the labeling.

Discussion

Jay Sitlani presented the slides. A factual background regarding the Astagraf XL approval was first discussed, followed by a discussion of options available to the Agency regarding the approval of Envarsus XR.

Factual Background

Astellas conducted bioequivalence studies evaluating Astagraf XL's once-daily formulation and Prograf twice-daily formulation, which revealed that Astagraf XL was not bioequivalent to Prograf (different C_{max} and AUC; higher mg:mg doses were needed with Astagraf XL than with Prograf). Therefore, DTOP required that clinical studies be conducted for approval of Astagraf XL (see Slide 3). Astellas complied with FDA's request. The safety and efficacy for Astagraf XL was supported by results from two efficacy studies.

Envarsus XR is, however, seeking approval pursuant to section 505(b)(2) of the FD&C Act, relying upon FDA's finding of safety and/or effectiveness for Prograf for nonclinical studies, as well as certain clinical pharmacology data, including drug interactions and PK in renal impairment and hepatic impairment. Envarsus XR did not rely on Astagraf XL as a listed drug because the two NDAs were developed in parallel (see slide 4).

DTOP explained that the *de novo* population of transplant recipients is different from the conversion population because the former population requires more frequent monitoring to titrate to the correct dose of tacrolimus (see slide 8). The Phase 3 clinical trials for Astagraf XL were performed only in a *de novo* kidney transplant population. Astellas did not conduct clinical trials deemed adequate and well-controlled in stable kidney transplant patients to convert them from an IR, twice-daily tacrolimus to Astagraf XL (three Phase 2 PK studies were performed in conversion patients). Accordingly, Astagraf XL's labeling contains dosing information only for the *de novo* population and does not contain dosing information for the conversion/maintenance population. The labeling, however, has PK data from one of the three Phase 2 PK studies in the conversion population. The indication is silent with respect to conversion. The Dosage and Administration section provides a dosing regimen (with starting concentrations and dose titrations to specific trough levels) for only the *de novo* population.

In contrast, Veloxis' clinical program for Envarsus XR entailed clinical studies in both the *de novo* population (Study 3002) and conversion population (Study 3001) (see slide 9). Veloxis initially proposed a clinical study only in the conversion population, but DTOP requested that they also conduct a study in the *de novo* population because the *de novo* population is more sensitive.

Regarding its 3-year exclusivity, Astellas claims that the conditions of approval for Astagraf XL encompass the once-daily formulation of tacrolimus indicated for the prophylaxis of organ rejection in transplant recipients regardless of patient setting, and no application for those conditions can be approved until expiration of the exclusivity period on July 19, 2016 (see slide 10). Veloxis argues that Envarsus XR has a different dosage form (tablet versus capsule), a different dosing regimen, and different PK properties compared to Astagraf XL, and that it did

not rely on the Agency's finding of safety and effectiveness of Astagraf XL for approval, and thus Astagraf XL's exclusivity should not block Envarsus XR's approval.

Both Astagraf XL and Envarsus XR are dosed once daily. There are, however, minor differences in the dosing regimens of Astagraf XL and Envarsus XR in that they have different starting concentrations, titration schedules and target trough concentration levels (see slide 12). If we were to tie exclusivity to the specific features of each product (for example, its specific formulation), exclusivity would only block the approval of generic products. The Agency, however, found that Astagraf XL's exclusivity was based on its once-daily extended-release form of tacrolimus. Therefore, products such as Envarsus XR that share these exclusivity-protected conditions of approval would be blocked from final approval until the expiry of Astagraf XL's exclusivity.

Options

Three options are available to the Agency. The first (Option 1) is to maintain the status quo, which is a tentative approval of Envarsus XR because it is blocked by Astagraf XL's exclusivity that would cover once-daily, extended-release dosage form for tacrolimus (see slide 14).

The second option (Option 2) is to approve Envarsus XR only for the conversion population because Astagraf XL's exclusivity only covers once-daily, extended-release dosage form of tacrolimus for the prophylaxis of organ rejection in *de novo* kidney transplant patients because clinical studies were only conducted in this setting (see slide 15). Under this option, no information regarding the use of the product in *de novo* transplant patients would be provided in the labeling (unless there is a compelling safety reason to include that information). The approved indication could either specifically state that the product is indicated for use only in the conversion setting, or could remain silent with respect to the patient setting (*de novo* or conversion) and be identical to that for Astagraf XL. DTOP required clinical studies specifically to include instructions on conversion from tacrolimus IR to ER, so there is a medical and scientific basis by which the Agency can approve Envarsus XR for the conversion indication.

(b) (5)

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/s/

LOIS A ALMOZA
01/14/2015



NDA 206406

GENERAL ADVICE

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

Dear Ms. McGuinness:

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

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

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

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

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

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

I. BACKGROUND

A. Immunosuppression in Kidney Transplant Patients¹

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

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

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

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

During the early post-transplant period, the patient's regimen of these immunosuppressants is carefully and frequently monitored, which may include measuring drug trough (predose) concentrations in blood³ and may be adjusted to minimize the development of adverse reactions while keeping the immune system from rejecting the kidney. The immunosuppressive regimen is adjusted according to the patient's individual course, including the occurrence of rejection episodes (signifying increased risk for rejection), and according to adverse events (signifying poor tolerance of the regimen). The goal is to customize the regimen to find the optimum balance between the efficacy and toxicity of the immunosuppressive regimen.

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

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

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

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

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

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

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

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

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

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

B. Tacrolimus and Prograf NDA 050708

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

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

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

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

⁵ Id. (Description section).

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

⁷ Id. (Dosage and Administration section).

⁸ Id.

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

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

indication of the drug product. Thus, even though tacrolimus was approved to prevent organ rejection rather than for antimicrobial use, it is considered an antibiotic drug.¹⁰ Because tacrolimus is an antibiotic drug substance that was the subject of an application for marketing received by FDA before November 21, 1997 (i.e., before enactment of the Food and Drug Administration Modernization Act (FDAMA¹¹)), it is commonly referred to as an *Old Antibiotic*.¹² There are no patents or exclusivities listed for the Prograf NDA in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book).^{13,14}

C. Astagraf XL

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

1. Astagraf XL NDA 050811 and Withdrawal¹⁶

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

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

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

¹¹ Public Law 105-115.

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

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

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

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

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

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

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

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

On September 12, 2007, Astellas submitted a complete response to the January 19, 2007, approvable letter for NDA 050811.²³ Astellas amended its NDA with results from the PK sub-study of Study 12-03,²⁴ as well as with some limited information on safety and efficacy in the population studied.²⁵

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

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

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

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

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

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

²² Astagraf XL CDTL Review at 2.

²³ *Id.*

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

²⁵ Astagraf XL CDTL Review at 2.

²⁶ *Id.*

²⁷ *Id.*

Specifically, while reviewing NDA 050815 (liver indication), FDA found that there was a substantial gender-related difference in 12-month mortality rates between the Astagraf XL and Prograf treatment groups and a gender difference in the onset of post-transplant diabetes mellitus.²⁸ The Agency concluded that data from a PK sub-study of Study 12-03 was insufficient to determine if the observed 20% higher AUC₀₋₂₄ for Astagraf XL, compared with Prograf, was related to this clinically significant higher incidence of tacrolimus-related adverse events for Astagraf XL.²⁹ Although these adverse events were observed in the liver transplant setting, the Agency remained concerned that these adverse events could also exist in kidney transplant patients.³⁰ To address this deficiency in the kidney transplant context, the Agency requested that Astellas submit the full study report for Study 12-03 and study datasets that included, among other things, exposure-response analyses between safety outcomes (i.e., post-transplant diabetes mellitus, renal dysfunction, CMV and other infections, cardiac disorders, and glucose intolerance), efficacy outcomes, and C_{trough} (trough concentrations) as a function of gender and treatment group.³¹ The Agency also requested that Astellas analyze by gender and treatment groups all “adverse events of special interest” for *all* existing Astagraf XL versus Prograf trials in solid organ transplantation, not just Study 12-03 or studies in kidney transplantation.³²

On January 29, 2009, Astellas requested withdrawal of NDA 050811.³³ In a letter dated February 10, 2009, the Agency informed Astellas that if it decided to resubmit the application, the withdrawal would not prejudice any future decisions on filing.³⁴ The Agency also informed Astellas that it could reference information contained in the withdrawn application in any resubmission and that it should address the deficiencies identified during the Agency’s review of the withdrawn application and described in the approvable letter dated March 13, 2008.³⁵

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

Eight months after it withdrew NDA 050811, Astellas met with FDA on September 29, 2009, to discuss its development program for Astagraf XL under IND 64,148.³⁶ Astellas proposed that Study 158 would be the primary basis for the efficacy and safety evaluation of Astagraf XL in the kidney transplant setting and that Study 12-03 would serve as a supportive study.³⁷ Although

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

²⁹ *Id.*

³⁰ *Id.*

³¹ *Id.* at 2.

³² *Id.*

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

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

³⁵ *Id.*

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

³⁷ Agency Prelim. Resp. at 1.

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

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

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

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

³⁸ Id.

³⁹ Id. at 3.

⁴⁰ Id. at 2.

⁴¹ Id. at 3.

⁴² Id.

⁴³ Id. at 3-4.

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

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

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

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

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

3. *Astagraf XL NDA 204096*

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

⁴⁶ Id. at 6.

⁴⁷ Id. at 4.

⁴⁸ Id. at 7.

⁴⁹ Id.

⁵⁰ Id.

⁵¹ Id.

⁵² Id. at 5.

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

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

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

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

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

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

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

⁵⁵ Astagraf XL Clinical Review at 32.

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

⁵⁷ Id. at 39.

⁵⁸ Id.

⁵⁹ Id. (italics omitted).

last row of Table 6.⁶⁰ This information was not intended to and does not imply approval of Astagraf XL for the conversion use. The text of the Clinical Studies and Dosing and Administration sections of the Astagraf XL labeling not only is silent on the conversion use but also is specific to *de novo* use in kidney transplant patients.

When Astagraf XL was approved, FDA determined that the NDA should receive 3-year exclusivity because Astellas conducted new clinical investigations essential to approval (Studies 158 and 12-03). This exclusivity covers the once-daily, ER dosage form for the prophylaxis of organ rejection for use in *de novo* kidney transplant patients and is reflected in the Orange Book with the exclusivity code *NDF* or *new dosage form*. The exclusivity expires on July 19, 2016.⁶¹

D. Envarsus XR

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

1. Envarsus XR NDA 206406

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

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

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

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

⁶¹ See the Orange Book.

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

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

⁶⁴ *Id.* at 60.

dosage adjustments based on the attainment of the protocol-specified target tacrolimus trough concentration ranges of 6-11 ng/mL in the first 30 days and 4-11 ng/mL thereafter. Because the trough concentrations in *de novo* patients taking Envarsus XR were higher than observed in *de novo* patients taking IR tacrolimus during the first 2 weeks and higher than the protocol specified target range during the first week post-transplant, the Agency questioned whether the 0.17 mg/kg/day starting dose of Envarsus XR used by Veloxis in Study 3002 would be safe and effective.⁶⁵ A Phase 2 PK study (Study 2017) provided support for a lower 0.14 mg/kg/day starting dose for Envarsus XR in *de novo* patients, which is currently in the proposed labeling.⁶⁶ Separately, in Study 3001, Envarsus XR was studied for converting patients who had previously been stable on Prograf. In the conversion study, stable kidney transplant patients receiving stable doses of Prograf twice daily and having tacrolimus trough concentrations within 4-15 ng/mL at the end of the 7-day run-in period were randomized (1:1) at baseline either to continue treatment with Prograf twice daily at the current dose or to switch to Envarsus XR once daily. Study 3001 and Study 2011, a PK study in stable kidney transplant patients, provided support for a recommended Prograf-to-Envarsus XR daily dose conversion ratio of 1:0.8.⁶⁷

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

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

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

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

⁶⁸ *Id.* at 9-10.

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

2. *Veloxis' Request for Orphan Designation*

On July 16, 2013, Veloxis requested orphan designation for tacrolimus for “prophylaxis of organ rejection in patients receiving allogeneic kidney transplant” based on a “plausible hypothesis” that its product in development (then referred to as LCP-tacro and later known as Envarsus XR) was clinically superior to Prograf.⁶⁹ Orphan designation was granted on December 20, 2013.⁷⁰ Astagraf XL had not been approved when the request for designation was made; neither the request for designation nor the reviews of that request considered whether Envarsus XR had a plausible hypothesis of clinical superiority to Astagraf XL.⁷¹

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

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

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

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

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

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

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

⁷³ *Id.* at 2.

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

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

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

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

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

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

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

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

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

⁷⁸ Id. at 1-2.

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

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

On November 10, 2014, FDA issued a General Advice/Information Request letter to Veloxis, explaining that at the November 6 meeting, Veloxis had presented new information for the Agency to evaluate and had asked FDA to reconsider its decision to tentatively approve the Envarsus XR NDA.⁸² FDA requested that this new information be submitted as an amendment to the Envarsus XR NDA, identified as a “Request For Final Approval.” Veloxis submitted the “Request For Final Approval” on November 14, 2014.⁸³ This submission contained an 18-page letter with six exhibits detailing Veloxis’ position that FDA should immediately approve the NDA. The submission also included declarations from Dr. Bloom and a representative of the National Kidney Foundation.⁸⁴

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

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

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

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

⁸³ Veloxis Submission.

⁸⁴ Id. (Exhibit 1).

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

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

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

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

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

On December 8, 2014, Veloxis sent a letter to FDA declining to pursue the proposed option discussed on December 5, 2014.⁸⁸ In its letter, Veloxis reiterated its position that FDA should immediately approve Envarsus XR for all of the uses reflected in the labeling previously submitted in the Envarsus XR NDA. With the December 8, 2014 submission, Veloxis also submitted a declaration from Dr. Anthony Langone regarding the Envarsus XR NDA. Veloxis later submitted a letter on December 12, 2014, containing an additional exclusivity precedent for the Agency's consideration.⁸⁹

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

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

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

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

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

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

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

II. STATUTORY AND REGULATORY BACKGROUND

A. Drug Approval Pathways Under the FD&C Act

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

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

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

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

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

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

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

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

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

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

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

⁹⁵ Public Law 98-417.

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

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

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

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

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

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

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

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

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

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

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

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

B. 3-Year Exclusivity

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

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

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

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

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

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

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

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

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

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

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

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

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

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

¹⁰⁴ 21 CFR 314.108(a).

¹⁰⁵ Id.

¹⁰⁶ Id.

¹⁰⁷ 21 CFR 314.108(b)(4)(iv).

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

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

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

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

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

¹⁰⁹ 1989 Proposed Rule at 28896-97.

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

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

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

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

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

(emphasis added).¹¹⁴

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

¹¹¹ 1989 Proposed Rule at 28901.

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

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

(emphasis added).

¹¹³ 1989 Proposed Rule at 28897.

¹¹⁴ Id.

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

C. Antibiotics and Exclusivity

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

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

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

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

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

¹¹⁷ Section 125(d)(1) of FDAMA.

¹¹⁸ Section 125(d)(1) of FDAMA.

¹¹⁹ Section 125(d)(2) of FDAMA.

¹²⁰ *Id.*

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

former were eligible for Hatch-Waxman benefits and the latter were not.¹²² FDA determined that the FDAMA exemption from Hatch-Waxman benefits for Old Antibiotics applied to all antibiotic moieties of antibiotic drugs that were the subjects of marketing applications received by FDA before November 21, 1997.¹²³

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

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

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

However, the QI Act did not make applications for Old Antibiotics submitted after the date of enactment of the QI Act eligible for exclusivity and other Hatch-Waxman benefits to the same extent as other section 505 drugs. Instead, for Old Antibiotics, such as tacrolimus, the exclusivity described in section 505(v)(1) of the FD&C Act is subject to the limitation in section 505(v)(3)(B) of the FD&C Act, which provides that 3-year exclusivity is not available for “any condition of use for which the [Old Antibiotic] . . . was approved before the date of the enactment [of the QI Act].”

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

¹²² Id.

¹²³ Proposed Rule on Old Antibiotics.

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

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

[The] availability of 3-year exclusivity for Old Antibiotics was not without limitation. Rather than simply placing new applications and supplements for Old Antibiotics under the pre-existing Hatch-Waxman regulatory scheme, Congress prescribed specific limits to this eligibility under section 505(v)(3)(B) of the FD&C Act. The QI Act provides that 3-year exclusivity period is not available for “any condition of use for which the [Old Antibiotic] . . . was approved before the date of the enactment [of the QI Act].”

section 505(v)(3)(B) to permit 3-year exclusivity for Old Antibiotics “only for a *significant new use* for an Old Antibiotic (such as a new indication for a previously approved antibiotic, or a new approval for a submitted but never previously approved antibiotic), not for refinements in labeling related to previously approved uses for Old Antibiotics.”¹²⁶

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

III. DISCUSSION

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

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

The QI Act does not expressly define what constitutes a “condition of use ... approved before the date of enactment.” As an initial matter, FDA concludes that this limitation must exclude from exclusivity some applications and supplements containing new clinical studies that otherwise would qualify a non-Old Antibiotic product for 3-year Hatch-Waxman exclusivity Thus, to give content to this limitation, FDA must find that *there is a higher hurdle for exclusivity* for an Old Antibiotic than there is for another kind of product seeking 3-year exclusivity.

(emphasis added).

See also *ViroPharma* at 13 (quoting the Agency’s position that “[t]o give content to this limitation, FDA must find that there is a higher hurdle for exclusivity for an Old Antibiotic than there is for another kind of product seeking 3-year exclusivity”).

¹²⁶ Vancocin CP Response at 70 (emphasis added).

¹²⁷ *ViroPharma* at 22.

¹²⁸ *Id.*

¹²⁹ *Id.*

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

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

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

1. Timing of Submission of Astagraf XL NDA

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

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

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

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

¹³¹ *Id.* at 2.

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

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

Third, Veloxis states that although the subsequent application may have been assigned a new NDA number for administrative purposes, Astellas' second NDA must be treated as a continuation of the original NDA (submitted before enactment of the QI Act) for exclusivity purposes because Astellas performed no new studies in support of its second NDA between the time of withdrawal and resubmission of its NDA.¹³⁴ Specifically, Veloxis states that Studies 158 and 12-03 were cited by FDA as the clinical trials that had provided the basis for 3-year exclusivity and that the studies were completed before Astellas withdrew the original NDA in 2009.¹³⁵

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

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

¹³³ *ViroPharma* at 20 (citing Senator Kennedy's statements in the Congressional Record that the QI Act "includes limits that would prevent pharmaceutical manufacturers from abusing the process to extend the life of old active ingredient drugs").

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

¹³⁵ *Id.* at 3.

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

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

¹³⁸ *Id.*

that FDA's work reviewing the first application can be applied in large measure to its review of the subsequent related application[,] and thus that a separate fee is not warranted."¹³⁹ Veloxis also speculates that Astellas did not pay a user fee for its "subsequent NDA for Astagraf XL" submitted in 2012.¹⁴⁰

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

2. *Approved Conditions of Use for Astagraf XL*

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

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

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

¹³⁹ Id.

¹⁴⁰ Id.

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

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

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

¹⁴⁴ Id. at 4-5.

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

B. Scope of 3-Year Exclusivity for Astagraf XL

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

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

The approval of the Astagraf XL NDA for the prophylaxis of organ rejection in patients receiving kidney transplants was supported by two 12-month, Phase 3, randomized studies in *de novo* kidney transplant patients that included treatment arms for both Astagraf XL and Prograf: Study 158¹⁴⁷ and Study 12-03.¹⁴⁸

¹⁴⁵ The Exclusivity Board acknowledged that the reviews for Astagraf XL state that there is no substantial evidence of a clinical benefit with respect to potential improved patient adherence with once-daily dosing of Astagraf XL compared to Prograf. See, e.g., Astagraf XL Clinical Review (June 19, 2013) at 6; Astagraf XL Cross-Discipline Team Leader Review at 18, 37. However, the Exclusivity Board observed that the once-daily dosing for Astagraf XL is a new dosing regimen. The Exclusivity Board concluded that at this time, FDA does not consider a demonstration of a clinical benefit of a new dosing regimen compared to a past dosing regimen to be a prerequisite to establishing a significant new condition of use for exclusivity purposes under section 505(v). See Exclusivity Board Memorandum re Astagraf XL (tacrolimus extended-release capsules) 3-year exclusivity (Jan. 8, 2015).

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

¹⁴⁷ Astagraf XL Clinical Review at 32.

¹⁴⁸ *Id.*

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

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

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

¹⁴⁹ Id..

¹⁵⁰ Id. at 42.

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

¹⁵² Id. at 32.

¹⁵³ Id. at 32 and 51.

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

¹⁵⁵ Id. at 38.

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

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

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

1. Differences Between Envarsus XR and Astagraf XL

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

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

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

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

¹⁵⁷ Veloxis Submission at 8-11.

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

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

- *PK Profiles*

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

- *Tremors*

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

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

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

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

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

- *Dosage Forms, Strengths, and Dosing Regimens*

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

2. *Orphan Designation*

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

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

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

¹⁶³ Veloxis Submission at 9-11.

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

¹⁶⁵ Veloxis Submission at 9-11.

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

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

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

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

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

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

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

¹⁶⁸ Wilate CP Response at 13.

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

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

3. *Lack of Reliance on Astagraf XL*

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

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

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

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

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

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

¹⁶⁹ Veloxis Submission at 11-14.

¹⁷⁰ Id. at 11.

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

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

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

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

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

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

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

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

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

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

4. *The Orange Book Exclusivity Code*

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

¹⁷² Veloxis Submission at 13-14.

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

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

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

¹⁷⁶ Veloxis Submission at 8.

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

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

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

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

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

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

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

¹⁷⁷ Id.

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

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

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

¹⁸¹ Astagraf XL Clinical Review at 39 and 41.

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

The PK section of the currently approved labeling includes only limited descriptive PK information from Study FG 506E-12-02 in the last row of Table 6.¹⁸⁴ The Clinical Studies and Dosing and Administration sections of the Astagraf XL labeling are not only silent on the conversion use, but are specific to *de novo* use.¹⁸⁵ The PK studies conducted in the conversion population were relative bioavailability studies and they were not “new clinical investigations” essential to the approval of Astagraf XL within the meaning of the statute and regulations.

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

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

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

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

¹⁸⁵ For example:

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

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

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

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

controlled studies to demonstrate safety and effectiveness of other immunosuppressants for the conversion use¹⁸⁷ and such studies would have been needed for approval for conversion for Astagraf XL as well. Astellas did not conduct those clinical investigations that would have been necessary to support that use. Consequently, the scope of 3-year exclusivity for Astagraf XL does *not* extend to a once-daily, ER dosage form of tacrolimus for prophylaxis of organ rejection for converting kidney transplant patients who are stable on IR tacrolimus.

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

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

¹⁸⁸ Envarsus XR Clinical Review at 8.

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

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

IV. ANALYSIS OF PRECEDENT CITED BY VELOXIS

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

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

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

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

¹⁹¹ 1989 Proposed Rule at 28872, 28897.

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

Sponsors have also developed alternative business arrangements to avoid conflicts involving 3-year exclusivity issues for competing products. For example, two firms recently announced an exchange of waivers of exclusivity for their respective competing single entity extended-release hydrocodone products.¹⁹² Zogenix's single entity extended-release hydrocodone capsule, Zohydro ER (NDA 202880), was approved first and is listed in the Orange Book as having 3-year exclusivity, which will expire on October 25, 2016.¹⁹³ Purdue's single entity extended-release hydrocodone tablet, Hysingla (NDA 206627), a 505(b)(2) NDA that did not rely on Zohydro for approval, was approved shortly after the mutual waiver agreement was announced.¹⁹⁴

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

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

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

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

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

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

for the same indication as Combivent. Duoneb had been submitted as a 505(b)(2) application that did not rely on Combivent.¹⁹⁶ FDA noted that the Duoneb applicant conducted its own clinical trials to establish the safety and effectiveness of the fixed-combination, but FDA concluded that it likely would not be able to fully approve Duoneb's 505(b)(2) NDA at that time due to Combivent's existing exclusivity, which was due to expire on October 24, 1999.¹⁹⁷

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

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

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

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

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

¹⁹⁹ See id. at 6, fn. 9.

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

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

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

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

A. Methylphenidate

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

²⁰¹ Id. at 3.

²⁰² Id. (emphasis added).

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

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

exclusivity period of another ER methylphenidate product, Concerta (ER methylphenidate tablets) (NDA 021121), that was approved on August 1, 2000.²⁰⁵ Veloxis claims that “[l]ike Envarsus XR and Astagraf XL, Concerta and Metadate CD are approved to treat the same indication and both are once-daily extended-release formulations of the same active ingredient,” but “[a]lso like the current situation, Concerta and Metadate CD are approved in different dosage forms (i.e., extended-release tablets and extended-release capsules, respectively).”²⁰⁶ Veloxis, thus, concludes that “[a]s a result of this critical difference, Concerta’s exclusivity did not block approval of Metadate CD.”²⁰⁷ In addition, Veloxis asserts that this example supports its view that a later-in-time 505(b)(2) NDA is not blocked if it does not rely on the NDA with exclusivity.²⁰⁸

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

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

²⁰⁵ Veloxis Submission at 15.

²⁰⁶ Id.

²⁰⁷ Id.

²⁰⁸ Id. at 15-16.

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

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

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

B. Testosterone

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

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

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

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

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

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

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

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

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

²¹⁴ Veloxis Submission at 15-16;

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

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

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

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

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

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

V. CONCLUSION

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

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

Sincerely,

{See appended electronic signature page}

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

APPENDIX

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

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

^a Refers to new clinical investigations listed on Exclusivity Summary.

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

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

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

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

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

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

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/s/

RENATA ALBRECHT
01/12/2015



NDA 206406

RESPONSE TO REQUEST FOR FINAL APPROVAL

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

Dear Ms. McGuinness:

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

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

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

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

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

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

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

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

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

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

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

Until we issue a final approval letter, this NDA is not approved.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

RENATA ALBRECHT
01/12/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206406

GENERAL ADVICE

Veloxis Pharmaceuticals, Inc.
Attention: William J. Polvino, MD
President & CEO
499 Thornall Street
3rd Floor
Edison, NJ 08837

Dear Dr. Polvino:

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

This letter, prepared in consultation with CDER's Office of Regulatory Policy, is to provide you with an update on the status of your "Request for Final Approval" for Envarsus XR (NDA206406), including the recent "Supplement To Request for Final Approval" submitted on December 8, 2014.

As you know, on October 30, 2014, FDA issued a tentative approval for your NDA for Envarsus XR because FDA determined that approval of the drug product was blocked by the three-year exclusivity of Astagraf XL (NDA 204096). As explained more fully below, we have had meetings and received several submissions from you providing arguments for why approval of the NDA for Envarsus XR should not be blocked by the exclusivity of Astagraf XL. We have been working diligently to review the record for both the Astagraf XL NDA and the Envarsus XR NDA, as well as to consider the arguments regarding this matter that were made in meetings and correspondence with FDA.

The question of whether Envarsus XR is blocked by Astagraf XL's exclusivity presents novel and complex legal and regulatory issues. After internal deliberations, FDA sent an Information Request to Veloxis on October 27, 2014, requesting your position on whether approval of the Envarsus XR 505(b)(2) NDA would be affected by Astagraf XL's exclusivity.¹ On

¹ Letter dated October 27, 2014, from Lois Almoza, DTOP, to Michelle McGuinness, Veloxis.

October 29, 2014, you responded by submitting a letter to the Envarsus XR NDA stating that Astagraf XL's "exclusivity does not affect the type of action letter FDA can issue for Envarsus XR, which has a different dosage form and different proposed conditions of use."² Further, you claimed that the "Envarsus XR development program did not rely upon any of the studies Astellas performed which were essential to the approval of Astagraf XL."³

FDA further considered whether the Envarsus XR application was blocked by Astagraf XL's exclusivity and concluded that the Agency was barred from approving Envarsus XR's NDA because Envarsus XR shares Astagraf XL's exclusivity-protected conditions of approval. Consequently, on October 30, 2014, FDA issued a tentative approval letter to Veloxis for Envarsus XR, stating that, "[a]s noted in the 'Approved Drug Products with Therapeutic Equivalence Evaluations' (the 'Orange Book'), the listed drug product Astagraf XL (NDA 204096), with which you share conditions of approval for which new clinical studies were essential, is subject to a period of exclusivity protection under sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the Act. Therefore, final approval of your application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until that product's exclusivity period has expired."

Counsel for Veloxis contacted the Office of Chief Counsel on October 31, 2014 requesting a meeting with FDA and asking FDA to retract its tentative approval and issue a letter approving the Envarsus XR NDA. On November 6, 2014, representatives of Veloxis met with representatives of FDA, including the Division of Transplant and Ophthalmology Products (DTOP), the Office of Regulatory Policy, and the Office of the Chief Counsel. At this meeting, you and your representatives explained that you believed FDA issued the tentative approval letter for Envarsus XR in error, because the "[c]onditions of approval of Envarsus XR do not overlap with Astagraf XL." You and your representatives noted that Envarsus XR differs from Astagraf XL in its dosage form, dosing regimen, strengths, and pharmacokinetic profile. As part of this discussion, you identified examples of past drug approval actions that you believe support approval of Envarsus XR notwithstanding Astagraf XL's exclusivity. Further, you reiterated that the Envarsus XR NDA did not rely on the Astagraf XL NDA.

On November 10, 2014, DTOP issued a General Advice/Information Request letter, explaining that at the November 6 meeting Veloxis presented new information for the Agency to consider in determining whether the Envarsus XR NDA should receive final approval.⁴ DTOP requested that this new information be submitted as an amendment to the Envarsus XR NDA, identified as "Request for Final Approval." You submitted your request for final approval on November 14, 2014.⁵ This submission contained an 18-page letter with multiple exhibits detailing your position that the Agency should immediately approve the NDA.⁶

² See NDA 206406/s0035; letter dated October 29, 2014, from Michelle McGuinness, Veloxis, to Lois Almoza, DTOP, at 1.

³ Id. 1-2.

⁴ Letter dated November 10, 2014, from Renata Albrecht, DTOP, to Michelle A. McGuinness, Veloxis.

⁵ See NDA 206406/s0037, received November 17, 2014.

⁶ The submission included journal articles and declarations from Dr. Bloom and Tonya Saffer regarding Envarsus XR.

On December 2, 2014, you submitted a supplement to your November 14, 2014 request for final approval which raised new issues.⁷ In the December 2, 2014 letter, you asserted, among other things, that Astagraf XL was ineligible to receive 3-year exclusivity pursuant to section 505(v) of the FD&C Act because Astagraf XL (NDA 050811) was the subject of a pending application prior to October 8, 2008, the date of enactment of the QI Program Supplemental Funding Act of 2008 (“QI Act”), and was therefore specifically excluded from eligibility for 3-year exclusivity under the provisions of the QI Act. You asserted that Astellas performed no new studies in support of its application between the time of withdrawal and resubmission of the Astagraf XL NDA in 2012. Your letter concluded that the NDA for Envarsus XR should be approved immediately because exclusivity for Astagraf XL was recognized in error.

After meeting with you and receiving your submissions, FDA had numerous internal meetings and, on December 2, 2014, met with Astellas—Astagraf XL’s sponsor—regarding the scope of exclusivity for Astagraf XL. As part of FDA’s consideration of the issues raised by Veloxis and Astellas, we are reexamining the studies conducted to support both the Astagraf XL and the Envarsus XR NDAs, as well as the reasoning for our prior determination that Astagraf XL is entitled to three-year exclusivity and that exclusivity blocks approval of the NDA for Envarsus XR. We are also examining the precedents you cited in support of the argument that Envarsus XR is not blocked.

In the midst of our review of the entire record, FDA determined that one possible path forward would be to approve the Envarsus XR NDA with an indication that would cover the conversion of patients who are stable on immediate-release tacrolimus to Envarsus XR, a condition of approval that would not be blocked by Astagraf XL’s exclusivity. To that end, FDA held a teleconference with you and your counsel on December 5, 2014, in which FDA suggested this option as a path forward for approval of the Envarsus XR NDA, subject to revised labeling for Envarsus XR. In response to questions, we discussed potential revised labeling for Envarsus XR that would omit the information regarding use of Envarsus XR in *de novo* patients while permitting approval for the conversion use.

On December 8, 2014, you sent a letter to FDA declining the proposed option discussed on December 5, 2014. This letter stated your position that FDA should immediately approve Envarsus XR for all of the uses reflected in the labeling previously submitted in the Envarsus XR NDA. With your December 8, 2014 submission, you also submitted a declaration from Dr. Anthony Langone regarding the Envarsus XR NDA. You submitted a letter on December 12, 2014 with an additional precedent for the Agency’s consideration.

Although you requested in your November 14, 2014 submission that FDA respond to your request for “[i]mmediate, unconditional approval of Envarsus XR,” within 21 days and FDA initially estimated that it could respond by the end of this week, FDA has not had adequate time to fully consider the entire record for this matter, including your latest submissions. In light of the volume of materials to consider and the complexity of the matter, FDA is not issuing a final decision at this time; however, FDA currently intends to complete our review of the record and issue a decision not later than January 12, 2015.

⁷ NDA 206406/s0038; letter dated December 2, 2014, from Michelle McGuinness, Veloxis, to Lois Almoza, DTOP.

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

Sincerely,

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

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/s/

RENATA ALBRECHT
12/12/2014

Teleconference Minutes

FDA Participants: Renata Albrecht, Ozlem Belen, Marc Cavaille Coll, Ergun Velidedeoglu, and Judit Milstein, Division of Transplant and Ophthalmology Products (DTOP), Center for Drug Evaluation and Research (CDER); Jay Sitlani and Nisha Shah, Office of Regulatory Policy (ORP), CDER; Nancy Booker and Sonia Nath, Office of the Chief Counsel (OCC)

Veloxis & Counsel

Participants: Bill Polvino and John Weinberg (Veloxis); Jennifer Bragg and Graham Robinson (Skadden, Arps, Slate, Meager & Flom LLP); Scott Lassman, (Kleinfeld, Kaplan, & Becker LLP)

Date/Time: December 5, 2014; 6:00 – 6:30 pm

Re: New Drug Application (NDA) 206406 for Envarsus XR

Minutes

FDA requested a teleconference with Veloxis to discuss NDA 206406 for Envarsus XR (tacrolimus) extended-release tablets, which was tentatively approved by FDA on October 30, 2014, because it was blocked by three-year exclusivity of Astagraf XL (NDA 204096). This teleconference was in response to Veloxis' "Request for Final Approval," which was submitted as an amendment to its NDA on November 17, 2014, and the Agency's ongoing review of the record for both the Astagraf XL NDA and the Envarsus XR NDA.

Mr. Sitlani informed Veloxis and their counsel that, based on FDA's ongoing review of the record, the Agency determined that it could approve Envarsus XR before expiry of Astagraf XL's exclusivity on July 19, 2016, but only with an indication that would cover "conversion" from tacrolimus immediate-release to Envarsus XR in kidney transplant patients (the "conversion setting"). Mr. Sitlani stated that the Agency believed this proposal is the best path forward for the approval of Envarsus XR before expiry of Astagraf XL's exclusivity. Mr. Sitlani also recognized that the company had originally sought approval for use of Envarsus XR only in the conversion setting. Veloxis expressed interest in hearing more detail about the Agency's proposal.

Dr. Albrecht described examples of the changes to the current draft labeling that would be consistent with an approval for Envarsus XR in the conversion setting. Dr. Albrecht suggested that, for instance, section 1 (Indications and Usage) may need to be revised to reflect conversion of patients from immediate release formulations of tacrolimus to Envarsus XR only; section (b) (4)

would be deleted; section 2.3 describing conversion from tacrolimus immediate-release formulations would be expanded to include the targeted trough levels; the adverse reactions described in section 6.1 (Adverse Reactions – Clinical Trials Experience) would focus only on the conversion setting and might omit some information about the *de novo* population; section 8.5 (Use in Special Populations – Geriatric Patients) would likely be revised to omit information

on patients from the *de novo* studies; section 12.3 (Clinical Pharmacology – Pharmacokinetics) would be updated and would highlight the safety concerns with a starting dose of 0.17 mg/kg/day; and section 14.1 (Clinical Studies – Clinical Studies in De Novo Kidney Transplant Recipients) would be deleted so that only information from the clinical study in the conversion setting would be presented in the labeling.

Dr. Polvino stated the company would want approval for use of Envarsus XR in the *de novo* setting once Astagraf XL's exclusivity expires. Mr. Sitlani explained that once Astagraf XL's exclusivity expired, then Envarsus XR could be approved for both *de novo* and conversion settings. Dr. Albrecht recommended that Veloxis submit the Request for Final Approval five months prior to the expiration of Astagraf XL's exclusivity to ensure approval of revised labeling to include the *de novo* setting no later than July 19, 2016.

Dr. Polvino stated that [REDACTED] (b) (4). He requested from the Agency a marked-up version of draft labeling. In response, Dr. Albrecht again reviewed possible changes to the current draft labeling of Envarsus XR, and offered to have daily teleconferences with Veloxis to work on specific language for that would cover approval for the conversion setting. The Agency agreed to send the draft labeling no later than December 9, 2014, if the company agreed with the conversion-only approval proposed by the Agency, and requested that Veloxis respond to the Agency's proposal no later than December 8, 2014.

Ms. Bragg asked about the Agency's timing in making effective the proposed conversion-only approval for Envarsus XR. Dr. Albrecht responded that it would depend on the labeling negotiations, but stated that the Agency would work towards expeditiously finalizing labeling.

Veloxis' counsel also inquired whether this proposal represented final Agency action on this matter. They asked what the alternative would be should Veloxis not agree with the Agency's proposal for approval of Envarsus XR in the conversion setting only. Mr. Sitlani responded that the objective of this teleconference with Veloxis was not to present the Agency's final decision, but only to present the option of approval for Envarsus XR in the conversion setting. Veloxis' counsel inquired whether the Agency in presenting its proposal for a conversion-only approval had considered Veloxis's latest submission (dated December 2, 2014) in which it stated that Astagraf XL is not eligible for exclusivity under section 505(v) of the FD&C Act. Mr. Sitlani stated that the Agency was not prepared to discuss this matter, or any other options or submissions, and that the focus of the teleconference was only the proposed approval of Envarsus XR in the conversion setting.

Veloxis and its counsel stated that it would consider the Agency's proposal and respond by December 8, 2014.

The call ended around 6:30pm.

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/s/

LOIS A ALMOZA
12/12/2014



NDA 206406

GENERAL ADVICE

Veloxis Pharmaceuticals, Inc.
Attention: William J. Polvino, MD
President & CEO
499 Thornall Street
3rd Floor
Edison, NJ 08837

Dear Dr. Polvino:

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

This letter, prepared in consultation with CDER's Office of Regulatory Policy, is to provide you with an update on the status of your "Request for Final Approval" for Envarsus XR (NDA206406), including the recent "Supplement To Request for Final Approval" submitted on December 8, 2014.

As you know, on October 30, 2014, FDA issued a tentative approval for your NDA for Envarsus XR because FDA determined that approval of the drug product was blocked by the three-year exclusivity of Astagraf XL (NDA 204096). As explained more fully below, we have had meetings and received several submissions from you providing arguments for why approval of the NDA for Envarsus XR should not be blocked by the exclusivity of Astagraf XL. We have been working diligently to review the record for both the Astagraf XL NDA and the Envarsus XR NDA, as well as to consider the arguments regarding this matter that were made in meetings and correspondence with FDA.

The question of whether Envarsus XR is blocked by Astagraf XL's exclusivity presents novel and complex legal and regulatory issues. After internal deliberations, FDA sent an Information Request to Veloxis on October 27, 2014, requesting your position on whether approval of the Envarsus XR 505(b)(2) NDA would be affected by Astagraf XL's exclusivity.¹ On

¹ Letter dated October 27, 2014, from Lois Almoza, DTOP, to Michelle McGuinness, Veloxis.

October 29, 2014, you responded by submitting a letter to the Envarsus XR NDA stating that Astagraf XL's "exclusivity does not affect the type of action letter FDA can issue for Envarsus XR, which has a different dosage form and different proposed conditions of use."² Further, you claimed that the "Envarsus XR development program did not rely upon any of the studies Astellas performed which were essential to the approval of Astagraf XL."³

FDA further considered whether the Envarsus XR application was blocked by Astagraf XL's exclusivity and concluded that the Agency was barred from approving Envarsus XR's NDA because Envarsus XR shares Astagraf XL's exclusivity-protected conditions of approval. Consequently, on October 30, 2014, FDA issued a tentative approval letter to Veloxis for Envarsus XR, stating that, "[a]s noted in the 'Approved Drug Products with Therapeutic Equivalence Evaluations' (the 'Orange Book'), the listed drug product Astagraf XL (NDA 204096), with which you share conditions of approval for which new clinical studies were essential, is subject to a period of exclusivity protection under sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the Act. Therefore, final approval of your application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until that product's exclusivity period has expired."

Counsel for Veloxis contacted the Office of Chief Counsel on October 31, 2014 requesting a meeting with FDA and asking FDA to retract its tentative approval and issue a letter approving the Envarsus XR NDA. On November 6, 2014, representatives of Veloxis met with representatives of FDA, including the Division of Transplant and Ophthalmology Products (DTOP), the Office of Regulatory Policy, and the Office of the Chief Counsel. At this meeting, you and your representatives explained that you believed FDA issued the tentative approval letter for Envarsus XR in error, because the "[c]onditions of approval of Envarsus XR do not overlap with Astagraf XL." You and your representatives noted that Envarsus XR differs from Astagraf XL in its dosage form, dosing regimen, strengths, and pharmacokinetic profile. As part of this discussion, you identified examples of past drug approval actions that you believe support approval of Envarsus XR notwithstanding Astagraf XL's exclusivity. Further, you reiterated that the Envarsus XR NDA did not rely on the Astagraf XL NDA.

On November 10, 2014, DTOP issued a General Advice/Information Request letter, explaining that at the November 6 meeting Veloxis presented new information for the Agency to consider in determining whether the Envarsus XR NDA should receive final approval.⁴ DTOP requested that this new information be submitted as an amendment to the Envarsus XR NDA, identified as "Request for Final Approval." You submitted your request for final approval on November 14, 2014.⁵ This submission contained an 18-page letter with multiple exhibits detailing your position that the Agency should immediately approve the NDA.⁶

² See NDA 206406/s0035; letter dated October 29, 2014, from Michelle McGuinness, Veloxis, to Lois Almoza, DTOP, at 1.

³ Id. 1-2.

⁴ Letter dated November 10, 2014, from Renata Albrecht, DTOP, to Michelle A. McGuinness, Veloxis.

⁵ See NDA 206406/s0037, received November 17, 2014.

⁶ The submission included journal articles and declarations from Dr. Bloom and Tonya Saffer regarding Envarsus XR.

On December 2, 2014, you submitted a supplement to your November 14, 2014 request for final approval which raised new issues.⁷ In the December 2, 2014 letter, you asserted, among other things, that Astagraf XL was ineligible to receive 3-year exclusivity pursuant to section 505(v) of the FD&C Act because Astagraf XL (NDA 050811) was the subject of a pending application prior to October 8, 2008, the date of enactment of the QI Program Supplemental Funding Act of 2008 (“QI Act”), and was therefore specifically excluded from eligibility for 3-year exclusivity under the provisions of the QI Act. You asserted that Astellas performed no new studies in support of its application between the time of withdrawal and resubmission of the Astagraf XL NDA in 2012. Your letter concluded that the NDA for Envarsus XR should be approved immediately because exclusivity for Astagraf XL was recognized in error.

After meeting with you and receiving your submissions, FDA had numerous internal meetings and, on December 2, 2014, met with Astellas—Astagraf XL’s sponsor—regarding the scope of exclusivity for Astagraf XL. As part of FDA’s consideration of the issues raised by Veloxis and Astellas, we are reexamining the studies conducted to support both the Astagraf XL and the Envarsus XR NDAs, as well as the reasoning for our prior determination that Astagraf XL is entitled to three-year exclusivity and that exclusivity blocks approval of the NDA for Envarsus XR. We are also examining the precedents you cited in support of the argument that Envarsus XR is not blocked.

In the midst of our review of the entire record, FDA determined that one possible path forward would be to approve the Envarsus XR NDA with an indication that would cover the conversion of patients who are stable on immediate-release tacrolimus to Envarsus XR, a condition of approval that would not be blocked by Astagraf XL’s exclusivity. To that end, FDA held a teleconference with you and your counsel on December 5, 2014, in which FDA suggested this option as a path forward for approval of the Envarsus XR NDA, subject to revised labeling for Envarsus XR. In response to questions, we discussed potential revised labeling for Envarsus XR that would omit the information regarding use of Envarsus XR in *de novo* patients while permitting approval for the conversion use.

On December 8, 2014, you sent a letter to FDA declining the proposed option discussed on December 5, 2014. This letter stated your position that FDA should immediately approve Envarsus XR for all of the uses reflected in the labeling previously submitted in the Envarsus XR NDA. With your December 8, 2014 submission, you also submitted a declaration from Dr. Anthony Langone regarding the Envarsus XR NDA. You submitted a letter on December 12, 2014 with an additional precedent for the Agency’s consideration.

Although you requested in your November 14, 2014 submission that FDA respond to your request for “[i]mmediate, unconditional approval of Envarsus XR,” within 21 days and FDA initially estimated that it could respond by the end of this week, FDA has not had adequate time to fully consider the entire record for this matter, including your latest submissions. In light of the volume of materials to consider and the complexity of the matter, FDA is not issuing a final decision at this time; however, FDA currently intends to complete our review of the record and issue a decision not later than January 12, 2015.

⁷ NDA 206406/s0038; letter dated December 2, 2014, from Michelle McGuinness, Veloxis, to Lois Almoza, DTOP.

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

Sincerely,

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

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/s/

RENATA ALBRECHT
12/12/2014



NDA 206406

**GENERAL ADVICE /
INFORMATION REQUEST**

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

Dear Ms. McGuinness:

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

We also refer to your Meeting with representatives of the Agency, including the Division, the Office of Regulatory Policy (ORP), and the Office of the Chief Counsel (OCC) on November 6, 2014. You stated at the meeting that you believe a tentative approval was issued by FDA in error and your NDA was eligible for final approval on October 30, 2014. You noted that the October 30, 2014 Tentative Approval letter stated that the status of this application, "...is subject to change on the basis of any new information that may come to our attention." Your materials for the November 6, 2014 meetings included new information you request the agency to consider in determining whether your NDA should receive final approval. We request that you submit to your NDA file the written materials presented at the meeting, written materials describing the additional information presented orally at the meeting, and any additional data, information, or analysis regarding the implications of Astagraf XL's three-year exclusivity listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (Orange Book) on the final approval of your NDA.

In your cover letter, clearly identify your amendment as "REQUEST FOR FINAL APPROVAL." This amendment should provide the legal/regulatory basis for your request for final approval for further consideration by the Agency. We may follow-up with additional information requests as appropriate.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

RENATA ALBRECHT
11/10/2014



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION TRANSMITTAL SHEET

DATE: October 27, 2014

To: Ms. Michelle McGuinness, VP, Global Regulatory Affairs & QA	From: Lois Almoza, Project Manager
Company: Veloxis Pharmaceuticals, Inc.	Division of Transplant and Ophthalmology Products
Phone Number: 732-321-3211	Phone Number: 301-796-1600
Email: mam@veloxis.com	Email: lois.almoza@fda.hhs.gov

Subject: NDA 206406/Envarsus XR (tacrolimus extended-release tablets)

Total no. of pages including cover: 3

Document to be mailed: ☐ YES ☒ NO

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Dear Ms. McGuinness:

Please refer to your December 28, 2013, submission, received December 30, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Envarsus XR (tacrolimus extended-release tablets), 0.75 mg, 1.0 mg and 4.0 mg.

We are continuing the review of your application.

We note that that the “Approved Drug Products with Therapeutic Equivalence Evaluations” lists new dosage form 3-year exclusivity for Astagraf XL, the approved extended-release tacrolimus product (NDA 204096), that expires on July 19, 2016. This exclusivity covers the conditions of approval for the studies Astellas performed which were essential to the approval of Astagraf XL. If your proposed NDA for Envarsus XR shares Astagraf XL’s conditions of approval, this may affect the type of action letter FDA can issue for Envarsus XR. Please let us know 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, and please submit the reasons for your position to your application, NDA 206406.

Please contact me at 301-796-1002 if you have any questions regarding the contents of this transmission.

Regards,

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

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/s/

LOIS A ALMOZA
10/27/2014



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION TRANSMITTAL SHEET

DATE: October 27, 2014

To: Ms. Michelle McGuinness, VP, Global Regulatory Affairs & QA	From: Lois Almoza, Project Manager
Company: Veloxis Pharmaceuticals, Inc.	Division of Transplant and Ophthalmology Products
Phone Number: 732-321-3211	Phone Number: 301-796-1600
Email: mam@veloxis.com	Email: lois.almoza@fda.hhs.gov

Subject: NDA 206406/Envarsus XR (tacrolimus extended-release tablets)

Total no. of pages including cover: 32

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Dear Ms. McGuinness:

Please refer to your December 28, 2013, submission, received December 30, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Envarsus XR (tacrolimus extended-release tablets), 0.75 mg, 1.0 mg and 4.0 mg.

Please also refer to your Medication Guide (MG), (b) (4) and Package Insert (PI) for your Envarsus XR product. We have attached a copy of the proposed MG, (b) (4) and PI for your review. Please note there are 5 comments embedded in the (b) (4) pdf document. If you have any questions, please do not hesitate to contact us.

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

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LOIS A ALMOZA
10/27/2014



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION TRANSMITTAL SHEET

DATE: October 20, 2014

To: Ms. Michelle McGuinness, VP, Global Regulatory Affairs & QA	From: Lois Almoza, Project Manager
Company: Veloxis Pharmaceuticals, Inc.	Division of Transplant and Ophthalmology Products
Phone Number: 732-321-3211	Phone Number: 301-796-1600
Email: mam@veloxis.com	Email: Lois.Almoza@fda.hhs.gov

Subject: NDA 206406/Envarsus XR (tacrolimus extended-release tablets)

Total no. of pages including cover: 3

Document to be mailed: ☐ YES ☒ NO

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Dear Ms. McGuinness:

Please refer to your December 28, 2013, submission, received December 30, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Envarsus XR (tacrolimus extended-release tablets), 0.75 mg, 1.0 mg and 4.0 mg.

Please also refer to your [REDACTED] ^{(b) (4)} for your Envarsus XR product.

We are providing the above information by email for your convenience. Contact me at 301-796-1600 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Lois Almoza, M. S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

General Comments

- The proposed (b) (4) is based on proposed (b) (4) for Envarsus XR.

(b) (4)

Specific Comments

(b) (4)

(b) (4)



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/s/

LOIS A ALMOZA
10/20/2014



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION TRANSMITTAL SHEET

DATE: October 10, 2014

To: Ms. Michelle McGuinness, VP, Global Regulatory Affairs & QA	From: Jacquelyn Smith, Project Manager for Lois Almoza, Project Manager
Company: Veloxis Pharmaceuticals, Inc.	Division of Transplant and Ophthalmology Products
Phone Number: 732-321-3211	Phone Number: 301-796-1600
Email: mam@veloxis.com	Email: jacquelyn.smith@fda.hhs.gov

Subject: NDA 206406/Envarsus XR (tacrolimus extended-release tablets)

Total no. of pages including cover: 6

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Dear Ms. McGuinness:

Please refer to your December 28, 2013, submission, received December 30, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Envarsus XR (tacrolimus extended-release tablets), 0.75 mg, 1.0 mg and 4.0 mg.

Please also refer to your Medication Guide (MG) for your Envarsus XR product. We have attached a copy of the proposed MG for your review. If you have any questions, please do not hesitate to contact us.

We are providing the above information by email for your convenience. Contact me at 301-796-1002 if you have any questions regarding the contents of this transmission. Thank you.

Regards,

Jacquelyn Smith, M.A.
Senior Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
FDA/CDER/OND/OAP

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/s/

JACQUELYN E SMITH
10/10/2014

MEMORANDUM

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

DATE: October 03, 2014

TO: NDA 206406

FROM: Lois Almoza, M.S.
Regulatory Health Project Manager

SUBJECT: Information Request sent on September 29, 2014

APPLICATION/DRUG: tacrolimus extended-release tablets

Veloxis Pharmaceuticals, LLC submitted a New Drug Application (NDA) on December 28, 2013 received December 30, 2013, Envarsus (tacrolimus extended-release tablets) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for prophylaxis or organ rejection in patients receiving a kidney transplant.

On October 01, 2014, the Agency requested further information from the Applicant, via e-mail(**see Attachment 1**).

The Applicant responded to the Agency on September 30, 2014 (**see Attachment 2**)

Attachment 1

From: Almoza, Lois

Sent: Monday, September 29, 2014 1:38 PM

To: mam@veloxis.com

Subject: Information Request - NDA 206406/ Envarsus XR (tacrolimus extended-release tablets) 0.75 mg, 1.0 mg, 4.0 mg/Veloxis Pharmaceuticals, Inc

Importance: High

Hi Michelle,

Please e-mail a picture and description of the overwrap for our review by COB today? Additionally please explain the purpose of the overwrap (added protection from light or moisture, etc)? Please also submit this formally to the application on file.

Thanks,
Lois

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6241
Silver Spring, MD 20993
Phone: 240-402-5146
Fax: 301-796-9881

Attachment 2

From: Michelle McGuinness [mailto:mam@Veloxis.com]
Sent: Tuesday, September 30, 2014 4:28 PM
To: Almoza, Lois
Cc: Silvina Garcia Rubio
Subject: RE: Information Request - NDA 206406/ Envarsus XR (tacrolimus extended-release tablets) 0.75 mg, 1.0 mg, 4.0 mg/Veloxis Pharmaceuticals, Inc

Dear Lois,

The FDA Information Request regarding the overwrap (bold text) & Veloxis's reply (blue text) are provided below:

- 1. Please e-mail a picture and description of the overwrap for our review by COB today?** Please refer to the attached artwork file. We propose the ability to use this artwork to develop (b) (4)
(b) (4) Kindly note: Samples of the container closure system, including unprinted/unlabeled (b) (4) were sent to FDA on 07 JUL 2014. This shipment was memorialized in sequence 0017. A description of the overwrap is provided in Sequence 0015 within 3.2.P.7.Container Closure System, subsection 3.4 (page 22-37).
- 2. Additionally please explain the purpose of the overwrap (added protection from light or moisture, etc)?** Veloxis adopted (b) (4)
(b) (4) Kindly note: In-use stability studies were performed over a 5 month time period. At the conclusion of the 5 month in-use study the product remained within specification. These data are included in Sequence 0000, 3.2.P.8 Stability Data – In-Use Stability Data and discussed in Sequence 0000, 3.2.P.8 Stability Summary and Conclusions.
- 3. Please also submit this formally to the application on file.** We agree to formally submit this response to the application. The sequence is scheduled for transmission to FDA via the gateway on: 8 October 2014.

I will be travelling on Wednesday and will not have access to phone or email during business hours. I have cc'd Silvina Garcia Rubio, my colleague & Sr. Director of Technical Operations. Should you require immediate assistance on Wednesday, please call Silvina at +1-732-251-6244.

Kindest Regards,
Michelle

Michelle McGuinness
VP, Global Regulatory Affairs & QA

Office Phone: +1 732 321 3211
Mobile Phone: (b) (6)
Fax: +1 732 906 7943
Email: mam@veloxis.com

Veloxis Pharmaceuticals
499 Thornall Street, 3rd floor
Edison, New Jersey 08837
United States
www.veloxis.com

The information in this e-mail and any attachment is strictly confidential and is intended solely for the individual or company to whom it is addressed. If you receive this communication by error, please notify the sender immediately and please return it to Veloxis Pharmaceuticals without producing, distributing or retaining copies hereof. Thank you.

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/s/

LOIS A ALMOZA
10/03/2014

MEMORANDUM

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

DATE: October 3, 2014

TO: NDA 206406

FROM: Lois Almoza, M.S.
Regulatory Health Project Manager

SUBJECT: Information Request sent on October 3, 2014

APPLICATION/DRUG: tacrolimus extended-release tablets

Veloxis Pharmaceuticals, LLC submitted a New Drug Application (NDA) on December 28, 2013 received December 30, 2013, Envarsus (tacrolimus extended-release tablets) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for prophylaxis or organ rejection in patients receiving a kidney transplant.

During the review process, a concern was raised based on the material submitted on December 28, 2013. On September 25, 2014, the Agency requested further information from the Applicant, via e-mail.

On September 29, 2014, the Applicant forwarded their responses to the Agency via e-mail which they plan to formally submit to the application on file by October 8, 2014(see Attachment 1).

On October 3, 2014, the Agency sent via e-mail additional comments in response to the Applicant's e-mail (see Attachment 2).

Attachment 1

From: Michelle McGuinness [<mailto:mam@Veloxis.com>]

Sent: Monday, September 29, 2014 7:01 PM

To: Almoza, Lois

Subject: RE: Information Request - NDA 206406/ Envarsus XR (tacrolimus extended-release tablets) 0.75 mg, 1.0 mg, 4.0 mg/Veloxis Pharmaceuticals, Inc

Dear Lois,

Thank you for forwarding the information request regarding revised initial dosage for Envarsus XR.

The FDA requests are presented below in bold text. The Veloxis responses are provided in blue text.

a.



[REDACTED] (b) (4)

b. 0.80 as the Prograf-to-ENVARUSUS XR conversion factor

[REDACTED] (b) (4)

- o Veloxis agrees to the revised conversion factor 0.80 and appreciates the prescribing simplicity of a single conversion rate for all patients, however, we wish to note that we do not necessarily agree with the underlying rationale provided by the Agency. As a practical matter though, we agree that: (a) the conversion dose of Envarsus should be lower than the dose of Prograf due to the greater bioavailability of Envarsus XR; and (b) a blood level should be obtained shortly after conversion to allow the physician to titrate to the correct final dose. These elements are adequately addressed by the proposed recommendation from the Agency. [REDACTED] (b) (4)

[REDACTED], we do believe that from a practical perspective that the Agency recommendations are unlikely to present a change in the clinical profile (given the limited long-term impact of the initial Day 1 switch dose recommendation), and there is arguable, theoretical value to a more simplified labeling statement.

We wish to confirm the teleconference for 1-2PM on Monday, October 6th. We would be most appreciative if comments could be provided to us by COB Thursday to allow us to adequately prepare for the teleconference. Please let us know if you agree with these times/dates. Upon your confirmation, we will distribute teleconference details.

Should you have any questions regarding this response, please call my cell or reply via email.

Kindest Regards,

Michelle McGuinness

VP, Global Regulatory Affairs & QA

Office Phone: +1 732 321 3211

Mobile Phone: [REDACTED] (b) (6)

Fax: +1 732 906 7943

Email: mam@veloxis.com

Veloxis Pharmaceuticals
499 Thornall Street, 3rd floor
Edison, New Jersey 08837
United States
www.veloxis.com

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Attachment 2

From: Almoza, Lois

Sent: Friday, October 03, 2014 6:36 AM

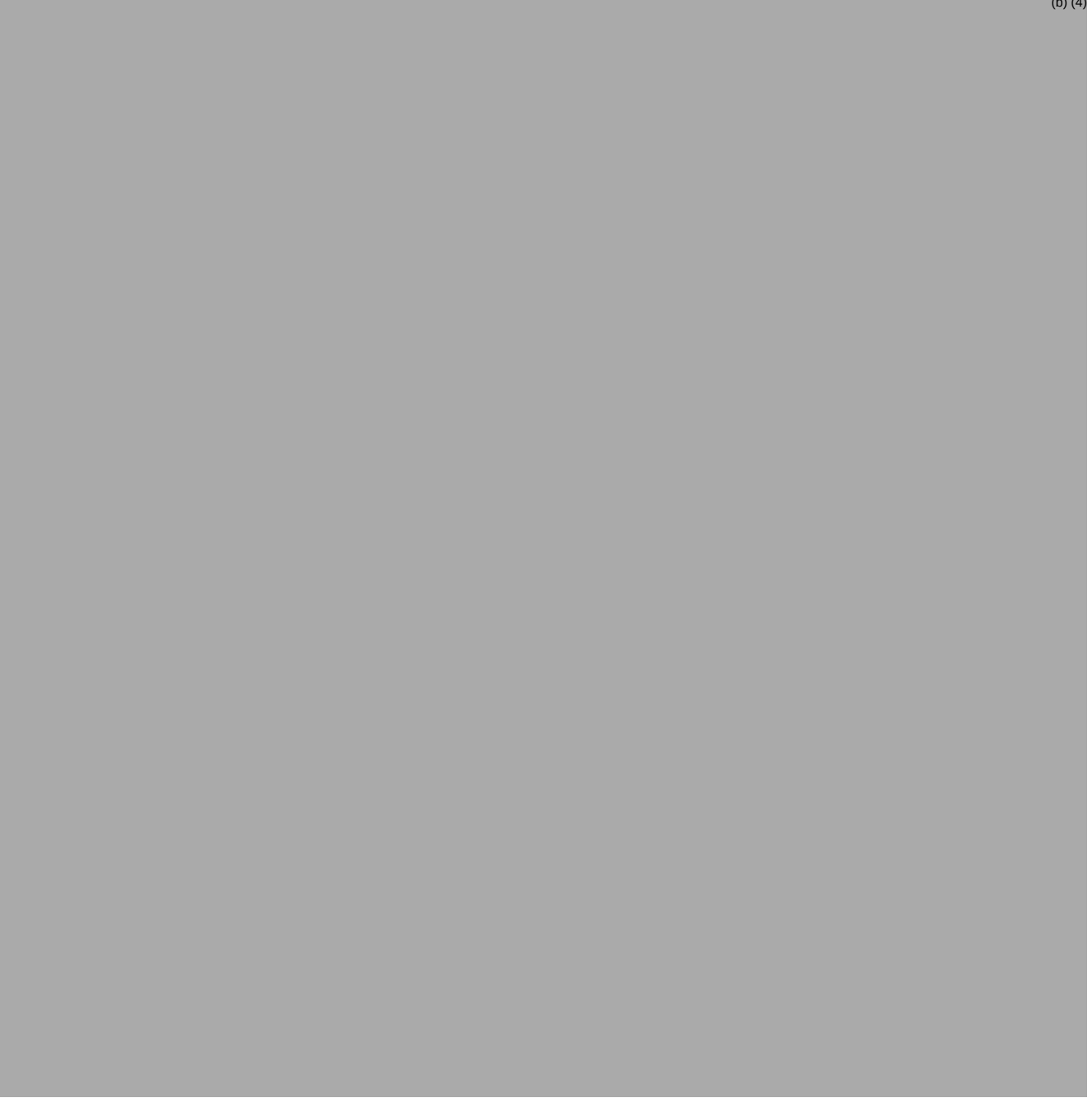
To: 'Michelle McGuinness'

Subject: RE: Information Request - NDA 206406/ Envarsus XR (tacrolimus extended-release tablets)
0.75 mg, 1.0 mg, 4.0 mg/Veloxis Pharmaceuticals, Inc

Hi Michelle,

Please find our preliminary response to your concerns about the Envarsus XR starting dose of

(b) (4)





Thanks,
Lois

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/s/

LOIS A ALMOZA
10/03/2014



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION SHEET

DATE: October 3, 2014

To: Ms. Michelle McGuinness	From: Lois Almoza Regulatory Health Project Manager
Company: Veloxis Pharmaceuticals, Inc.	Division of Transplant and Ophthalmology Products
Email: mam@veloxis.com	Email: lois.almoza@fda.hhs.gov
Cell Phone Number: 732-321-3211	Phone number: 301-796-1600
Subject: NDA 206406/Envarsus XR (tacrolimus extended-release tablets), 0.75 mg, 1.0 mg and 4.0 mg/Veloxis Pharmaceuticals, Inc. – comments regarding December 28, 2013, submission	

Total no. of pages including cover: 35

Comments:

Document to be mailed: ☐ YES ☒ NO

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Dear Ms. McGuinness,

Please refer to your December 28, 2013, submission, received December 30, 2013 that contained a New Drug Application (NDA) submission for Envarsus XR (tacrolimus extended-release tablets) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for prophylaxis or organ rejection in patients receiving a kidney transplant.

Please also refer to your package insert (PI) labeling revisions submission, received on September 19, 2014. We are providing revisions to the proposed PI for the Envarsus XR product submitted under NDA 206406. We ask that you review the attachment in advance of the teleconference on October 8, 2014.

We are providing the above information by email for your convenience. Contact me at 301-796-1600 if you have any questions regarding the contents of this transmission.

Thanks,

Lois Almoza, M. S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

33 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LOIS A ALMOZA
10/03/2014

MEMORANDUM

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

DATE: October 01, 2014

TO: NDA 206406

FROM: Lois Almoza, M.S.
Regulatory Health Project Manager

SUBJECT: Information Request sent on October 01, 2014

APPLICATION/DRUG: tacrolimus extended-release tablets

Veloxis Pharmaceuticals, LLC submitted a New Drug Application (NDA) on December 28, 2013 received December 30, 2013, Envarsus (tacrolimus extended-release tablets) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for prophylaxis or organ rejection in patients receiving a kidney transplant.

On October 01, 2014, the Agency requested further information from the Applicant, via e-mail(see attached).

From: Almoza, Lois

Sent: Wednesday, October 01, 2014 11:20 AM

To: mam@veloxis.com

Cc: Bhandari, Navdeep

Subject: NDA 206406 Proposed CMC PMCs - NDA 206406/ Envarsus XR(tacrolimus extended-release tablets) 0.75 mg, 1.0 mg, 4.0 mg/Veloxis Pharmaceuticals, Inc

Good Morning Michelle,

Please see the attached proposed CMC PMCs and let me know if you are in agreement. In addition to sending your response via e-mail, please also submit your response to the application on file.

Thank you,
Lois

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6241
Silver Spring, MD 20993
Phone: 240-402-5146
Fax: 301-796-9881

PMC #1: Develop and validate a regulatory X-Ray Powder Diffraction (XRPD) test, with a limit of detection of not more than (b) (4), for determination of crystalline tacrolimus content in tacrolimus extended-release tablets. Revise 3.2.P.5 Drug Product Specification accordingly. Submit a supplemental NDA to add the XRPD testing facility.

Add XRPD testing to the on-going drug product stability protocol (first three commercial batches of each strength or next three consecutive commercial batches of each strength and annual stability commitment batches).

Notes: As soon as a validated XRPD test is developed and an analytical laboratory selected to perform this testing, submit this information in a prior approval supplement.

We acknowledge your proposal to “evaluate sunsetting this test or implementing skip testing when sufficient supportive data are available” (July 18, 2014, seq. no. 0018). When sufficient supporting data are available we would consider deletion of the XRPD test from the drug product specification (via a prior approval supplement). However, XRPD testing would be needed to support subsequent changes to the formulation or manufacturing process.

We also acknowledge your proposal to evaluate tablet stability at 25°C/60% RH and 30°C/65% RH. However, testing the drug products under accelerated and stress conditions should be conducted as part of the evaluation of conditions that may promote crystallization. See PMC #4.

PMC #2: Develop and validate an X-Ray Powder Diffraction (XRPD) test, with a limit of detection of not more than (b) (4)

Add XRPD testing to tacrolimus (b) (4) stability protocol.

Notes: We acknowledge your proposal to evaluate (b) (4) stability at (b) (4) and (b) (4). However, testing the tacrolimus (b) (4) under accelerated and stress conditions should be conducted as part of the evaluation of conditions that may promote crystallization. See PMC #4.

PMC #3: Evaluate the crystalline content of available legacy batches of tacrolimus (b) (4) and of drug product stability batches by XRPD.

PMC #4: Evaluate conditions that might be expected to promote crystallization of tacrolimus in (b) (4) tablets, including:

- Any relationship between (b) (4) and crystalline tacrolimus content in tacrolimus extended-release tablets.
- The (b) (4) stability of tacrolimus in (b) (4) tablets under accelerated and stress conditions.

PMC #5: Evaluate the effect of MeltDose manufacturing process parameters on crystalline content of (b) (4) tablets.

We propose the following timelines for PMCs #1, #2 and 3:

PMC Schedule Milestones:	Final Protocol Submission:	2 months from date of approval
	Study/Trial Completion:	9 months from date of approval
	Final Report Submission:	12 months from date of approval
	Other: Interim Report	6 months from date of approval

We propose the following timelines for PMCs #4 and #5:

PMC Schedule Milestones:	Final Protocol Submission:	3 months from date of approval
	Study/Trial Completion:	15 months from date of approval
	Final Report Submission:	18 months from date of approval
	Other: Interim Report	9 months from date of approval

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/s/

LOIS A ALMOZA
10/01/2014

MEMORANDUM

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

DATE: September 26, 2014

TO: NDA 206406

FROM: Lois Almoza, M.S.
Regulatory Health Project Manager

SUBJECT: Information Request sent on September 25, 2014

APPLICATION/DRUG: tacrolimus extended-release tablets

Veloxis Pharmaceuticals, LLC submitted a New Drug Application (NDA) on December 28, 2013 received December 30, 2013, Envarsus (tacrolimus extended-release tablets) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for prophylaxis or organ rejection in patients receiving a kidney transplant.

During the review process, a concern was raised based on the material submitted on December 28, 2013. On September 25, 2014, the Agency requested further information from the Applicant, via e-mail(see attached).

From: Almoza, Lois

Sent: Thursday, September 25, 2014 4:33 PM

To: mam@veloxis.com

Subject: Information Request - NDA 206406/ Envarsus XR (tacrolimus extended-release tablets) 0.75 mg, 1.0 mg, 4.0 mg/Veloxis Pharmaceuticals, Inc

Good Afternoon Michelle,

Please see the following information request below along with the attached slides.

We propose to recommend in the prescribing information the following initial dosages for ENVARSUS XR oral tablets:

- [REDACTED] (b) (4) and
- 0.80 as the Prograf-to-ENVARSUS XR conversion factor [REDACTED] (b) (4) [REDACTED].

Our rationale for this proposal is outlined in the attached slides. Let us know if you concur with this proposal, and if you disagree, provide your rationale/justification by COB Monday, September 29, 2014.

We plan to schedule a teleconference with you towards the end of next week to have a discussion about these and other labeling issues.

<< File: ClinPharm Slide -EV-Envarsus_24Sept2014.ppt >>

Thank you,

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6241
Silver Spring, MD 20993
Phone: 240-402-5146
Fax: 301-796-9881

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/s/

LOIS A ALMOZA
09/26/2014

From: Bhandari, Navdeep
To: ["mam@veloxis.com"](mailto:mam@veloxis.com)
Bcc: [Cruz, Celia](#); [Madurawe, Rapti](#); [Shanmugam, Balajee](#); [Seggel, Mark R](#)
Subject: NDA 206406 CMC Information request
Date: Thursday, September 18, 2014 2:21:00 PM
Importance: High

Hello Michelle,

My team has asked that I send the following comment to you. Please confirm receipt.

The proposed acceptance criterion for Total Degradation Products, Not More Than (b) (4) %, is not supported by the available batch release and stability data. Please revise the limit to Not More Than (b) (4) %.

In reference to the voicemail I left you, my team has requested a short T-con. Please call me back so we may make arrangements to have a 30 minute call either later today or tomorrow morning.

Thank you,

Navi Bhandari, Pharm.D
Regulatory Health Project Manager
Office of New Drug Quality Assessment
OPS/CDER/FDA
240-402-3815

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/s/

NAVDEEP BHANDARI
09/18/2014

From: Bhandari, Navdeep
To: "[Michelle McGuinness](#)"
Subject: RE: NDA 206406 September 10th Turnaround
Date: Monday, September 08, 2014 8:13:00 AM
Importance: High

Good Morning Michelle,

Please see the below response from my team. Please confirm receipt of this email.

A. Because a laboratory to perform XRPD testing of the (b) (4) and finished drug product has not been identified, and the procedure has not be validated at the test site, all actions regarding XRPD will be addressed through Post Marketing Commitments. Therefore, please update the drug product specification, excluding the test for XRPD, by September 10th.

B. While the registration / primary stability batches manufactured at (b) (4) they were not manufactured using production equipment in a production facility as specified in the application (ICH Q1AR2 definition of production batch). We therefore recommend that three batches of each strength manufactured at Rottendorf using the commercial process at production scale be placed on long-term and accelerated stability.

C. Please note that your new drug application is for tacrolimus, not (b) (4).

Regards,
Navi

From: Michelle McGuinness [mailto:mam@Veloxis.com]
Sent: Friday, September 05, 2014 4:30 PM
To: Bhandari, Navdeep
Subject: RE: NDA 206406 September 10th Turnaround

Hi Navi,

I don't mean to be a pest, but the Information Request deadline is approaching. Please provide feedback regarding our questions in the email below.

If I do not have the details by Monday afternoon it will be difficult to update all the files and send these to our eCTD publishing team in time to make a Sep 12th response date & we will respectfully request an extension until the 17th.

Regarding item C (below). I believe the issue was that the references to (b) (4) " in the aquatic environment should be "tacrolimus". Please confirm that this is the issue with the Environmental Assessment.

Kindest Regards,

Michelle McGuinness
VP, Global Regulatory Affairs & QA

Office Phone: +1 732 321 3211
Mobile Phone: (b) (6)
Fax: +1 732 906 7943
Email: mam@veloxis.com

Veloxis Pharmaceuticals
499 Thornall Street, 3rd floor
Edison, New Jersey 08837
United States
www.veloxis.com

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/s/

NAVDEEP BHANDARI
09/08/2014



NDA 206406

INFORMATION REQUEST

Veloxis Pharmaceuticals, Inc.
Attention: Free Peay
Sr. Vice President
499 Thornall Street, 3rd Floor
Edison, NJ 08837

Dear Mrs. Peay:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Envarsus (tacrolimus extended-release tablets), 0.75 mg, 1.0 mg and 4.0 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have identified the following deficiencies. We request a prompt written response by September 10, 2014, in order to continue our evaluation of your NDA.

(b) (4)

(b) (4)



If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402- 3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURawe
09/03/2014



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION SHEET

DATE: September 02, 2014

To: Ms. Michelle McGuinness	From: Lois Almoza Regulatory Health Project Manager
Company: Veloxis Pharmaceuticals, Inc.	Division of Transplant and Ophthalmology Products
Email: mam@veloxis.com	Email: lois.almoza@fda.hhs.gov
Cell Phone Number: 732-321-3211	Phone number: 301-796-1600

Subject: NDA 206406/Envarsus XR (tacrolimus extended-release tablets), 0.75 mg, 1.0 mg and 4.0 mg/Veloxis Pharmaceuticals, Inc. – comments regarding December 28, 2013, submission

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ☒ NO

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Dear Ms. McGuinness,

Please refer to your December 28, 2013, submission, received December 30, 2013 that contained a New Drug Application (NDA) submission for Envarsus XR (tacrolimus extended-release tablets) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for prophylaxis or organ rejection in patients receiving a kidney transplant.

To facilitate our review of your NDA submission, please provide the following information.

The Form FDA 356h has the following checked in box number 20, “statement of no relevant patents.” The patent certification must match this statement. The patent certification that was submitted is not a valid patent certification for this 505(b)(2) NDA.

Please provide a valid patent certification for this 505(b)(2) NDA by September 5, 2014.

Contact me at 301-796-1600 if you have any questions regarding this request, or if you are unable to provide the requested documentation by September 5, 2014.

Thank you,

Lois Almoza, M. S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

LOIS A ALMOZA
09/02/2014



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION SHEET

DATE: August 28, 2014

To: Ms. Michelle McGuinness	From: Lois Almoza Regulatory Health Project Manager
Company: Veloxis Pharmaceuticals, Inc.	Division of Transplant and Ophthalmology Products
Email: mam@veloxis.com	Email: lois.almoza@fda.hhs.gov
Cell Phone Number: 732-321-3211	Phone number: 301-796-1600

Subject: NDA 206406/Envarsus XR (tacrolimus extended-release tablets), 0.75 mg, 1.0 mg and 4.0 mg/Veloxis Pharmaceuticals, Inc. – comments regarding December 28, 2013, submission

Total no. of pages including cover: 5

Comments:

Document to be mailed: ☐ YES ☒ NO

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Dear Ms. McGuinness,

Please refer to your December 28, 2013, submission, received December 30, 2013 that contained a New Drug Application (NDA) submission for Envarsus XR (tacrolimus extended-release tablets) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for prophylaxis or organ rejection in patients receiving a kidney transplant.

We are providing revisions to the proposed carton/container labeling text for the Envarsus XR product submitted under NDA 206406. We ask that you review the carton/container labeling revisions and submit revised carton/container labeling by September 27, 2014.

We are providing the above information by email for your convenience. Contact me at 301-796-1600 if you have any questions regarding the contents of this transmission, or if you are unable to provide your comments by September 27, 2014.

Thanks,

Lois Almoza, M. S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

A. Container Label (All Strengths)

- i. Add the modifier 'XR' to the proprietary name, Envarsus, since the product's name is Envarsus XR.
- ii. Increase the prominence of the established name to ensure that it is displayed with equal prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2).
- iii. Add a statement on the principal display panel stating that this product must be dispensed with a Medication Guide per 21 CFR 208.24(d).
- iv. Add the National Drug Code (NDC) number to the top panel and the principal display panel of the container label. As per the 21 Code of Federal Regulations 207.35 (b)(3), the NDC number should appear prominently in the top third of the principal display panel.
- v. The established name for Envarsus XR is tacrolimus extended-release tablets and should be written as follows:

Envarsus XR
(Tacrolimus Extended-release Tablets)

Currently, part of your established name will be on (b) (4) and will not be visible right away as it is located closer to the end of the label. Thus, we recommend placement of the established name as above.

- vi. Decrease the prominence of the company logo as it is almost as prominent as the proprietary name of the product. As per the Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors¹ the most prominent information on the label should be the proprietary and established names.
- vii. Consider increasing the prominence of the strength by using more intense color to ensure adequate legibility of this very important information.
- viii. Increase the prominence of the statement "Swallow tablet whole. Do not chew, divide, or crush tablet" by bolding the font and placing this information prior to the statement "Dosage: See Package Insert for Dosage Information". We recommend this revision to help identify the correct technique of product administration.
- ix. Decrease the prominence of the net quantity by removing (b) (4) around it and decreasing its font size. Currently, although your net quantity is located off to the side, it is still more prominent than the strength of the product because it is in a (b) (4). Thus, the confusion between the strength and net quantity can occur.

¹ 2013 Draft Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

B. Carton Labeling (All Strengths)

- i. See A.i through A.vii and revise carton labeling accordingly.
- ii. Increase the prominence of the statement “Swallow tablet whole. Do not chew, divide, or crush tablet” by bolding the font.
- iii. Decrease the prominence of the net quantity by removing the (b) (4) around it, decreasing its font size, and moving above the proprietary name or away from the “ONCE DAILY” statement. As currently presented, the net quantity is more prominent than the strength of the product.

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/s/

LOIS A ALMOZA
08/28/2014

From: Bhandari, Navdeep
To: ["Michelle McGuinness"](#)
Subject: NDA 206406 Quick Turnaround Requested
Date: Wednesday, August 27, 2014 1:43:00 PM
Importance: High

Hello Michelle,

My review team has asked that I convey the following comments to you:

“Drug substance analytical testing site (b) (4) was not identified on Form 356h or in 3.2.S.2. Please clarify if this site will be performing routine regulatory testing of the drug substance and clarify any role of this facility in commercial manufacturing.”

Please note that there is a **24 hour response time** for this information request. Please send me a courtesy copy of your response via email as well as your official submission to your NDA.

Thank you,
Navi

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/s/

NAVDEEP BHANDARI

08/27/2014

From: Bhandari, Navdeep
To: "[Michelle McGuinness](#)"
Subject: RE: NDA 206406 Quick Turnaround Requested
Date: Wednesday, August 27, 2014 4:20:00 PM
Importance: High

Hello Michelle,

My team has included an additional comment for your review:

“You have included reference of “drug product manufacturer’s contract laboratory” responsible for testing of drug substance in 3.2.S.4.2 and 3.2.S.4.3. Drug substance analytical testing site (b) (4) was not identified on Form 356h or in 3.2.S.2. Please clarify if this site will be performing routine regulatory testing of the drug substance and clarify any role of this facility in commercial manufacturing”

Thank you,
Navi

From: Michelle McGuinness [<mailto:mam@Veloxis.com>]
Sent: Wednesday, August 27, 2014 3:20 PM
To: Bhandari, Navdeep
Subject: RE: NDA 206406 Quick Turnaround Requested

Hi Navi,

Thank you for your email.

Could you please reply with the CTD section that is the genesis of this question? Your email below states that the (b) (4) site is not contained in 3.2.S.2 or 356h, but it does not state the origin of the reference.

Many thanks,
Michelle

Michelle McGuinness
VP, Global Regulatory Affairs & QA

Office Phone: +1 732 321 3211
Mobile Phone: (b) (6)
Fax: +1 732 906 7943
Email: mam@veloxis.com

Veloxis Pharmaceuticals
499 Thornall Street, 3rd floor
Edison, New Jersey 08837
United States
www.veloxis.com

From: Bhandari, Navdeep [<mailto:Navdeep.Bhandari@fda.hhs.gov>]
Sent: Wednesday, 27 August, 2014 1:43 PM
To: Michelle McGuinness
Subject: NDA 206406 Quick Turnaround Requested
Importance: High

Hello Michelle,

My review team has asked that I convey the following comments to you:

“Drug substance analytical testing site (b) (4) was not identified on Form 356h or in 3.2.S.2. Please clarify if this site will be performing routine regulatory testing of the drug substance and clarify any role of this facility in commercial manufacturing.”

Please note that there is a **24 hour response time** for this information request. Please send me a courtesy copy of your response via email as well as your official submission to your NDA.

Thank you,
Navi

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/s/

NAVDEEP BHANDARI

08/27/2014



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION SHEET

DATE: August 14, 2014

To: Ms. Michelle McGuinness	From: Lois Almoza Regulatory Health Project Manager
Company: Veloxis Pharmaceuticals, Inc.	Division of Transplant and Ophthalmology Products
Email: mam@veloxis.com	Email: lois.almoza@fda.hhs.gov
Cell Phone Number: 732-321-3211	Phone number: 301-796-1600

Subject: NDA 206406/Envarsus XR (tacrolimus extended-release tablets), 0.75 mg, 1.0 mg and 4.0 mg/Veloxis Pharmaceuticals, Inc. – comments regarding December 28, 2013, submission

Total no. of pages including cover: 40

Comments:

Document to be mailed: ☐ YES ☒ NO

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Dear Ms. McGuinness,

Please refer to your December 28, 2013, submission, received December 30, 2013 that contained a New Drug Application (NDA) submission for Envarsus XR (tacrolimus extended-release tablets) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for prophylaxis or organ rejection in patients receiving a kidney transplant.

We are providing revisions to the proposed package insert (PI) text for the Envarsus XR product submitted under NDA 206406. We ask that you review these PI revisions and submit a revised PI by September 14, 2014.

We are providing the above information by email for your convenience. Contact me at 301-796-1600 if you have any questions regarding the contents of this transmission, or if you are unable to provide your comments by September 14, 2014.

Thanks,

Lois Almoza, M. S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

37 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LOIS A ALMOZA
08/14/2014



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION SHEET

DATE: July 11, 2014

To: Ms. Michelle McGuinness	From: Lois Almoza Regulatory Health Project Manager
Company: Veloxis Pharmaceuticals, Inc.	Division of Transplant and Ophthalmology Products
Email: mam@veloxis.com	Email: lois.almoza@fda.hhs.gov
Cell Phone Number: 732-321-3211	Phone number: 301-796-1600

Subject: NDA 206406/Envarsus (tacrolimus extended-release tablets), 0.75 mg, 1.0 mg and 4.0 mg/Veloxis Pharmaceuticals, Inc. – comments regarding December 28, 2013, submission

Total no. of pages including cover: 5

Comments:

Document to be mailed: ☐ YES ☒ NO

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Dear Ms. McGuinness,

Please refer to your December 28, 2013, submission, received December 30, 2013 that contained a New Drug Application (NDA) submission for Envarsus (tacrolimus extended-release tablets) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for prophylaxis or organ rejection in patients receiving a kidney transplant.

To facilitate our review of your NDA submission, please provide the following information. Alternatively, if the information was previously included in the NDA submission, please direct us to the location(s). Please provide a response to both items by July 25, 2014 (if possible).

Clinical Pharmacology/Pharmacometrics

The clinical study report (CSR) of Phase 3 Study 3002 (pages 35 and 56) states:

“LCP-Tacro was started at 0.17 mg/kg/day given as a single morning dose. Prograf was started at a total daily dose (TDD) of 0.1 mg/kg/day, given as 2 equally divided doses 12 hours apart (1 in the morning before noon and 1 in the evening). Subsequent doses of each study drug were adjusted to maintain trough concentrations of tacrolimus in whole blood within the target range of 6 to 11 ng/mL for the first 30 days, then 4 to 11 ng/mL for the remainder of the study.

The initial dosage was calculated and indicated via an interactive, automated system and subsequent doses were determined by the investigator. The administration of the first dose of study drug was to be given in the morning following transplantation or no later than 48 hours following transplantation; patients who could not fulfill this criterion were not randomly assigned to study drug.”

The investigator may have adjusted the dosage of drug as necessary to titrate the desired blood level of tacrolimus by accessing the interactive, automated system to request a dosage adjustment. While the investigator requested a dosage adjustment as an equivalent Prograf dosage, the automated system issued dispensing instructions for the assigned treatment dose (LCP-Tacro or Prograf) and equivalent placebos as appropriate. The automated system was validated for the intended use under the ISPE GAMP guidelines, 21 CFR 11, and ICH E6(R1). Study drug was dispensed to the patients, as needed, at study visits throughout the 12-month study treatment period and the 12-month extension period except at Visit 21, Month 24.

A similar description is found in the CSR of Phase 2 Study 2019.

To facilitate our review of the NDA submission, please address the following:

1. When looking at “lcp-tacro-3002-e3-16-2-05.pdf” file for the double-blinded Study 3002, it appears that the use of the approximately 1.7 conversion factor persisted beyond the initial dosing phase of the trial (for example, see attached data listing for the actual LCP-Tacro doses received by Patient 00109/020). Please clarify whether (and if so, why) LCP-Tacro patients received consistently higher daily equivalent tacrolimus doses than their

prescribed Prograf equivalent daily doses by the investigators, even though the bioavailability of LCP-Tacro is supposedly higher compared to Prograf.

LCP-Tacro

Site ID/ Patient No.	Visit Name [1]	Visit Window [2]	Sample Date (Study Day)	Results (ng/mL)	Analysis Flag [3]	Daily Dose Prior to Tacrolimus Trough Level Sampling (mg)		
						Dispensing Date	Prescribed Prograf [4]	Actual LCP-Tacro [5]
001009/020	Day 2	Day 2	08MAR2012 (2)	44.356	Y	07MAR2012	10	17
	Day 3	Day 3	09MAR2012 (3)	33.080	Y	07MAR2012	10	17
	Day 4	Day 4	10MAR2012 (4)	15.213	Y	07MAR2012	10	17
	Day 7	Day 7	13MAR2012 (7)	13.681	Y	10MAR2012	4	6.75
	Day 10	Day 10	16MAR2012 (10)	6.395	Y	13MAR2012	3	5
	Day 14	Week 2	20MAR2012 (14)	9.000	Y	16MAR2012	4	6.75
	Day 21	Week 3	26MAR2012 (20)	10.180	Y	20MAR2012	4	6.75
	Day 30	1 Month	06APR2012 (31)	11.676	Y	29MAR2012	4	6.75
	Day 45	1.5 Months	20APR2012 (45)	13.585	Y	13APR2012	4	6.75
	Day 60	2 Months	04MAY2012 (59)	9.015	Y	20APR2012	3	5
	Day 90	3 Months	01JUN2012 (87)	8.246	Y	17MAY2012	2	3
	Unscheduled	6 Months	03AUG2012 (150)	6.172	Y	01JUN2012	2	3

- In your May 20, 2014 response to the Information Request regarding the calculation of daily tacrolimus dosage administered in Study 2019, you indicated that example LCP Tacro Patient # 000005-001 missed the evening dose on Day 3, did not receive any drug (or missed the AM and PM dose) on Day 4, and missed the AM dose on Day 5. We acknowledge that the missed evening (placebo) administrations in this particular patient would not matter in terms of the calculation of the total daily doses of LCP-Tacro. We are not able to find the Case Report Forms (CRF) for this particular patient; please explain why this patient missed several tacrolimus doses during the first week of therapy in this double-blinded study. If the CRF and the tacrolimus trough levels for the purpose of determining tacrolimus dose adjustment for this patient were included in the NDA submission, please direct us to the location.

LCP-Tacro. This is a once daily form of tacrolimus. Need to convert assigned daily dose from Prograf to LCP-Tacro first (*use table in SAP*), and then do calculations – but only morning dose matters.

Example subject:

Subject ID	Sex/Age/ Ethnicity/ Race (a)	Assigned Daily Dose (mg)(b)	Start Date(Day) (c)	Stop Date(Day) (c)	Doses Taken
000005-001	M/64/NL/C	9.0	14FEB2013(1)	15FEB2013(2)	AM, PM
		9.0	16FEB2013(3)	16FEB2013(3)	AM
		9.0	17FEB2013(4)	17FEB2013(4)	NEITHER AM OR PM DOSE TAKEN
		2.5	18FEB2013(5)	18FEB2013(5)	PM
		2.0	19FEB2013(6)	19FEB2013(6)	AM
		3.0	19FEB2013(6)	19FEB2013(6)	PM
		3.0	20FEB2013(7)	20FEB2013(7)	AM, PM
		3.0	21FEB2013(8)	21FEB2013(8)	AM
		4.0	21FEB2013(8)	21FEB2013(8)	PM
		4.0	22FEB2013(9)	26FEB2013(13)	AM, PM
		4.0	27FEB2013(14)	27FEB2013(14)	AM
		6.0	27FEB2013(14)	27FEB2013(14)	PM
		6.0	28FEB2013(15)	28FEB2013(15)	AM, PM
		6.0	01MAR2013(16)	01MAR2013(16)	AM
		8.0	01MAR2013(16)	01MAR2013(16)	PM

Day 1 – 15 (9.0 mg Prograf dose is 15 mg LCP-Tacro Dose)

Day 2 – 15

Day 3 – 15 (missed evening dose doesn't matter)

Day 4 – 0

Day 5 – 0 (only evening dose taken so placebo)

Day 6 – 3 (2.0 mg Prograf dose is 3 mg LCP-Tacro)(evening dose doesn't matter)

Day 7 – 5 (3.0 mg Prograf dose is 5 mg LCP-Tacro)

Etc.

If you have any questions regarding this communication, please contact me at (301) 796-1600.

Sincerely,

Lois Almoza, M. S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

LOIS A ALMOZA
07/11/2014



NDA 206406

INFORMATION REQUEST

Veloxis Pharmaceuticals, Inc.
Attention: Free Peay
Sr. Vice President
499 Thornall Street, 3rd Floor
Edison, NJ 08837

Dear Mrs. Peay:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Envarsus (tacrolimus extended-release tablets), 0.75 mg, 1.0 mg and 4.0 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have identified the following deficiencies. We request a prompt written response by July 18, 2014, in order to continue our evaluation of your NDA.

(b) (4)

(b) (4)



If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402- 3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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RAPTI D MADURawe
06/24/2014

MEMORANDUM

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

DATE: June 11, 2014

TO: NDA 206406

FROM: Lois Almoza, M.S.
Regulatory Health Project Manager

SUBJECT: Information Request

APPLICATION/DRUG: tacrolimus extended-release tablets

Veloxis Pharmaceuticals, LLC submitted a New Drug Application (NDA) on December 28, 2013 received December 30, 2013, Envarsus (tacrolimus extended-release tablets) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for prophylaxis or organ rejection in patients receiving a kidney transplant.

During the review process, a concern was raised based on the material submitted on December 28, 2013. On June 11, 2014, the Agency requested further information from the Applicant, via e-mail(see Attached).

From: Almoza, Lois

Sent: Wednesday, June 11, 2014 2:25 PM

To: fpe@veloxis.com

Subject: Information Request - NDA 206406/Envarsus(tacrolimus extended-release tablets)/Veloxis Pharmaceuticals, Inc.

Good Afternoon Free,

Please submit several samples of the container / closure systems (labeled cartons, (b) (4) overwrap, and bottles [with (b) (4)] for each strength and tablet count.

Thanks,

Lois

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6241
Silver Spring, MD 20993
Phone: 240-402-5146
Fax: 301-796-9881

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/s/

LOIS A ALMOZA
06/11/2014

MEMORANDUM

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

DATE: May 29, 2014

TO: NDA 206406

FROM: Lois Almoza, M.S.
Regulatory Health Project Manager

SUBJECT: Information Request

APPLICATION/DRUG: tacrolimus extended-release tablets

Veloxis Pharmaceuticals, LLC submitted a New Drug Application (NDA) on December 28, 2013 received December 30, 2013, Envarsus (tacrolimus extended-release tablets) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for prophylaxis or organ rejection in patients receiving a kidney transplant.

During the review process, a concern was raised based on the material submitted on December 28, 2013. On May 29, 2014, the Agency requested further information from the Applicant, via e-mail(see Attached).

From: Almoza, Lois
Sent: Thursday, May 29, 2014 2:35 PM
To: fpe@veloxis.com
Subject: Information Request - NDA 206406/Envarsus(tacrolimus extended-release tablets)/Veloxis Pharmaceuticals, Inc.

Good Afternoon Free,

Please submit the proposed container closure systems for all of the Envarsus strengths by June 6, 2014.

Thanks,

Lois

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6241
Silver Spring, MD 20993
Phone: 240-402-5146
Fax: 301-796-9881

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LOIS A ALMOZA
05/29/2014

MEMORANDUM OF TELECONFERENCE

DATE: May 13, 2014 12:00 PM to 1:00 PM, (EST)

APPLICATION NUMBER: NDA 206406

BETWEEN:

Applicant (Veloxis)

William Polvino
John Weinberg
Breian Knudsen
Free Peay

CMC Consultants

(b) (4)
[Redacted]

On the phone from (b) (4)
(b) (4)

AND

FDA

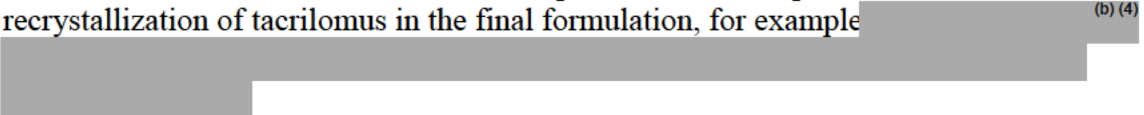
Navi Bhandari, ONDQA Regulatory Project Manager
Angelica Dorantes, ONDQA Biopharm Team Leader
Banu Zolnik, ONDQA Biopharm Reviewer
Mark Seggel, ONDQA Chemist
Mansoor Khan, OTR Director of DPQR
Celia Cruz, OPS/IO Senior Product Quality Reviewer

SUBJECT: Information Request NDA 206406

Background: FDA teleconference to discuss FDA's comments on the pending NDA.

The Call:

1. FDA expressed concerns regarding sensitivity of (b) (4) method. Directed applicant towards continuing efforts on developing a (b) (4) pXRD method capable of detecting changes in crystallinity.
2. FDA requested that Sponsor provide validation of any method eventually used for release or stability testing of the drug product.
3. FDA requested samples of (b) (4) tablets of all strengths.

4. FDA recommended the inclusion of development data on the potential for recrystallization of tacrilomus in the final formulation, for example (b) (4)

5. Sponsor was informed that their control strategy should include approach and justification for intermediate, release, and stability testing, as necessary.

Navdeep Bhandari, Pharm.D.
Regulatory Health Project Manager

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NAVDEEP BHANDARI

05/14/2014

MEMORANDUM

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

DATE: May 14, 2014

TO: NDA 206406

FROM: Lois Almoza, M.S.
Regulatory Health Project Manager

SUBJECT: Follow-up to Information Request Response received May 13, 2014

APPLICATION/DRUG: tacrolimus extended-release tablets

Veloxis Pharmaceuticals, LLC submitted a New Drug Application (NDA) on December 28, 2013 received December 30, 2013, Envarsus (tacrolimus extended-release tablets) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for prophylaxis or organ rejection in patients receiving a kidney transplant.

During the review process, a concern was raised based on the material submitted on December 28, 2013. On May 1, 2014, the Agency requested further information from the Applicant, via e-mail. The Applicant, responded to the information request on May 13, 2014. The Agency made a follow-up request via e-mail (**see Attachment 1**) on May 14, 2014 regarding the Applicant's response received on May 13, 2014.

Attachment 1

From: Almoza, Lois

Sent: Wednesday, May 14, 2014 10:09 AM

To: fpe@veloxis.com

Subject: Follow-up Information Request to Clinical Pharmacology Information Request dated May 1, 2014 #3 - NDA 206406/Envarsus(tacrolimus extended-release tablets)/Veloxis Pharmaceuticals, Inc.

Good Morning Free,

Regarding your response to the Clinical Pharmacology Information Request #3 dated May 1, 2014, we have the following follow-up comment/request.

1. We acknowledge receipt of the bioanalytical method report for T32 Version 03 of the LC/MS/MS assay used by the central laboratory to measure tacrolimus whole blood concentrations collected during the conduct of Study 3002. We were not able to find all the validation parameters in the report. Please fill in the necessary assay validation information in the attached table.
2. Your plan to submit the remaining requested information regarding the local laboratory assays (item #2) used in Study 3002 and Study 3001 by June 15, 2014 is acceptable.

Validated LC/MS/MS assay	T32 (version 03)	T32 (version 02)
Phase 3 Study	Study 3002	Study 3001
Analyte (s)	tacrolimus	tacrolimus
Calibration range (ng/mL)	0.200 to 25.6 ± 10.0%	0.200 to 25.6 ± 10.0%
Accuracy (% RE): intra-assay inter-assay		-6.4 to 20.0 -6.3 to 8.0
Precision (% CV) intra-assay inter-assay		2.3 to 10.4 2.8 to 15.3
Freeze thaw stability		4 cycles at -70°C ± 10°C
In Process stability		27.5 hours at room temperature
Autosampler stability		73 hours at 7°C ± 4°C
Autosampler re-injection reproducibility		70 hours at 7°C ± 4°C
Processed sample integrity		76 hours at 4°C ± 4°C
Whole blood stability ☐ Without flash freezing ☐ With flash freezing		2.5 hours at 4°C ± 4°C 3 hours at 4°C ± 4°C
Matrix effect Long term stability matrix effect		No significant matrix effect 1003 days at -70°C ± 10°C

Thank you,
Lois

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 6241
Silver Spring, MD 20993
Phone: 240-402-5146
Fax: 301-796-9881

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/s/

LOIS A ALMOZA
05/14/2014



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION SHEET

DATE: May 9, 2014

To: Ms. Free M. Peay	From: Lois Almoza Regulatory Health Project Manager
Company: Veloxis Pharmaceuticals, Inc.	Division of Transplant and Ophthalmology Products
Email: fpe@veloxis.com	Email: lois.almoza@fda.hhs.gov
Cell Phone Number: 732-321-3200	Phone number: 301-796-1600

Subject: NDA 206406/Envarsus (tacrolimus extended-release tablets), 0.75 mg, 1.0 mg and 4.0 mg/Veloxis Pharmaceuticals, Inc. – comments regarding December 28, 2013, submission

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ☒ NO

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Dear Ms. Peay,

Please refer to your December 28, 2013, submission, received December 30, 2013 that contained a New Drug Application (NDA) submission for Envarsus (tacrolimus extended-release tablets) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for prophylaxis or organ rejection in patients receiving a kidney transplant.

To facilitate our review of your NDA submission, please provide the following information. Alternatively, if the information was previously included in the NDA submission, please direct us to the location(s). Please provide a response to both items by May 23, 2014.

Clinical Pharmacology/Pharmacometrics

To facilitate our review of the results of Phase 2 Study 2019, please address the following requests by May 23, 2014 (if possible).

1. We are not able to reproduce the post-hoc figures for tacrolimus total daily dose (mg) over time in addendum 1 of the Study 2019 CSR using either the data listing for total daily doses in the PK study report (Table 06) or by analysis of the EX.xpt and ADEX.xpt datasets. Please provide clarification as to how you calculated the daily doses of LCP-Tacro and Prograf at each study visit. Please submit a revised EX.xpt dataset including columns for the tacrolimus daily dose on the day of PK profiling (Days 1, 14, and 28), as well as the average tacrolimus daily doses during the following dosing periods: Days 2 to 14, and Days 15 to 28. Additionally, submit revised post-hoc figures that include Day 1 of dosing, and where the total tacrolimus daily dose is expressed in both mg and mg/kg units.
2. We are not able to reproduce the data presented in Table 11-3 (proportion of patients within target tacrolimus C_{trough} range by study day) of the Study 2019 CSR report body, using the individual tacrolimus C_{min} data provided in the PK report for this study. Please submit (or direct us to the location of) the analysis dataset(s) used to generate this table and the post-hoc figures for tacrolimus trough concentrations in the Study 2019 CSR addendum 1.

If you have any questions regarding this communication, please contact me at (301) 796-1600.

Sincerely,

Lois Almoza, M. S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

LOIS A ALMOZA
05/09/2014



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION SHEET

DATE: May 1, 2014

To: Ms. Free M. Peay	From: Lois Almoza Regulatory Health Project Manager
Company: Veloxis Pharmaceuticals, Inc.	Division of Transplant and Ophthalmology Products
Email: fpe@veloxis.com	Email: lois.almoza@fda.hhs.gov
Cell Phone Number: 732-321-3200	Phone number: 301-796-1600

Subject: NDA 206406/Envarsus (tacrolimus extended-release tablets), 0.75 mg, 1.0 mg and 4.0 mg/Veloxis Pharmaceuticals, Inc. – comments regarding December 28, 2013, submission

Total no. of pages including cover: 4

Comments:

Document to be mailed: ☐ YES ☒ NO

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Dear Ms. Peay,

Please refer to your December 28, 2013, submission, received December 30, 2013 that contained a New Drug Application (NDA) submission for Envarsus (tacrolimus extended-release tablets) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for prophylaxis or organ rejection in patients receiving a kidney transplant.

To facilitate our review of your NDA submission, please provide the following information. Alternatively, if the information was previously included in the NDA submission, please direct us to the location(s). Please provide a response to both items by May 15, 2014.

Clinical Pharmacology/Pharmacometrics

Your NDA submission dated December 28, 2013, does not contain the following:

1. Please submit (or direct us to the location in the NDA of) the bioanalytical report for the T32 version 3 of the tacrolimus HPLC/MS/MS assay used in Study 3002.
2. Please submit a table summarizing the type of assay used and the number of blood samples assayed for tacrolimus trough concentrations by the local laboratories included in Study 3002 and Study 3001.

If you have any questions regarding this communication, please contact me at (301) 796-1600.

Sincerely,

Lois Almoza, M. S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

LOIS A ALMOZA
05/01/2014



NDA 206406

INFORMATION REQUEST

Veloxis Pharmaceuticals, Inc.
Attention: Free Peay
Sr. Vice President
499 Thornall Street, 3rd Floor
Edison, NJ 08837

Dear Mrs. Peay:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Envarsus (tacrolimus extended-release tablets), 0.75 mg, 1.0 mg and 4.0 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have identified the following deficiencies. We request a prompt written response by April 25, 2014, in order to continue our evaluation of your NDA.

1. Provide the complete multipoint dissolution profile data from the bio-batches and registration stability batches supporting the selection of the sampling time-points and range values for your proposed acceptance criteria.
2. Provide a comparative table including the composition of all the formulations used during product development; from A to G (include all the strengths). Please use a similar format as the one used for Table 8 batch formula (Module 3.2.P.2 Pharmaceutical Development page 12), but report the values in mg/tablet units.
3. We were not able to locate the PK data from the Study 1018 in your submission. Please submit the following PK data from the BE Study 1018 in SAS Transport format in two separate files as described below:
 - a. SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX KE Thalf
 - b. SUBJ SEQ PER TRT C1 C2 C3 Cn

Separate each field with a blank space and indicate missing values with a period (.).

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402- 3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURawe
04/18/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206406

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Veloxis Pharmaceuticals
499 Thornall Street, 3rd Floor
Edison, NJ 08837

ATTENTION: Free M. Peay
Manager, Global Regulatory Affairs & Operations

Dear Ms. Peay:

Please refer to your New Drug Application (NDA) dated December 28, 2013, received December 30, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Tacrolimus Extended-Release Tablets, 0.75 mg, 1 mg, and 4 mg.

We also refer to:

- your correspondence, dated and received, January 23, 2014, requesting review of your proposed proprietary name, Envarsus
- our e-mail to you, dated March 14, 2014, noting that a modifier should be added to the proposed name, Envarsus, to differentiate it from immediate - release tacrolimus formulations
- your proprietary name amendment, dated and received, March 21, 2014, to add the modifier "XR" to your proposed proprietary name

We have completed our review of the proposed proprietary name, Envarsus XR, and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your January 23, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application, contact Lois Almoza, Regulatory Project Manager in the Office of New Drugs, at 240-402-5146.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
04/18/2014



NDA 206406

INFORMATION REQUEST

Veloxis Pharmaceuticals, Inc.
Attention: Mr. Ronald Guido
Sr. Vice President
499 Thornall Street, 3rd Floor
Edison, NJ 08837

Dear Mr. Guido:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Envarsus (tacrolimus extended-release tablets), 0.75 mg, 1.0 mg and 4.0 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have identified the following deficiencies. We request a prompt written response by April 15, 2014, in order to continue our evaluation of your NDA.

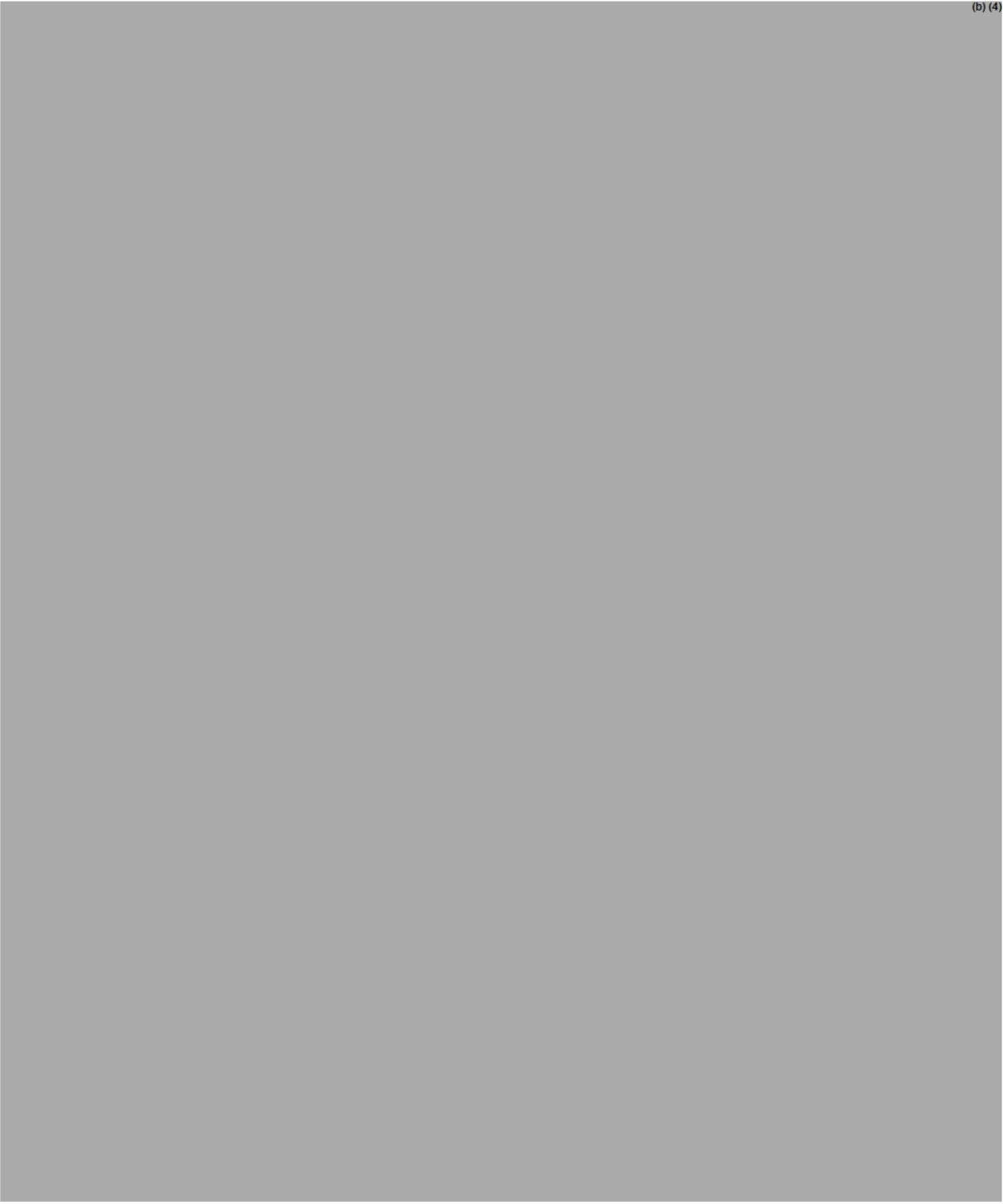
As noted in the August 2, 2013 Meeting Preliminary Comments and during the August 7, 2013 meeting, (b) (4)



(b) (4)



(b) (4)



If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402- 3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

BALAJEE SHANMUGAM
04/01/2014

From: [Free Peay](#)
To: [Flowers, Louis](#)
Cc: [Townsend, Karen](#)
Subject: RE: Envarsus NDA 206406
Date: Tuesday, March 18, 2014 7:36:18 AM

Dear Mr Flowers,

We have taken your recommendation under consideration and will send an amendment to proposed proprietary name by the end of this week.

Best regards,

Free Peay
Manager, Regulatory Operations

Phone: +1 732 321 3224
Mail: fpe@veloxis.com

Veloxis Pharmaceuticals
499 Thornall Street, 3rd floor
Edison, New Jersey 08837
United States

The information in this e-mail and any attachment is strictly confidential and is intended solely for the individual or company to whom it is addressed. If you receive this communication by error, please notify the sender immediately and please return it to Veloxis Pharmaceuticals without producing, distributing or retaining copies hereof. Thank you.

From: Flowers, Louis [<mailto:Louis.Flowers@fda.hhs.gov>]
Sent: Friday, March 14, 2014 1:13 PM
To: Free Peay
Cc: Townsend, Karen
Subject: Envarsus NDA 206406

Dear Free M. Peay:

This email is to notify you of DMEPA's preliminary findings regarding the proprietary name.

The proposed proprietary name Envarsus appears acceptable from the promotional perspective. Additionally, our preliminary safety evaluation indicates that the root name Envarsus is also acceptable. However, because Envarsus is a new extended-release formulation of tacrolimus, it should be differentiated from immediate-release tacrolimus formulations. To be consistent with current tacrolimus terminology, we recommend the modifier 'XL' be added to the proposed proprietary name Envarsus.

Given the PDUFA dates, we recommend you submit an amendment to the proposed proprietary name "Envarsus" **by COB, Tuesday, March 18, 2014.**

If you decide not to submit an amendment with the modifier 'XL' to express the extended-

release of the product, we will continue the review of the proposed proprietary name “Envarsus” and will send you the “unacceptable name” letter outlining the need for the modifier ‘XL’ on OSE PDUFA date of 04/23/2014 or before that date.

Thank you,

Louis R. Flowers III, PharmD, MS, CPH
Captain - USPHS
Project Management Staff
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
BLDG 22, Room 4476
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-3158
Email: louis.flowers@fda.hhs.gov

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/s/

KAREN F TOWNSEND
03/27/2014

MEMORANDUM

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

DATE: March 20, 2014

TO: NDA 206406

FROM: Lois Almoza, M.S.
Regulatory Health Project Manager

SUBJECT: Disregard Verbal Information Request on March 10, 2014

APPLICATION/DRUG: tacrolimus extended-release tablets

Veloxis Pharmaceuticals, LLC submitted a New Drug Application (NDA) on December 28, 2013 received December 30, 2013, Envarsus (tacrolimus extended-release tablets) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for prophylaxis or organ rejection in patients receiving a kidney transplant.

During the review process, a concern was raised based on the material submitted on December 28, 2013. On March 10, 2014, the Agency requested further information from the Applicant, via phone call. The request was to provide all updated Form FDA 3542a to answer question number 5, regarding No Relevant Patents that was left blank on the original submission submitted December 28, 2013. During the phone conversation the Applicant committed to sending the updated forms no later than March 11, 2014.

On March 11, 2014, the Applicant called to say after additional consideration, they felt that the information requested was unnecessary because they actually submitted relevant patents therefore question number 5, did not need to be filled out. After checking with Chief Project Management Staff on March 12, 2014, it was verified that this request was unnecessary and the Applicant was informed verbally to disregard the previous verbal request on March 10, 2014.

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/s/

LOIS A ALMOZA
03/20/2014



NDA 206406

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Veloxis Pharmaceuticals, Inc.
Attention: Mr. Ronald Guido
Sr. Vice President
499 Thornall Street
3rd Floor
Edison, NJ 08837

Dear Mr. Guido:

Please refer to your New Drug Application (NDA) dated December 28, 2013, received December 30, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Envarsus (tacrolimus extended-release tablets), 0.75 mg, 1.0 mg and 4.0 mg.

We also refer to your amendments dated:

January 10, 2014
February 12, 2014

January 14, 2014
February 27, 2014

January 23, 2014

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 3, 2014.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan product designation, the PREA requirements do not apply to your application.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

RENATA ALBRECHT
03/13/2014

MEMORANDUM

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

DATE: March 10, 2014

TO: NDA 206406

FROM: Lois Almoza, M.S.
Regulatory Health Project Manager

SUBJECT: Verbal Information Request

APPLICATION/DRUG: tacrolimus extended-release tablets

Veloxis Pharmaceuticals, LLC submitted a New Drug Application (NDA) on December 28, 2013 received December 30, 2013, Envarsus (tacrolimus extended-release tablets) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for prophylaxis or organ rejection in patients receiving a kidney transplant.

During the review process, a concern was raised based on the material submitted on December 28, 2013. On March 10, 2014, the Agency requested further information from the Applicant, via phone call. The request was to provide all updated Form FDA 3542a to answer question number 5, regarding No Relevant Patents that was left blank on the original submission submitted December 28, 2013. During the phone conversation the Applicant committed to sending the updated forms no later than March 11, 2014.

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/s/

LOIS A ALMOZA
03/10/2014



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION SHEET

DATE: February 14, 2014

To: Ms. Free M. Peay	From: Lois Almoza Regulatory Health Project Manager
Company: Veloxis Pharmaceuticals, Inc.	Division of Transplant and Ophthalmology Products
Email: fpe@veloxis.com	Email: lois.almoza@fda.hhs.gov
Cell Phone Number: 732-321-3200	Phone number: 301-796-1600

Subject: NDA 206406/Envarsus (tacrolimus extended-release tablets), 0.75 mg, 1.0 mg and 4.0 mg/Veloxis Pharmaceuticals, Inc. – comments regarding December 28, 2013, submission

Total no. of pages including cover: 4

Comments:

Document to be mailed: ☐ YES ☒ NO

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-1600. Thank you.

Dear Ms. Peay,

Please refer to your December 28, 2013, submission, received December 30, 2013 that contained a New Drug Application (NDA) submission for Envarsus (tacrolimus extended-release tablets) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for prophylaxis or organ rejection in patients receiving a kidney transplant.

To facilitate our review of your NDA submission, please provide the following information. Alternatively, if the information was previously included in the NDA submission, please direct us to the location(s). Please provide a response to items #1, #4, and #5 by February 28, 2014, and items #2 and #3 by March 14, 2014.

Clinical Pharmacology/Pharmacometrics

1. Our preliminary check of the analysis datasets suggests that tacrolimus dose and/or concentration data are missing for some patients in Studies 3002 and 3001, as specified in the summary table below. Please submit revised analysis datasets that provide the missing data, and/or include in the dataset a column that explains the reason for the non-inclusion of the dose/concentration data for the individual patients. For the adctac.xpt and adltac.xpt datasets of Study 3001, provide also the information on the last dose prior to the trough concentration, (or if this information is not available, the last known dose in proximity with the appropriate flag identifier).

Study ID	Analysis dataset	Number of patients with missing tacrolimus exposure data	
		DOSE (EXDOSTOT, LEXDOSE or TACDOSE)	TROUGH CONCENTRATION (AVGTAC12 or AVALC)
3002 (543 patients with efficacy data)	Adex.xpt	20	not applicable
	Adtac.xpt	40	17
	Adltac.xpt	10	10
3001 (324 patients with efficacy data)		TROUGH CONCENTRATION (AVAL)	
	Adctac.xpt	3	

2. Addendum 1 of the Clinical Study report of 3002 provides summary tables for the total daily dose of mycophenolate equivalent per visit, and the total daily dose of prednisone equivalent per visit. Please submit the analysis datasets used to generate the dose data of the concomitant immunosuppressives in these tables. In these datasets, please include the necessary variables that would allow the reviewer to calculate the average daily doses of mycophenolate and prednisone equivalents for any given time period during the first 12 months of the study. Please submit similar summary tables and the supporting analysis datasets for Study 3001.
3. Please submit the analysis datasets for the tacrolimus PK parameters generated for LCP-Tacro once daily and Prograf twice daily for the studies referenced in the annotated drug

labeling (Studies 2019, 2011, 1011, 1012, 1014, 1016, 1017), as well as the other PK studies conducted.

Include in the dataset, columns that would flag (and the reason for) non-inclusion of the individual subject data in the calculation of the reported average PK parameter value.

Clinical

4. Please provide the “coding dictionary” used for mapping investigator verbatim terms to preferred terms. A coding dictionary consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).
5. During the August 7, 2013 pre-NDA meeting, we requested narratives for all patients who discontinue study drug, regardless of the reasons for discontinuation in Studies Study LCP-Tacro-3002 and LCP-Tacro-3001. All requested narratives were provided for Study 3002. However, for Study 3001 only the narratives for deaths, serious adverse events and adverse events leading to discontinuation were provided. Please submit narratives for discontinuations due to reasons other than AEs for Study 3001 (7 patients in the LCP-Tacro arm and 5 patients in the Prograf arm).

If you have any questions regarding this communication, please contact me at (301) 796-1600.

Sincerely,

Lois Almoza, M. S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

LOIS A ALMOZA
02/14/2014



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION SHEET

DATE: February 12, 2014

To: Ms. Free M. Peay	From: Lois Almoza Regulatory Health Project Manager
Company: Veloxis Pharmaceuticals, Inc.	Division of Transplant and Ophthalmology Products
Email: fpe@veloxis.com	Email: lois.almoza@fda.hhs.gov
Cell Phone Number: 732-321-3200	Phone number: 301-796-1600

Subject: NDA 206406/Envarsus (tacrolimus extended-release tablets), 0.75 mg, 1.0 mg and 4.0 mg/Veloxis Pharmaceuticals, Inc. – comments regarding December 28, 2013, submission

Total no. of pages including cover: 4

Comments:

Document to be mailed: ☐ YES ☒ NO

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Dear Ms. Peay,

Please refer to your December 28, 2013, submission, received December 30, 2013 that contained a New Drug Application (NDA) submission for Envarsus (tacrolimus extended-release tablets) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for prophylaxis or organ rejection in patients receiving a kidney transplant.

We are currently reviewing your NDA submission and have the following comments.

Statistics

Your NDA submission dated December 28, 2013, does not contain the following:

1. We were not able to find in the Study 3001 analysis datasets the variable that identifies the country where the patients were enrolled in the study. This variable is needed for us to perform the subgroup analysis regarding geographic regions. If the variable is included in the analysis datasets, please inform where the data is located. Otherwise please resubmit the efficacy analysis dataset (ADTTE.xpt) that includes this variable.
2. On the last page of the define files for Study 3002 and Study 3001, theodelist for PARAMCD/PARAM does not match with the variable PARAMCD/PARAM in the efficacy analysis datasets for respective studies (ADEFF.xpt for Study 3001 and ADTTE.xpt for Study 3002). Please clarify.
3. The efficacy analysis datasets were set up differently for Study 3002 and Study 3001. The analysis dataset for Study 3001 (ADEFF.xpt) identifies whether the central biopsy reading or local reading was used to determine the outcome for primary endpoint BPAR/D/GL/LTFU. However, we are not able to identify this information in the analysis dataset for Study 3002 (ADTTE.xpt).
4. We found discrepancies regarding number of study sites in the Study report and efficacy analysis dataset ADTTE.xpt for Study 3002. In the dataset, there are 69 study sites that randomized patients for Study 3002. However, your study report states 68 sites enrolled patients (page 2). The study report also states patients at 70 sites were randomized (page 3). Please clarify the discrepancies.
5. Please submit all SAS (or R) programs for Study 3002 and Study 3001 that were used to create analysis variables as well as programs that were used to produce analysis results.

Please provide this information to us no later than February 27, 2014. If you have any questions regarding this communication, please contact me at (301) 796-1600.

Sincerely,

Lois Almoza, M. S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

LOIS A ALMOZA
02/12/2014

From: Bhandari, Navdeep
To: rgu@veloxis.com
Subject: NDA 206406 Manufacturing Facility Information Needed
Date: Wednesday, January 08, 2014 9:25:00 AM

Good morning Ron,

Please provide me with the following:

Name of Facility
FEI Number
Name of Facility Contact
Contact Phone Number
Contact Fax Number
Contact Email Address
Role of each facility
Indicate if facility is ready to be inspected

Provide above information for all **API facilities (and/or drug intermediate facility)** and **Drug Product facilities**. Please submit this information as an amendment and please send me a courtesy copy via email.

You may contact me if you have any questions.

Thank you,

Navi Bhandari, Pharm.D
Regulatory Health Project Manager
Office of New Drug Quality Assessment
OPS/CDER/FDA
240-402-3815

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/s/

NAVDEEP BHANDARI
02/05/2014



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

COMMUNICATION SHEET

DATE: February 4, 2014

To: Ms. Free M. Peay	From: Lois Almoza Regulatory Health Project Manager
Company: Veloxis Pharmaceuticals, Inc.	Division of Transplant and Ophthalmology Products
Email: fpe@veloxis.com	Email: lois.almoza@fda.hhs.gov
Cell Phone Number: 732-321-3200	Phone number: 301-796-1600

Subject: NDA 206406/Envarsus (tacrolimus extended-release tablets), 0.75 mg, 1.0 mg and 4.0 mg/Veloxis Pharmaceuticals, Inc. – comments regarding December 28, 2013, submission

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ☒ NO

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Dear Ms. Peay,

Please refer to your December 28, 2013, submission, received December 30, 2013 that contained a New Drug Application (NDA) submission for Envarsus (tacrolimus extended-release tablets) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for prophylaxis or organ rejection in patients receiving a kidney transplant.

We are currently reviewing your NDA submission and have the following comment.

Clinical Pharmacology/Pharmacometrics

Your NDA submission dated December 28, 2013, does not contain the following:

The datasets and analysis scripts used to generate the information provided in the addendum to LCP-Tacro 3002 (titled: Addendum CSR LCP-Tacro 3002) which was requested by the Agency at the pre-NDA meeting cannot be located within the submission. Specifically, we are requesting these materials for the dose/concentration time course assessments for major demographic subgroups, immunosuppressant use by treatment group analysis, and time-to-event analysis. Alternatively, if the datasets and scripts were already included in the submission, we request information regarding the location of those materials.

Please let us know within 5 business days when we can expect this information. If you have any questions regarding this communication, please contact me at (301) 796-1600.

Sincerely,

Lois Almoza, M. S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

LOIS A ALMOZA
02/04/2014



NDA 206406

NDA ACKNOWLEDGMENT

Veloxis Pharmaceuticals, Inc.
Attention: Mr. Ronald Guido
Sr. Vice President
499 Thornall Street
3rd Floor
Edison, NJ 08837

Dear Mr. Guido:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Envarsus (tacrolimus extended-release tablets),
0.75 mg, 1.0 mg and 4.0 mg

Date of Application: December 28, 2013

Date of Receipt: December 30, 2013

Our Reference Number: NDA 206406

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 28, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and Ophthalmology
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

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

Sincerely,

{See appended electronic signature page}

Lois Almoza, M.S.
Regulatory Health Project Manager
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

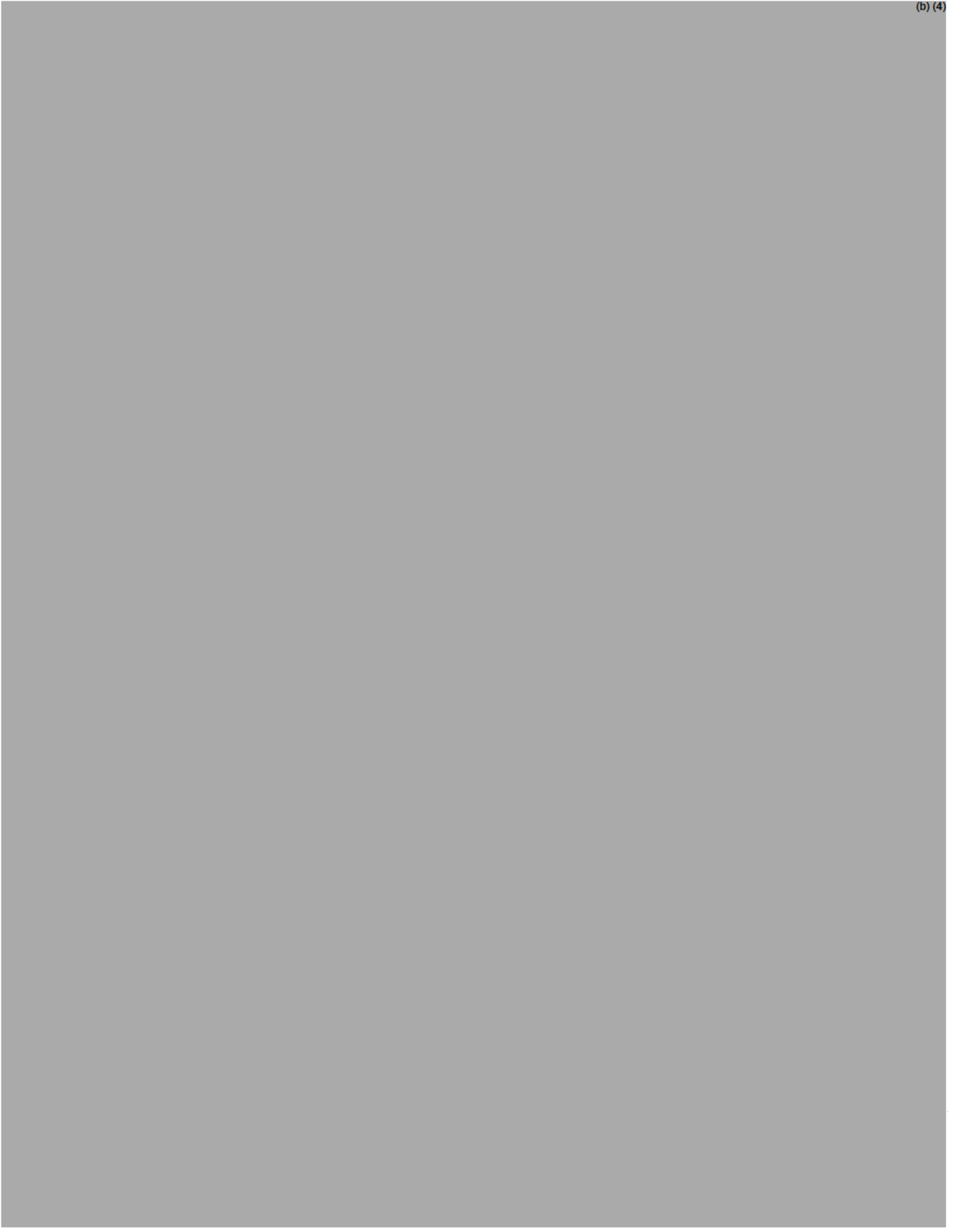
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/s/

LOIS A ALMOZA
01/17/2014

Date Submitted: 12/28/2013
Date Received: 12/30/2013

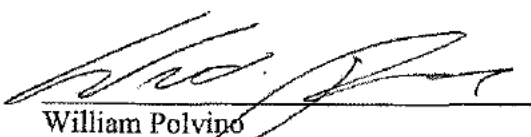
(b) (4)



2013 RELEASE UNDER E.O. 13526



Signed: Veloxis Pharmaceuticals A/S

By: 
Its: William Polvino
President and CEO

1.3 Administrative Request

APPENDIX A: Selected List of Relevant Published Studies Investigating the use of Tacrolimus in Kidney Transplant Patients

Astellas Pharma Ltd. Prograf 0.5mg, 1mg, 5mg hard capsules. Summary Product Characteristics, 2012. *Available at:*
<http://www.medicines.org.uk/emc/medicine/11102>

Astellas Pharma US, Inc. Prograf US Product Label. dated May 2012. Available at:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/050708s027,050709s0211bl.pdf

Fung JJ, Starzl TE. FK506 in solid organ transplantation. *Ther Drug Monit.* 1995;17:592-5.

Jonas S, Neuhaus R, Junge G, Klupp J, Theruvath T, Langrehr JM et al. Primary immunosuppression with tacrolimus after liver transplantation: 12-years follow-up. *Int Immunopharmacol.* 2005;5:125-8.

Kramer BK, Charpentier B, Bäckman L, Silva HT Jr, Mondragon-Ramirez G, Cassuto-Viguier E, Mourad G, Sola R, Rigotti P, Mirete JO: Tacrolimus once daily (ADVAGRAF) versus twice daily (PROGRAF) in de novo renal transplantation: a randomized phase III study. *Am J Transplant.* 2010;10(12):2632-43.

Silva HT Jr, Yang HC, Abouljoud M, Kuo PC, Wisemandle K, Bhattacharya P, Dhadda S, Holman J, Fitzsimmons W, First MR: One-year results with extended-release tacrolimus/MMF, tacrolimus/MMF and cyclosporine/MMF in de novo kidney transplant recipients. *Am J Transplant.* 2007 Mar;7(3):595-608.

Venkataramanan R, Swaminathan A, Prasad T, Jain A, Zuckerman S, Warty V et al. Clinical pharmacokinetics of tacrolimus. *Clin Pharmacokinet.* 1995;29:404-30.

Vincenti F, Jensik SC, Filo RS, Miller J, Pirsch J. A long-term comparison of tacrolimus (FK506) and cyclosporine in kidney transplantation: evidence for improved allograft survival at five years. *Transplantation.* 2002;73:775-82.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of Orphan Products Development
Food and Drug Administration
10903 New Hampshire Avenue
WO32- 5271
Silver Spring, MD 20993

DEC 20 2013

Veloxis Pharmaceuticals
499 Thornall St.
3rd Floor
Edison, NJ 08837

Attention: Ronald Guido
Senior VP, Quality and Regulatory Affairs

Re: Designation Request # 13-4071

Amendment dated: October 25, 2013
Amendment received: October 28, 2013

Dear Mr. Guido:

Reference is made to your request for orphan-drug designation of tacrolimus (trade name: Envarsus) for "prophylaxis of organ rejection in patients receiving allogeneic kidney transplant."

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your orphan-drug designation request of tacrolimus is granted for *prophylaxis of organ rejection in patients receiving allogeneic kidney transplant*. Please be advised that it is the active moiety or principal molecular structural features of the drug¹ and not the formulation of the drug that is designated.

Your designation is based on a *plausible hypothesis* that your drug may be clinically superior to the same drug that is already approved for the same orphan indication. See 21 CFR 316.3(b)(3) & (14) (defining "clinically superior" and "same drug" in this context). In order to obtain orphan-drug exclusivity upon approval, you will need to demonstrate that your drug is clinically superior to this already approved same drug (and any other versions of the same drug approved for the same orphan indication before your drug is approved). Failure to demonstrate clinical superiority over the already approved same drug(s) will result in your drug not receiving orphan-drug exclusivity.

¹ The term "drug" in this letter includes drug and biological products.

If your drug receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. 360cc). Therefore, prior to submission of your marketing application, we request that you compare the drug's orphan designation with the proposed marketing indication and submit additional information to amend the orphan-drug designation if warranted.

You must submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until marketing approval.

Please notify this Office within 30 days of submitting a marketing application for the drug's designated use. Once your marketing application is approved, please contact Stephanie Donahoe, RPh, MPH, at 301-796-8681 or alternatively at 301-796-8660 to assess eligibility for orphan-drug exclusivity.

If you have questions regarding the development of your designated product, please feel free to contact Soumya Patel, PharmD, at 301-796-8678 or alternatively at 301-796-8660. Congratulations on obtaining your orphan-drug designation.

Sincerely,

A handwritten signature in cursive script that reads "Gayatri Rao".

Gayatri R. Rao, MD, JD
Director
Office of Orphan Products Development



IND 75250

MEETING MINUTES

Veloxis Pharmaceuticals
Attention: Ronald Guido
Senior Vice President Quality and Regulatory Affairs
499 Thornall Street
Edison, NJ 08837

Dear Mr. Guido:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LCP-Tacro (tacrolimus extended-release tablets).

We also refer to the meeting between representatives of your firm and the FDA on August 7, 2013. The purpose of the meeting was to discuss and come to agreement on specific CMC aspects regarding the NDA filing for LCP-Tacro.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have questions, call me, at 240-402-3815.

Sincerely,

{See appended electronic signature page}

Navi Bhandari, Pharm.D
Regulatory Health Project Manager
Office of Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: August 7, 2013 10:00 a.m. to 11:00 a.m.
Meeting Location: CDER White Oak Building 22 Room 1419

Application Number: IND 75250
Product Name: LCP-Tacro (tacrolimus extended-release tablets)
Indication: Prevention of rejection and/or loss of organ after allogeneic kidney
(b) (4) transplantation

Sponsor/Applicant Name: Veloxis Pharmaceuticals As

FDA ATTENDEES

Rapti Madurawe, Ph.D., Branch Chief, ONDQA
Balajee Shanmugam, Ph.D., CMC Lead, ONDQA
Mark Seggel, Ph.D., Chemist, ONDQA
John Duan, Ph.D., Reviewer, BioPharmaceutics, ONDQA
Renata Albrecht, M.D., Supervisory Medical Officer, OND
Lori Kotch, Ph.D., Team Leader, Pharmacology/Toxicology, OND
Ilona Bebenek, Ph.D., Reviewer, Pharmacology/Toxicology, OND
Joette Meyer, Lead Clinical Analyst, OND
Ergun Velidedeoglu, M.D. Medical Officer, OND
Aaron Ruhland, Ph.D., Reviewer, Pharmacology/Toxicology OND
Catherine Tran-Zwanetz, Regulatory Health Project Manager ONDQA
Navdeep Bhandari, Pharm.D, Regulatory Health Project Manager, ONDQA

SPONSOR ATTENDEES

William J. Polvino, M.D. President and Chief Executive Officer
Christina Sylvest, Senior Vice President, Global Clinical Operations and Development
Lars Bjorn-Christensen, Senior Vice President Global Technical Operations, Manufacturing
John D. Weinberg, MD Executive Vice President, Chief Commercial Officer
(b) (4)
Ronald Guido, Senior Vice President Global Regulatory Affairs
(b) (4)
Free Peay, Manager, Regulatory Operations

Meeting Minutes
Type B meeting

1.0 BACKGROUND

Veloxis Pharmaceuticals A/S (Veloxis, formerly known as LifeCycle Pharma A/S [LCP]) has developed LCP-Tacro (tacrolimus extended-release tablets) utilizing its MeltDose technology.

Veloxis requested a Type B meeting to discuss and come to agreement on specific Chemistry, Manufacturing and Controls aspects of an NDA filing of LCP-Tacro for the indication of prophylaxis of organ rejection in patients receiving allogeneic kidney transplantation on the basis of analyzed results Phase II (2011, (b) (4), 2017, (b) (4) 2019) and Phase III trials (3001, 3002).

2. Questions

1. Is the CMC Format and Content as reflected by the NDA Table of Contents adequate to permit review of the CM&C aspects of this application?

Agency Response:

The format appears to be adequate. As for the content, following the 2001 Guidance for Industry, ICH M4Q: The CTD – Quality, and references cited therein, should result in a reviewable new drug application.

Discussion: The applicant responded that they concur with the FDA's comments.

2. In reviewing the Overview of Formulation Development vs. Clinical Support, is sufficient detail provided to allow the Division to adequately review the intended market formulation?

Agency Response:

Because of the numerous formulations and tablet strengths evaluated in clinical studies, it will be important that sufficient CMC data be provided to adequately link the investigational product and the commercial product. To this end, we recommend that you provide a detailed tabulation of all batches used in clinical studies (and stability studies), as well as registration / commercial batches that identify the formulation, batch number, and manufacturing details (date, location, scale, etc.). Analytical results, including dissolution profiles and impurity profiles, should be provided for each batch.

The tabulations of the compositions of all strengths and of all formulations should be broken down to clearly reflect the quantitative compositions of the tacrolimus (b) (4) placebo (b) (4) and (b) (4) excipients.

Discussion: The applicant acknowledged the agencies request to provide a tabulated comparison of the formulation but requested some flexibility in formatting the data. In response to the Agencies comment about identifying analytical methods used, Veloxis stated that no changes have occurred and that the methods used reflect current methods.

3. Does the application adequately reflect the extent of full-scale manufacturing experience?

Agency Response:

Based on the limited information presented it is not possible for the Agency to make a determination. It is the applicant's responsibility to insure that the application adequately reflect the extent of full-scale manufacturing experience.

We note that, per Table 26, no full-scale batches of commercial image (Formulation G) 4-mg tablets have been manufactured, while four batches of 5-mg Formulation G tablets were manufactured at full scale. Please indicate if you will be providing any release and stability data for 4-mg commercial tablets.

Discussion: The applicant agreed to provide detailed information including critical process parameters and data to reflect the manufacturing process. Veloxis acknowledged that real time stability data for the 4-mg commercial formulation is available and will be provided in the NDA.

4. The meeting brief presents an overview of the intended Stability Data tables encompassing:

- Primary Stability
- In-Use Stability
- 2 tier stability
- Photostability

Does the Division believe the presentation of stability data to be adequate and complete?

Agency Response:

Available stability data from the commercial image (Formulation G) manufactured at the commercial site should be submitted in the application along with the primary stability batches (Formulation F). Justification for extrapolation of the stability of Formulation F tablets or tablets manufactured at sites other than the intended commercial site, to the

Meeting Minutes
Type B meeting

stability of the commercial product should be provided. All stability studies should include data from the '0' month time point.

The stability studies should include tests for (b) (4) content, (b) (4) and, as discussed below, a measure of crystalline tacrolimus content.

It is not clear if the in-use stability study includes repeated (i.e., daily) opening of the container/closure system and removal of drug product.

Open-dish stability studies should be conducted in order to characterize the effect of (b) (4) on drug product performance and on the conversion of (b) (4) tacrolimus to the crystalline form (see below).

At the time of submission, the NDA should provide 12-months long-term and 6-months accelerated stability data for three registration batches of each to be marketed strength.

Discussion: Applicant agreed to provide 24 months real-time stability data for Formulation G. Veloxis mentioned that testing of (b) (4) was discontinued because it remained stable over the course of the stability study.

The Agency commented that open dish data may provide useful information on potential degradation and how moisture could potentially affect crystallization.

5. Are there any additional Agency specified queries that may be better detailed in the intended NDA application?

Agency Response:

Please note that the established name of the drug product is "tacrolimus extended-release tablets".

Conversion of (b) (4) tacrolimus in the tacrolimus (b) (4) and in the drug product could adversely affect drug solubility and dissolution, and consequently bioavailability. It is critical that the stability of the (b) (4) and drug product with respect to crystallization be demonstrated, either with a suitably discriminating direct spectroscopic or calorimetric method, or with a discriminating in vitro dissolution test method. A method suitable for detection of less than (b) (4) crystalline content is desired. The effect of (b) (4) on crystallization should be evaluated. Please note that the (b) (4) may require different conditions than used in the previously proposed regulatory method.

The NDA should include a detailed description of the manufacturing process. It is important to demonstrate critical quality attributes of tacrolimus (b) (4) including

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Type B meeting

(b) (4) crystallinity content, particle size and (b) (4), are adequately controlled during manufacture.

The maximum hold time for the tacrolimus (b) (4) should be proposed. Supporting stability data, including a measure of crystalline content, covering the proposed hold time should be provided in the application.

Please note that all impurities in the proposed formulation that exceed ICH Q3 limits should be adequately qualified, and the nonclinical and/or clinical data required to support safety should be provided in the application. In addition, justification should be provided for limits greater than those established for tacrolimus capsules, USP.

To facilitate discussion on the prevention of medication / dispensing errors, at the pre-NDA meeting, please provide samples of each strength of the drug product, container / closure system, and preliminary color mock-ups of the labels for each strength.

Discussion: In discussing the crystallinity issue, FDA explained FDA's concern on (b) (4) to crystalline conversion was based on recent experiences and to ensure that Veloxis was aware of it.

Upon further discussions, Veloxis agreed to evaluate the (b) (4) and the finished dosage form for crystalline content using discriminating methods and to submit in the NDA all relevant information and data.

Biopharmaceutics Comments:

1. Although there are dissolution data provided in your submission, the dissolution conditions are not specified. Please clarify the following:
 - a. What methodology was used to generate the dissolution data you provided in this submission?
 - b. What formulation changes you have made since our communication dated 9/27/2010, in which we accepted your dissolution method.
 - c. What acceptance criteria for dissolution testing you are proposing? As previously conveyed in our communication dated 9/27/2010, your proposed criterion for the time point of 2.5 hours ((b) (4)%) is not appropriate, because it does not comply with FDA and ICH guidance recommendations (target $\pm$ 10%). Based on the information provided in your briefing document, it seems that this unacceptable limit still is included in the specifications of your drug product.

Meeting Minutes
Type B meeting

2. Provide information/data to support the extended release claim of your product based on 21 CFR 320.25(f).
3. We recommend that you evaluate the alcohol induced dose dumping of your product. First, you should conduct the in vitro alcohol induced dose dumping testing; and depending on the result of this testing you may have to follow-up with an in vivo alcohol-dose dumping study. Note that if the results show an interaction of your MR product with alcohol, you should discuss these results with FDA prior to NDA submission. The following points should be considered during the evaluation of the in vitro alcohol induced dose dumping of your product:
 - Dissolution testing should be conducted using the optimal dissolution apparatus and agitation speed. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.
 - The following alcohol concentrations for the in vitro dissolution studies are recommended: 0%, 5%, 10%, 20%, and 40%.
 - In general:
 - If the optimal dissolution medium is 0.1N HCl; dissolution profiles in this 0.1 N HCl (pH 1.2) containing the above range of alcohol concentrations would be sufficient.
 - If the optimal dissolution medium is NOT 0.1N HCl; dissolution profiles using the above range of alcohol concentrations in 0.1N HCl and in the optimal dissolution medium are recommended.
 - If the optimal dissolution medium has not been identified; dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (pH 1.2, 4.5, and 6.8) are recommended.
 - If the dissolution of the MR product is pH independent; then dissolution data in 0.1N HCl with the above range of alcohol concentrations is sufficient.
 - The shape of the dissolution profiles should be compared to determine if the modified release characteristics are maintained, especially in the first 2 hours.

Meeting Minutes
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- The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated (using 0% alcohol as the reference).
- The report with the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study should be provided to FDA for review and comments.

Discussion: The sponsor agreed with the FDA comments.

The sponsor presented data of in vitro alcohol dose dumping study using pH 4.5 as medium. FDA responded that the sponsor needs to provide additional alcohol dose dumping data using 0.1 N HCl.

FDA mentioned that if a

(b) (4)

to set the dissolution acceptance criteria.

5.0 ATTACHMENTS AND HANDOUTS

A PowerPoint Presentation was provided by Veloxis.

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

/s/

RAPTI D MADURawe
09/05/2013



IND 75250

MEETING MINUTES

Veloxis Pharmaceuticals
Attention: Ronald Guido
Senior Vice-President, Quality and Regulatory Affairs
499 Thornall Street, 3rd Floor
Edison, NJ 08837

Dear Mr. Guido:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LCP Tacro (tacrolimus extended-release tablets).

We also refer to the Type-B, Pre-NDA meeting held between representatives of your firm and the FDA on August 7, 2013.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Michael Puglisi, Regulatory Project Manager, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Date/Time: August 7, 2013, 11:00 am
Meeting Location: 10903 New Hampshire Avenue
Silver Spring, MD 20903
Building 22, Room 1419

Meeting Type: Type B – Pre-NDA

Application: IND 75250
Drug: LCP Tacro (tacrolimus extended-release tablets)
Sponsor: Veloxis Pharmaceuticals
Indication: For prophylaxis of organ rejection in patients receiving allogenic kidney transplants

Meeting Chair: Renata Albrecht
Meeting Recorder: Michael Puglisi

FDA PARTICIPANTS:

Renata Albrecht/ Division Director
Joette Meyer/ Clinical Team Leader
Ergun Velidedeoglu/ Medical Officer
Marc Cavaille-Coll/ Medical Officer
Ozlem Belen/ Deputy Director for Safety
Gerlie Gieser/ Clinical Pharmacology Reviewer
Philip Colangelo/Clinical Pharmacology Team Leader
Yaning Wang/ Pharmacometrics Associate Director
Jee Eun Lee/ Pharmacometrics Reviewer
Hongling Zhou/ Statistics Reviewer
Shukal Bala/ Immunology Team Leader
Yan Wang/ Statistics Team Leader
Michael Puglisi/ Project Manager

SPONSOR PARTICIPANTS:

William Polvina/ Chief Executive Officer
John Weinberg/ Executive Vice-President, Chief Commercial Officer
Ronald Guido/ Senior Vice-President, Quality and Regulatory Affairs
Christina Sylvest/ Senior Vice-President, Global Clinical Development

(b) (4)

Free Peay/ Manager, Regulatory Operations
Lars Bjørn-Christensen/ Senior Vice President, Global Technical Operations, Manufacturing

(b) (4)

MEETING OBJECTIVE:

To discuss the planned NDA submission of LCP Tacro (tacrolimus extended-release tablets) for prophylaxis of organ rejection in patients receiving allogeneic kidney transplants.

SUMMARY OF DISCUSSION:

Agency responses to the questions outlined in the July 8, 2013, background package (see bolded text below) were provided to the Sponsor in an email dated August 5, 2013 (see text in italics below). This meeting served to clarify those responses. In addition, the sponsor provided a set of slides to the Agency to facilitate the discussion during the meeting, which is attached at the end of this document. Discussion during the meeting is reflected in normal font.

QUESTIONS FOR DISCUSSION:

Question #1: Does FDA agree with the approach to database integration?

FDA Response:

We agree with your proposed approach to database integration. The table below summarizes the duration of the kidney trials.

<i>Kidney Population</i>	<i>Study Number</i>	<i>Duration</i>
<i>De Novo</i>	<i>2019 (n=36)</i>	<i>28 days</i>
	<i>2017 (n=63)</i>	<i>12 months</i>
	<i>3002 (N=543)</i>	<i>12 months</i>
<i>Conversion</i>	<i>2011 (n=47)</i>	<i>52 days</i>
	<i>3001 (n=302)</i>	<i>12 months</i>

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Meeting Comment:

There was no discussion of this matter.

Question #2: Does the Agency Agree with the proposed content and format of the NDA Application, as provided for in the table of contents appended to the Briefing Package?

FDA Response:

In general we agree with the proposed content and format of the NDA application as provided in the table of contents appended to the Briefing Package, starting on page 554. However, we note that certain elements such as FDA form 356h are not mentioned in this table.

Please refer to “Comprehensive Table of Contents Headings and Hierarchy” published by the FDA

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM315023.pdf>) for the missing items in your table.

You can also obtain more information on Electronic Common Technical Document (eCTD) requirements at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>.

Medication Errors: In addition, please provide a plan to address possible medication errors due to lack of interchangeability with the tacrolimus immediate release formulation. Your proposal should include planned communications (e. [REDACTED] (b) (4)) and a Medication Guide.

Additional Clinical Pharmacology Requests: In Section 2.7.2 Summary of Clinical Pharmacology Studies, we have the following requests:

- For both de novo and stable (conversion) kidney transplant patients, include a justification for the proposed starting LCP-Tacro doses and the target tacrolimus trough concentration range(s) for the first 12 months, based mainly on the actual/observed drug exposure data in the Phase 3 trials (assuming favorable efficacy and safety outcomes). If appropriate, the findings of exposure-response analyses should also be included to support your justification.
- In tables summarizing the study design of and the exposure to tacrolimus in Phase 1, 2, and 3 studies, include also the following information (whichever applies): (1) LCP-Tacro Formulation ID and specific tablet strengths evaluated, (2) tacrolimus dose, frequency and duration of the test and reference treatments, (3) the protocol-specified and the actual initial or starting tacrolimus doses, (4) the protocol-specified target tacrolimus trough concentration range(s) and the observed tacrolimus trough concentrations (mean/median, 10th to 90th percentile) at each study visit for LCP-Tacro and the tacrolimus comparator (Prograf BID or Astagraf QD, (5) concomitant immunosuppressive drugs.
- In the tables summarizing the PK parameters of LCP-Tacro and the tacrolimus comparator, include statistical comparison parameters (i.e., geometric means ratio and 90% CI for AUC, C_{max}, C_{trough}). In the title or the footnotes of these tables, include information regarding the study population (healthy subjects, de novo/stable, kidney transplant patients), study number, actual mean/median tacrolimus daily doses (mg and mg/kg) on the PK profiling days, fed/fasted conditions, whether dosage adjustments were allowed during the study period, whether C_{trough} is C_{12h}, C_{24h} or C_{0h}, the type of PK assay used to quantify tacrolimus in whole blood. If applicable, include also summary tables for dose-normalized PK parameters.
- Provide graphs showing the correlation of tacrolimus AUC₂₄ and C_{trough} with LCP-Tacro and with the tacrolimus comparator at different PK profiling days in healthy subjects, in de novo kidney transplant patients and in stable kidney transplant patients.
- For Phase 3 trials 3001 and 3002 and Phase 2 Study 2019, in addition to summary tables, provide plots comparing treatments in terms of the time course of mean/sd daily tacrolimus doses and mean/sd tacrolimus trough concentrations. If feasible, present also similar plots for race, gender and other subgroups of interest.
- For Phase 3 trials 3001 and 3002 and Phase 2 Study 2019, provide tables comparing the treatments in terms of the actual mean daily doses of concomitant immunosuppressive drugs (in

a format similar to the tables proposed for the study drug).

- *In anticipation of a full safety review of your application, with the exception of Bullet #1, please follow the above format for the studies involving de novo and stable (conversion) ^{(b) (4)} transplant patients.*

Regarding your supporting exposure-response and Population PK analyses, we have the following recommendations:

- *Given your plan to conduct exploratory analysis on the relationship of tacrolimus concentrations and efficacy/safety outcomes (e.g., BPAR, graft failure), tacrolimus concentration should be treated as a time-dependent covariate in your exposure-response analyses. Appropriate imputation of tacrolimus concentration over time may be necessary. For example, the population PK model can be used to impute the concentrations at those time points when an event happened and no concentration was measured. The population PK analysis should utilize the actual daily dosing data and the imputed tacrolimus concentrations.*
- *All supporting analysis datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt). A model development decision tree and/or table which give an overview of modeling steps should be included. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed tacrolimus concentrations, the individual prediction line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/hr) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results. Additionally, we encourage you to refer to the following pharmacometrics data and models submission guidelines (<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm180482.htm>)*

Meeting Discussion:

The meeting began with a slide presentation by the Sponsor which provided the history of the product development to date. These slides are attached at the end of this document.

Biopharmaceutics:

The sponsor highlighted the major biopharmaceutics and clinical pharmacology characteristics of LCP-Tacro including, higher bioavailability compared to Prograf and Astagraf XL (tacrolimus extended-release capsules), and the absence of diurnal variation in the pharmacokinetics (PK) of tacrolimus following administration with LCP-Tacro vs. Prograf.

The sponsor stated that the NDA application will be filed with Study 3002 in *de novo* kidney transplant patients as the “pivotal” trial and Study 3001 in stable (conversion) transplant patients

as the “supportive” trial. LCP-Tacro Formulation F was used in the “pivotal” *de novo* Study 3002, and the final to-be-marketed formulation is Formulation G. The only change from Formulation F to G was in (b) (4) tablet curvature. The sponsor believes that an adequate “PK / bio-link” has been established between Formulation F and Formulation G, and that no additional bioequivalence studies are needed

The “supportive” conversion Study 3001 in stable kidney transplant recipients used LCP-Tacro Formulation D. The Agency asked what “PK / bio-link” exists between Formulations D and G. The Sponsor cited the in-vitro dissolution data and the in-vivo bioequivalence data comparing Formulation D and F.

A food effect study was conducted with LCP-Tacro Formulation B. The Sponsor also believes that because there were minor formulation differences between Formulation B and Formulation G, there is no need to repeat a food effect study. In regard to the food-effect study, the Agency stated that an adequate PK / bio-link should be established and provided in the NDA submission between the formulation used in this study and the to-be-marketed formulation (Formulation B vs. Formulation G).

Clinical / Clinical Pharmacology:

The Sponsor presented a summary of the efficacy / safety results of the *de novo* Study 3002. In the study patients received either LCP-Tacro once daily or Prograf twice daily in combination with basiliximab induction, mycophenolate mofetil (MMF) and corticosteroids. The patients received LCP-Tacro at a starting dose of 0.17 mg/kg/day or Prograf at 0.1 mg/kg/day (given as two divided doses). During the first few days post-transplant, the majority of the LCP-Tacro patients had tacrolimus trough concentrations that exceeded the target range (i.e., 6-11 ng/mL for the first 30 days). Starting at Month 3, the total daily tacrolimus doses were 15% lower for LCP-Tacro than that for Prograf.

The Agency asked the sponsor whether the tacrolimus trough concentration profiles observed in Study 3002 were similar to those observed in the PK study involving *de novo* kidney transplant patients (Study 2019), and whether information could be provided regarding the tacrolimus C_{max} , AUC_{0-24} and C_{min} of LCP-Tacro and Prograf during the first 28 days as measured in Study 2019. The Sponsor clarified that the PK results of Study 2019 are still undergoing review.

Clinical Pharmacology:

The sponsor stated that (b) (4)

(b) (4). The Agency stated that the exposure-response analyses could be done with exposure metrics such as daily tacrolimus trough concentrations for time-to-event analyses for efficacy and safety endpoints. Tacrolimus trough concentrations should be treated as a time-dependent covariate and be imputed for days when measurement did not occur. To ensure adequate evaluation, a population PK analysis is recommended. The sponsor agreed to consider including the results of any analyses they perform in the ISE.

The Agency asked if the sponsor could perform simulations to determine how a missed dose of LCP-Tacro should be managed (to provide guidance to the patient in the labeling). The Agency added that such analysis should be uncomplicated given that LCP-Tacro does not exhibit diurnal variation in tacrolimus pharmacokinetics. The sponsor agreed to provide this information in the NDA.

Question #3 : Veloxis has taken an inventory of the electronic datasets available for the LCP-Tacro studies. The largest and most important studies (3001 and 3002) will have raw and derived datasets in FDA preferred format that FDA (SDTM raw data files and ADaM-like analysis datasets). For older studies, however, the raw data is not in SDTM format and will require extensive time and expense to do the conversion. Veloxis would like to propose that SAS datasets be provided for individual studies in traditional format, along with integrated analysis datasets (ADaM-like format) for the ISS and ISE. Each dataset will be provided as a SAS transport file in accordance with FDA guidelines. Raw data will be provided for all studies; analysis datasets will be provided where available. Is this approach acceptable to the Agency?

FDA Response:

Yes, in principle your approach is acceptable. However, though it is acceptable to present the analysis results using the pooled mITT analysis set in the ISE section, we do not agree that the pooled efficacy analysis dataset includes only mITT population, i.e., excluding 11 randomized patients who were not treated (7 from study 3002, and 2 from study 3001), as proposed on page 75 of the meeting package. The ISE as well as ISS analysis dataset should include all subjects in the individual analysis datasets. All analysis datasets should include a flag for ITT, mITT, PP and any other analysis population that was used for the data analysis.

Regarding the define files you submitted through email on 8/1/13 and 8/2/13, we have the following comments:

- Please provide the define files in pdf format. For more detailed specification on data definition files, please see Study Data Specifications (<http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf>).*
- The define files for analysis datasets for individual studies (3001 and 3002) were not included in the email sent to us on 8/1/13 and 8/2/13. We understand these files may still be work in progress. However, based on the draft define file for dataset ADEF, it is not clear to us whether the central biopsy reading or local reading was used to determine the outcome for primary endpoint BPAR/Death/GL/LTFU. For example, PARAMN appears to be the outcome variable. However, it does not include the outcome for BPAR (central reading). According to the Protocol 3002 that was submitted as an SPA, the BPAR component of the primary endpoint will be based on central assessment. Please clarify.*
- When you work on finalizing these files, please give a more detailed description for the variables in the Variable Label column.*

If we have additional requests regarding the datasets during the review process, we will communicate those to you in a timely manner.

Meeting Discussion:

The Agency reiterated the comments above regarding the define files. The sponsor agreed to provide a more detailed description for the variables in the Variable Label column. The Agency recommended the sponsor create variables for local reading and central BPAR readings separately so it will be clear which reading is being used for the outcome variable. The sponsor agreed with the recommendation. The sponsor will provide define files for individual studies in the NDA submission.

Question #4: Does the Agency Agree that this application may be filed electronically?

FDA Response:

It is acceptable to submit the application electronically. A filing decision will be made upon preliminary review of the application. Please find the link below for information concerning electronic submission.

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm149719.htm>

Additional FDA Comments:

In kidney transplantation, certain adverse events or adverse events specific to an organ system such as CMV infection, BK infection, cardiovascular events, dyslipidemia, gastroenteritis, gastrointestinal disturbances, new onset diabetes, glucose abnormalities, hepatic function, hypertension, infections and infestations, malignancy, neurotoxicity and renal function may need to be analyzed and discussed in detail under separate headings. We request that analyses and discussion of these adverse events of special interest, tacrolimus related AEs and MPA related AEs be included for each pivotal trial and also as part of the ISS.

Please provide narratives for patients who died, lost a graft, had a cardiac SAE, discontinued study drug or were lost to follow-up grouped separately for each of these events.

In Study 3001 please provide subgroup analyses for patients treated with MMF vs. MPA delayed release tablets both for efficacy and safety across the two arms of the study.

In your NDA submission, please include the materials you submitted to justify the NI margin for Study 3002 as well as information to justify the NI margin for Study 3001. Please also include your responses to our comments in August 5, 2010 SPA Agreement letter asking for further details regarding the NI margin sensitivity analyses.

Meeting Comment:

In response to the Agency's request for narratives, the sponsor summarized the patients for whom narratives and Case Report Forms (CRFs) would be provided (Slide #36). The Agency agreed with the sponsor's proposal for providing CRFs and narratives, but also requested that narratives be submitted for all study drug discontinuations, not just for those patients who discontinued due to SAEs. The Sponsor stated that these additional narratives may not be very informative and the additional request may result in a mismatch between the narratives and the CRFs. The Agency offered to follow up with the sponsor after the meeting to clarify which CRFs and narratives should be provided in the NDA.

The Agency clarified that the AEs of interest, as noted above, for Studies 3001 and 3002 should be discussed in the individual study reports and also carried over to the ISS, including tabulations and interpretation.

In addition, the Agency's requested that the sponsor submit the source(s) of information that will be relied on to support a 505(b)(2) NDA. The sponsor agreed to summarize this information in advance of NDA submission for the Agency's review.

The Sponsor stated the NDA is expected to be submitted in October, 2013.

ACTION ITEMS:

1. The Agency will respond to the sponsor's request to submit CRFs and narratives for patients who discontinued the study due to SAEs, but not those who discontinued for other reasons.
2. The sponsor agreed to submit for the Agency's review a summary the source(s) of information that will be relied on to support a 505(b)(2) NDA, in advance of the NDA submission.
3. The Agency agreed to issue minutes of this teleconference within 30 days.

POST MEETING ADDENDA;

1. Regarding patient CRFs and narratives

The Agency sent a follow-up communication on August 13, 2013 to address Action Item #1.

2. Regarding Biopharmaceutics Issues Raised at the Meeting:

(a) Given that in vivo bioequivalence appears to have been demonstrated between Formulations F and G at the 4 mg dose, it has been deemed by the OND/QA-Biopharmaceutics and Clinical Pharmacology reviewers that no additional in vivo BA/BE studies are needed between these two formulations, unless during the NDA review, the bioequivalence claim could not be confirmed.

- A biowaiver request should be submitted for the lower strengths of Formulation G (i.e., 0.75 mg and 1 mg).

(b) Given the comparable in vitro dissolution profiles and chemical compositions of Formulations D and G, and the indirect in vivo BA/BE link established between Formulation D and G, it has been deemed by the OND/QA-Biopharmaceutics and Clinical Pharmacology reviewers that an in vivo BA/BE study between these two formulations (D vs. G) is not needed, unless during the NDA review, the bioequivalence claim could not be confirmed and/or "biodrift"/"biocreep" concerns arise.

(c) Food-effect is formulation dependent. If during the NDA review the CMC reviewer determines that there was a substantive change (i.e., SUPAC Level 3) made between

Formulation B and Formulation G, another food effect study using Formulation G would need to be conducted by the sponsor. If the change is relatively minor (i.e., either SUPAC Level 1 or Level 2), the PK / bio-link between the two formulations can be demonstrated in a comparative in vitro dissolution study.

HANDOUTS: Attached are slides provided by the sponsor to facilitate the meeting discussion.

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

/s/

RENATA ALBRECHT
08/27/2013