

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206406Orig1s000

CHEMISTRY REVIEW(S)

NDA 206406

Envarsus[®] XR
(tacrolimus extended-release tablets)
0.75 mg, 1 mg and 4 mg

Veloxis Pharmaceuticals, Inc.

Anamitro Banerjee
ONDP
Division of New Drug Products I
Branch III

for the Division of Transplant and Ophthalmology Products (DTOP)

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 206406
2. REVIEW #: 2
3. REVIEW DATE: July 01, 2015
4. REVIEWER: Anamitro Banerjee
5. PREVIOUS DOCUMENTS:

Previous Documents

Refer to EDR

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Resubmission

Amendment

General Correspondence

Amendment

Document Date

June 12, 2015

June 18, 2015

June 25, 2015

June 26, 2015

7. NAME & ADDRESS OF APPLICANT:

Name:	Veloxis Pharmaceuticals, Inc.
Address:	499 Thornall Street 3 rd Floor Edison, NJ 08837
Telephone:	(732) 321-3200

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Envarsus®XR
- b) Non-Proprietary Name (USAN): tacrolimus extended-release tablets
- c) Code Name/#: LCP-Tacro
- d) CAS Registry Number: 109581-93-3 [tacrolimus monohydrate]; 104987-11-3 [anhydrous]
- e) Chem. Type/Submission Priority:
 - i. Chem. Type: 3
 - ii. Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Maintenance Immunosuppression (9010004)

11. DOSAGE FORM: Extended-release tablets

12. STRENGTH/POTENCY: 0.75 mg, 1 mg, and 4 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)

☐ SPOTS product – Form Completed☒ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT

CAS:

15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-

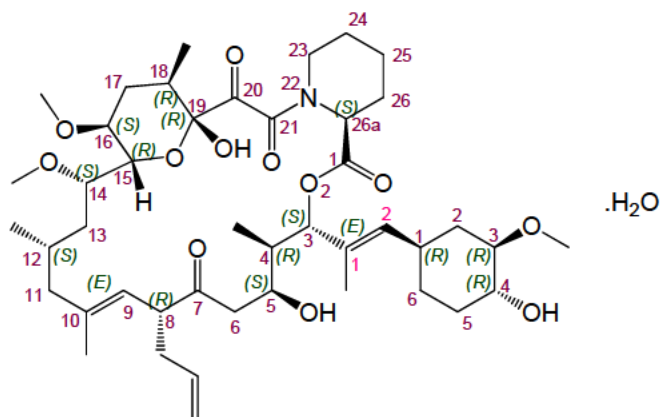
Chemistry Review Data Sheet

,monohydrate, [3S-
[3R*,E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-;

IUPAC:

(-)-(3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)-8-Allyl-
5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[(E)-2-
[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylvinyl]-14,16-dimethoxy-4,10,12,18-
tetramethyl-15,19-epoxy-3Hpyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone,
monohydrate

USAN: Tacrolimus



Chemical Formula: C₄₄H₇₁NO₁₃
Molecular Weight: 822.03

17. RELATED/SUPPORTING DOCUMENTS

Please refer to the Review 1

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Overall Acceptable recommendation	09/01/2014	No Change since previous review. (see attached report)

The Chemistry Review for NDA 206406

I. Recommendations

A. Recommendation and Conclusion on Approvability

The original NDA reviewed by Dr. Mark Seggel dated September 25, 2014 with an addendum dated October 28, 2014 had recommended approval of the NDA from the CMC perspective with five (5) post marketing commitments (PMC). The new information provided since the last review does not change the initial CMC recommendation.

This NDA is recommended for APPROVAL from CMC perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The following PMC were identified and agreed upon by the applicant as documented in Review 1. The target dates should be adjusted based on the NDA action date.

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).

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

(b) (4)

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

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

Chemistry Assessment Section

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

C. Comments to be conveyed to the applicant

For consistency with the rest of the labeling, we recommend changing the title in medguide to :

MEDICATION GUIDE
ENVARUSUS XR® (En var' sus XR)
(tacrolimus extended-release tablets)

II. Facilities

The OC has provided an overall acceptable recommendation on September 01, 2014.

Chemistry Assessment Section

III. Labeling & Package Insert

The Review #1, Addendum #1 dated October 29, 2014 (by Dr. Mark Seggel) concluded that the “revised labels and package insert are complete and factually correct, and are acceptable from the CMC perspective. The labels and PI are acceptable to DMEPA.”

The current medguide title reads:

MEDICATION GUIDE
ENVARUSUS XR® (En var' sus XR)
(tacrolimus)
extended-release tablets

For consistency with the rest of the labeling, we recommend changing it to :

MEDICATION GUIDE
ENVARUSUS XR® (En var' sus XR)
(tacrolimus extended-release tablets)

IV. Administrative**A. Reviewer's Signature**

{see electronic signature page}

B. Endorsement Block

Anamitro Banerjee, Ph. D.
Acting Quality Assessment lead, Branch III,
Division of New Drug Products I,
Office of New Drug Products

07/01/2015

Date

Balajee Shanmugam, Ph. D.
Acting Branch Chief, Branch III,
Division of New Drug Products I,
Office of New Drug Products

07/01/2015

Date

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

/s/

ANAMITRO BANERJEE
07/01/2015

BALAJEE SHANMUGAM
07/01/2015

NDA 206406

Envarsus[®] XR
(tacrolimus extended-release tablets)
0.75 mg, 1 mg and 4 mg

Veloxis Pharmaceuticals, Inc.

Mark R. Seggel
ONDQA
Division of New Drug Quality Assessment II
Branch V

for the Division of Transplant and Ophthalmology Products (DTOP)

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1. NDA 206406
2. REVIEW #: 1, Addendum #1
3. REVIEW DATE: 28-OCT-2014
4. REVIEWER: Mark R. Seggel
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Not Applicable	

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed (eCTD)</u>	<u>Document Date</u>
Original NDA (0000)	30-DEC-2013
Amendment (0001) Updated 356h with facilities / status	10-JAN-2014
Amendment (0002) Updated 356h with facilities / status	14-JAN-2014
Amendment (0009) Response to Information Request	16-APR-2014
Amendment (0010) Response to Biopharm. Request	25-APR-2014
Amendment (0015) Container Closure System Information	06-JUN-2014
Amendment (0016) Product Samples for OTR [06/17/14]	17-JUL-2014
Amendment (0017) Container Closure System - Samples	08-JUL-2014
Amendment (0018) Response to Information Request	18-JUL-2014
Amendment (0019) Response to Information Request	18-JUL-2014
Amendment (0021) Response to Information Request	29-AUG-2014
Amendment (0023) Response to Information Request	10-SEP-2014
Amendment (0024) Labeling	19-SEP-2014
Amendment (0025) Response to Information Request	25-SEP-2014
Amendment (0026) Labeling	26-SEP-2014
Amendment (0027) Labeling	09-OCT-2014
Amendment (0030) Response to proposed PMCs	10-OCT-2014
Amendment (0032) Labeling	16-OCT-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Veloxis Pharmaceuticals, Inc.
Address:	499 Thornall Street, 3 rd Floor Edison, New Jersey 08837

Chemistry Review Data Sheet

Representative(s):	Michelle A. Mc Guinness, VP, Global Regulatory and Quality Assurance
Telephone:	732-321-3211
Fax:	732-906-7943
Email:	mam@veloxis.com

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Envarsus™ XR
- b) Non-Proprietary Name (USAN): tacrolimus extended-release tablets
- c) Code Name/#: LCP-Tacro
- d) CAS Registry Number: 109581-93-3 [tacrolimus monohydrate]; 104987-11-3 [anhydrous]
- e) Chem. Type/Submission Priority:
 - i. Chem. Type: 3
 - ii. Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Maintenance Immunosuppression (9010004)

11. DOSAGE FORM: Extended-release tablets

12. STRENGTH/POTENCY: 0.75 mg, 1 mg, and 4 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT

CAS Chemical Name:

15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-, monohydrate, [3S-[3R*,E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-;

IUPAC Chemical Name:

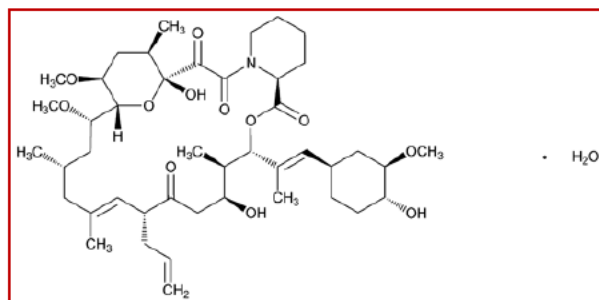
(-)-(3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)-8-Allyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[(E)-2-[(1R,3R,4R)-4-hydroxy-3-

Chemistry Review Data Sheet

methoxycyclohexyl]-1-methylvinyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate

USAN: Tacrolimus

Structural Formula: (as presented in USAN Dictionary)



Molecular Formula: $C_{44}H_{69}NO_{12} \cdot H_2O$.

Molecular Weight: 822.03 [monohydrate]

17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3,4	Adequate	G.J.Kang, OGD 12/19/2013	LoA 11/21/2013
	III			4	N/A	-	LoA 09/05/2013
	III			4	N/A	-	LoA 07/19/2013
	III			4	N/A	-	LoA 09/03/2013
	III			4	N/A	-	LoA 09/04/2013

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

APPLICATION NUMBER	DESCRIPTION	DOCUMENT
IND 75,250	LCP-Tacro (tacrolimus extended-release tablets);	-

Chemistry Review Data Sheet

	Veloxis (previously dba Lifecycle Pharma)	
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18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	na		
EES	Overall ACCEPTABLE recommendation	09/01/14	See attached EES report
Pharm/Tox	<i>No new non-clinical studies conducted to support this NDA</i>		
ONDQA Biopharmaceutics	Approval	~~09/25/14~~ 10/16/14	Banu Zolnik
LNC	na		
Methods Validation	na		
DMEPA	Trademark acceptable	04/15/14, 04/18/14	Rachna Kapoor
	Recommendations and comments	08/26/14, 10/02/14, 10/07/14	
	Labels and labeling acceptable	10/23/14 (email)	
EA	Categorical exclusion - Acceptable	this review	M.Seggel
Quality Microbiology	Recommended for Approval*	01/13/14	Bryan Riley
CDER Office of Testing and Research	Recommendations regarding test methods for crystalline tacrolimus	-	Mansoor Khan

* "The Microbial Limits specification for Envarsus is acceptable from a Product Quality Microbiology perspective."

19. GOAL DATES

GRMP Goal:	25-SEP-2014
PDUFA Goal:	30-OCT-2014

The Chemistry Review for NDA 206406

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Veloxis' NDA 206406, Envarsus XR (tacrolimus extended-release tablets), 0.75, 1 and 4 mg, as amended, has in general, provided sufficient information to assure the identity, strength, quality, purity, potency and bioavailability. Because of the potential for crystallization of (b) (4) tacrolimus in the drug product, and resulting decrease in solubility and bioavailability, and the absence of an analytical procedure sufficiently sensitive and robust to detect such crystallization, the applicant has agreed to develop and implement an X-ray powder diffraction test (XRPD) as a post-marketing commitment (PMC).

The Office of Compliance has issued an overall recommendation of 'Acceptable' based on the satisfactory cGMP status of the manufacturing facilities (see attached EES report). Product labels and labeling, as revised, are accurate and complete from the CMC perspective. Both Product Quality Microbiology and ONDQA Biopharmaceutics reviewers have recommend approval of this NDA.

Therefore, from the CMC perspective, this NDA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Agreement has been reached with Veloxis on Post-Marketing Commitments to (1) develop and validate a regulatory X-ray powder diffraction (XRPD) test for the determination of crystalline content in the drug product, (2) develop an XRPD test for (b) (4), (3) test legacy samples for crystalline content by XRPD, (4) evaluate conditions that might promote crystallization, and (5) evaluate impact of manufacturing process parameters on crystalline content.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Envarsus XR (tacrolimus extended-release tablets, 0.75, 1 and 4 mg) is a once-daily formulation of the calcineurin-inhibitor, tacrolimus. Approved formulations of tacrolimus include tacrolimus injection, tacrolimus capsules (e.g., Prograf and generic versions), and tacrolimus extended-release capsules (Astagraf XL, 0.5, 1, and 5 mg).

Executive Summary Section

Envarsus XR and Astagraf XL are (b) (4). Envarsus XR is also (b) (4) to Prograf Capsules.

The drug product is manufactured in (b) (4)

The drug product specification includes (b) (4)

(b) (4) makes detection of crystalline material challenging. Post-marketing commitments to address test methodology and product stability have been developed as described in this review.

When protected from heat, light and moisture, tacrolimus exhibits good chemical stability as demonstrated by little increase in related substances on stability. Originally, the applicant intended to base their calculation of the expiration date on (b) (4). However, the final approved shelf-life of 24 months will begin at the time of (b) (4).

Inactive ingredients include hypromellose, lactose monohydrate, polyethylene glycol, poloxamer, magnesium stearate, tartaric acid, butylated hydroxytoluene, and dimethicone. All excipients meet USP/NF compendial requirements.

Tacrolimus, the active ingredient in Envarsus XR, is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. There is a significant body of literature covering the characterization of tacrolimus. Tacrolimus monohydrate used in the manufacture of Envarsus XR is sourced from (b) (4). Drug substance CMC is documented in DMF (b) (4).

B. Description of How the Drug Product is Intended to be Used

Envarsus XR (tacrolimus extended-release tablets) is indicated for the prophylaxis of organ rejection in patients receiving a kidney transplant.

Envarsus XR is to be taken once daily at the same time, preferably in the morning on an empty stomach. It should not be taken with an alcoholic beverage or grapefruit juice. The tablets should not be chewed, divided (split) or crushed. Monitoring of whole blood tacrolimus trough concentrations is recommended.

Envarsus XR tablets are packaged in 30-count and 100-count HDPE bottles with (b) (4) closures. The closures include a (b) (4) Bottles are sealed in (b) (4) overwraps and packaged in cartons.

The drug product is labeled for storage at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature]. An expiration dating period of 24 months, starting from the date that of (b) (4) and including up to 3 months storage of the (b) (4), has been granted.

C. Basis for Approvability or Not-Approval Recommendation

The quality of the drug substance, tacrolimus monohydrate, has been adequately documented (via cross-reference to (b) (4) for Tacrolimus; the open portion of the DMF was included in the NDA application). DMF (b) (4) was recently reviewed for (b) (4) and was found adequate.

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent quality of tacrolimus extended-release tablets.

The NDA, as amended, also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period. The Post-Marketing Commitments will provide additional assurance that potential crystallization of tacrolimus does not adversely impact product performance. Drs. Bryan Riley and Banu Zolnik have recommended approval of the NDA from the Product Quality Microbiology and ONDQA Biopharmaceutics perspectives, respectively.

All facilities have acceptable site recommendations. An overall recommendation of Acceptable was issued by the Office of Compliance on September 1, 2014 (see attached EES Report).

The proposed trademark, Envarsus XR, has been found acceptable by DMEPA. Other labeling recommendations (package insert, container and carton labels) have been provided by DMEPA. The only apparent error in the original labeling from the CMC

Executive Summary Section

perspective was listing of the manufacturer as [REDACTED] (b) (4)
[REDACTED] Envarsus XR is manufactured by Rottendorf
Pharma GmbH. [REDACTED] (b) (4) is only responsible for regulatory
oversight of the release of the finished product. References to Veloxis' [REDACTED] (b) (4)
[REDACTED] were removed from the labeling; it is promotional and provides no useful
information to healthcare provider or patient. As revised, the labels and package insert
are complete and accurate from the CMC perspective.

III. Lifecycle Knowledge Management

RISK IDENTIFICATION [note: completed concurrently with review]

Product attribute/CQA	Factors that can impact the CQA	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment, if any (+) = considerations that increase risk (-) = considerations that reduce risk
Assay	Raw materials Formulation Scale/Equipment/Site Process parameters Container closure	3	5	1	15	(b) (4)
Related substances	“	3	3	2	18	
Content Uniformity	“	3	3	4	36	
(b) (4)	“	1	5	1	5	
(b) (4) form of drug substance in product (b) (4) / Crystalline Content)	“	3	5	5	75	

Executive Summary Section

Dissolution ^	“	3	5	2	30	(b) (4)
Appearance	“	1	2	1	2	

RPN Values: Low Risk (1-25); Moderate Risk (26-60); High Risk (61-125)

^ See ONDQA Biopharmaceutics Review

RISK MITIGATION AND LIFECYCLE CONSIDERATIONS

From Initial Quality Assessment			Review Assessment		
Product attribute / CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation Approach / Control Strategy	Risk Evaluation [Acceptable/ Not Acceptable]	Lifecycle Considerations/ Comments**
Assay	Raw materials Formulation Scale/Equipment/Site Process parameters Container closure	L	Manufacturing process controls; container closure system	Acceptable	(b) (4)
Related substances	“	L	Manufacturing process controls (e.g., limit exposure to (b) (4)); container closure system (b) (4) to protect from light and moisture.	Acceptable	
Content Uniformity	“	M	Manufacturing process controls	Acceptable	

Executive Summary Section

(b) (4)	“	L	Manufacturing process controls, environmental controls, and container closure system	Acceptable	(b) (4)
(b) (4) form of drug substance in product (b) (4) / Crystalline Content)	“	H	Conditions potentially contributing to conversion to be evaluated by applicant (PMC); (b) (4) may be critical (crystalline form is the monohydrate)	Acceptable	
Dissolution ^	Potential risk to crystalline conversion can impact the dissolution	M	XRPD method will be used to monitor crystalline content (b) (4)	Acceptable	
Appearance	“	L	Formulation; manufacturing (tableting controls); packaging	Acceptable	

* Risk ranking applies to product attribute/CQA (L, M, and H)

** For example, post marketing commitment, knowledge management post approval, etc. {e.g. Continue monitoring, especially during stability studies}

^ See ONDQA Biopharmaceutics Review

IV. Administrative**A. Reviewer's Signature**

{see electronic signature page}
Mark R. Seggel, Chemistry Reviewer

B. Endorsement Block

{see electronic signature page}
Celia Cruz, Ph.D., Secondary Reviewer

{see electronic signature page}
Rapti Madurawe, Ph.D., Branch Chief

C. CC Block

{see electronic record}

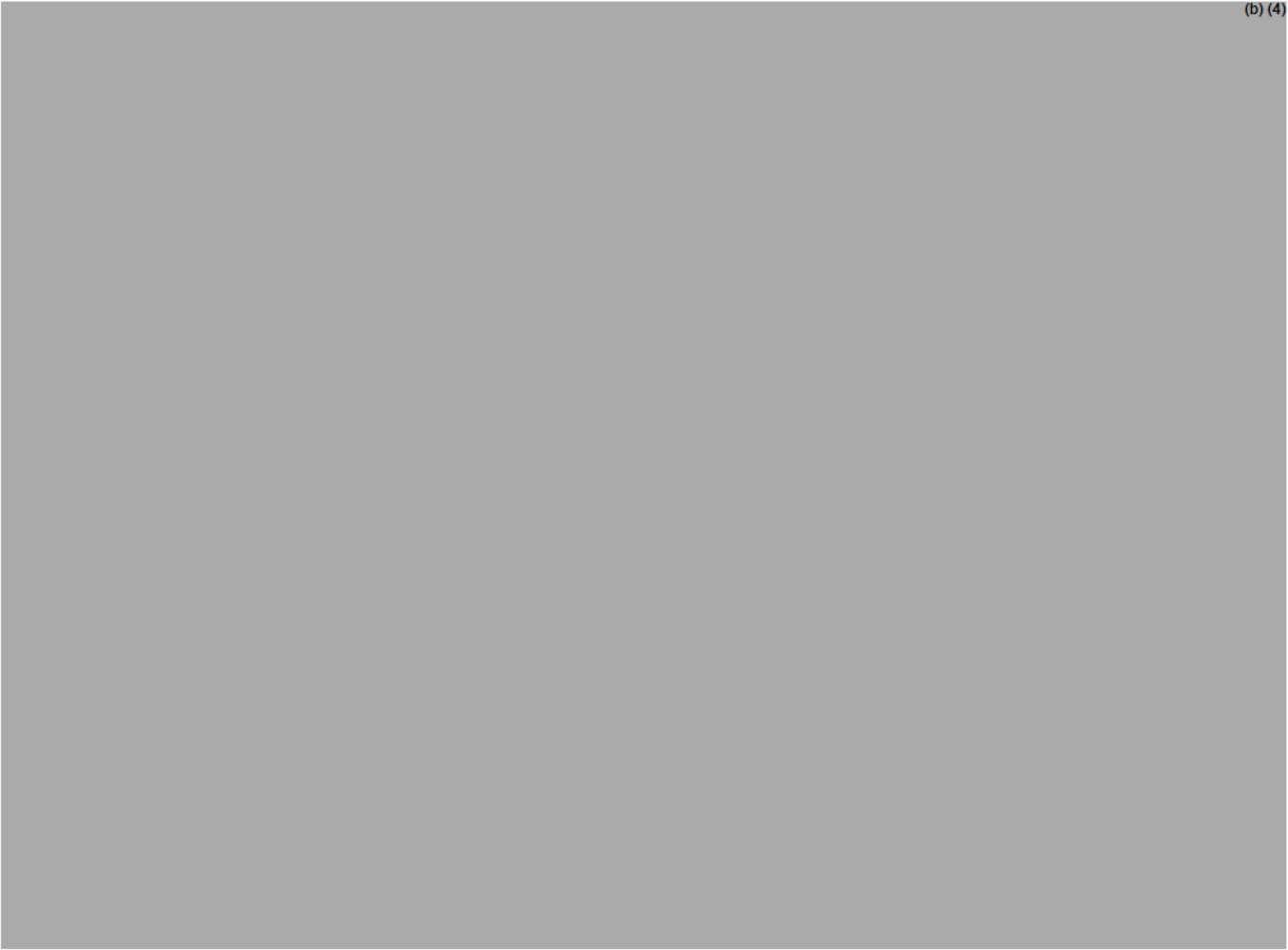
Chemistry Assessment**I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2:
Body of Data****S DRUG SUBSTANCE**

See NDA 206406 Chemistry Review #1, dated September 25, 2014.

P DRUG PRODUCT

See NDA 206406 Chemistry Review #1, dated September 25, 2014. This addendum covers the two outstanding issues noted in Review #1, post-marketing commitments to evaluate crystalline tacrolimus content in the product and drug product labeling.

(b) (4)



4 pages have been withheld immediately following this page as b4 (CCI/TS)

A APPENDICES

See Chemistry Review #1

R REGIONAL INFORMATION**R1 Executed Batch Records**

See Chemistry Review #1

R2 Comparability Protocols

Not applicable.

R3 Methods Validation Package

See Chemistry Review #1

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1**A. Labeling & Package Insert**

Trademark: The proposed trademark, Envarsus, was found acceptable by DMEPA. “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.” [DMEPA email to applicant dated 14-MAR-2014] On 21-MAR-2014, Veloxis proposed use of ‘XR’ as the proprietary name modifier, noting that Envarsus was not interchangeable with Astagraf XL. Use of ‘XR’ as the modifier would help differentiate the products. This was found acceptable by DMEPA and the clinical review team.

Container Labels: (0026, 09/26/2014)

(b) (4)

3 pages have been withheld immediately following this page as b4 (CCI/TS)

B. Environmental Assessment Or Claim Of Categorical Exclusion

See Chemistry Review #1.

IIIA. List Of Deficiencies To Be Communicated

There are no deficiencies to be communicated to the applicant.

IIIB. Communications with Applicant

See Chemistry Review #1.

Iv. Miscellaneous Attachments

Attachment A. EES Report

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT					
Application:	NDA 206406/000	Action Goal:			
Stamp Date:	30-DEC-2013	District Goal:	31-AUG-2014		
Regulatory:	30-OCT-2014				
Applicant:	VELOXIS PHARMS INC 499 THORNALL ST 3RD FL EDISON, NJ 08837	Brand Name:	ENVARUS XR		
		Estab. Name:	TACROLIMUS		
		Generic Name:			
Priority:	3	Product Number; Dosage Form; Ingredient; Strengths			
Org. Code:	500	001; TABLET, EXTENDED RELEASE; TACROLIMUS; .75MG 002; TABLET, EXTENDED RELEASE; TACROLIMUS; 1MG 003; TABLET, EXTENDED RELEASE; TACROLIMUS; 4MG			
Application Comment:					
FDA Contacts:	M. SEGCEL	Prod Qual Reviewer	3017961455		
	O. SIMAKOVA	Product Quality PM	2404023814		
	L. ALMOZA	Regulatory Project Mgr	2404025146		
	B. SHANMUGAM	Team Leader	3017961457		
Overall Recommendation:	ACCEPTABLE	on 01-SEP-2014	by R. XU	()	3017966187
	PENDING	on 08-APR-2014	by EES_PROD		
	ACCEPTABLE	on 18-FEB-2014	by J. WILLIAMS	()	3017964196
	PENDING	on 17-FEB-2014	by EES_PROD		
	PENDING	on 03-FEB-2014	by EES_PROD		
	PENDING	on 03-FEB-2014	by EES_PROD		
	PENDING	on 03-FEB-2014	by EES_PROD		

Establishment:	CFN:	FEI:	(b) (4)
	(b) (4)		
DMF No:	AADA:		
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Establishment Comment:	API SUPPLIER (on (b) (4)) by N. BHANDARI () 2404023815)		
Profile:	(b) (4)	OAI Status:	NONE
Milestone Name	Milestone Date	Request Type	Planned Completion
Comment			
OAI Submit To OC			
Request to Extend Re-eval Date To			
Extension Request Comment			
Reason			
SUBMITTED TO OC	(b) (4)		BHANDARIN
OC RECOMMENDATION		ACCEPTABLE	DOBBINE

Chemistry Assessment Section

Establishment:	CFN: (b) (4)	FEI: (b) (4)
		(b) (4)
DMF No:	AADA:	
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER	
Establishment Comment:	DRUG PRODUCT MICROBIOLOGICAL TESTING. (on (b) (4) by M. SEGEL (J) 3017961455) CONTRACT TEST FACILITY FOR VELOXIS. PERFORMS TESTING OF TACROLIMUS DRUG SUBSTANCE. FACILITY APPARENTLY NOT IDENTIFIED ON FORM 356H OR IN 3.2.S.2.1. SITE IDENTIFIED IN APPLICANTS METHOD VALIDATION REPORT. (on (b) (4) by M. SEGEL (J) 3017961455)	
Profile:	CONTROL TESTING LABORATORY	OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					
SUBMITTED TO OC	(b) (4)				SEGELM
OC RECOMMENDATION				ACCEPTABLE	RHX

Establishment:	CFN: (b) (4)	FEI: (b) (4)
DMF No:	AADA:	
Responsibilities:	FINISHED DOSAGE OTHER TESTER	
Establishment Comment:	DRUG PRODUCT TESTING. SITE NAME IS LISTED AS (b) (4) ON 356H FORM. (on (b) (4) by N. BHANDARI (J) 2404023815)	
Profile:	CONTROL TESTING LABORATORY	OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
<u>Reason</u>					
SUBMITTED TO OC	(b) (4)				BHANDARIN
OC RECOMMENDATION				ACCEPTABLE	WITTORFR

Chemistry Assessment Section

Establishment:	CFN:	FEI: 3003732290
	ROTTENDORF PHARMA GMBH	
	OSTENFELDER STR 51 - 81	
	ENNIGERLOH, , GERMANY	
DMF No:	AADA:	
Responsibilities:	(b) (4)	
	FINISHED DOSAGE MANUFACTURER	
	(b) (4)	
Establishment Comment:	(b) (4) DRUG PRODUCT MANUFACTURING	(b) (4)
	JAN-2014 by N. BHANDARI (J) 2404023815)	(b) (4) (on 14-
Profile:	TABLETS, EXTENDED RELEASE	OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	03-FEB-2014				BHANDARIN
SUBMITTED TO DO	03-FEB-2014	GMP Inspection			CAPACCIDANIC
TTR PROFILE TO EXPIRE BEFORE	(b) (4)				
DO RECOMMENDATION	(b) (4)			ACCEPTABLE	MROSE
DO RECOMMENDATION EXTENSION REQUEST				ACCEPTABLE	MROSE
OC RECOMMENDATION				ACCEPTABLE	WILLIAMSJU

####

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

/s/

MARK R SEGCEL
10/28/2014

CELIA CRUZ
10/28/2014

RAPTI D MADURAWA
10/29/2014

NDA 206406

Envarsus[®] XR
(tacrolimus extended-release tablets)
0.75 mg, 1 mg and 4 mg

Veloxis Pharmaceuticals, Inc.

Mark R. Seggel
ONDQA
Division of New Drug Quality Assessment II
Branch V

for the Division of Transplant and Ophthalmology Products (DTOP)

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Chemistry Review Data Sheet

1. NDA 206406
2. REVIEW #: 1
3. REVIEW DATE: 25-SEP-2014
4. REVIEWER: Mark R. Seggel
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Not Applicable	

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed (eCTD)</u>	<u>Document Date</u>
Original NDA (0000)	30-DEC-2013
Amendment (0001) Updated 356h with facilities / status	10-JAN-2014
Amendment (0002) Updated 356h with facilities / status	14-JAN-2014
Amendment (0009) Response to Information Request	16-APR-2014
Amendment (0010) Response to Biopharm. Request	25-APR-2014
Amendment (0015) Container Closure System Information	06-JUN-2014
Amendment (0016) Product Samples for OTR [06/17/14]	17-JUL-2014
Amendment (0017) Container Closure System - Samples	08-JUL-2014
Amendment (0018) Response to Information Request	18-JUL-2014
Amendment (0019) Response to Information Request	18-JUL-2014
Amendment (0021) Response to Information Request	29-AUG-2014
Amendment (0023) Response to Information Request	10-SEP-2014
Amendment (0024) Labeling	19-SEP-2014
Amendment (0025) Response to Information Request	25-SEP-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Veloxis Pharmaceuticals, Inc.
Address:	499 Thornall Street, 3 rd Floor Edison, New Jersey 08837
Representative(s):	Michelle A. Mc Guinness, VP, Global Regulatory and Quality Assurance
Telephone:	732-321-3211
Fax:	732-906-7943
Email:	mam@veloxis.com

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Envarsus™ XR
- b) Non-Proprietary Name (USAN): tacrolimus extended-release tablets
- c) Code Name/#: LCP-Tacro
- d) CAS Registry Number: 109581-93-3 [tacrolimus monohydrate]; 104987-11-3 [anhydrous]
- e) Chem. Type/Submission Priority:
 - i. Chem. Type: 3
 - ii. Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Maintenance Immunosuppression (9010004)

11. DOSAGE FORM: Extended-release tablets

12. STRENGTH/POTENCY: 0.75 mg, 1 mg, and 4 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)

☐ SPOTS product – Form Completed☒ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT

CAS Chemical Name:

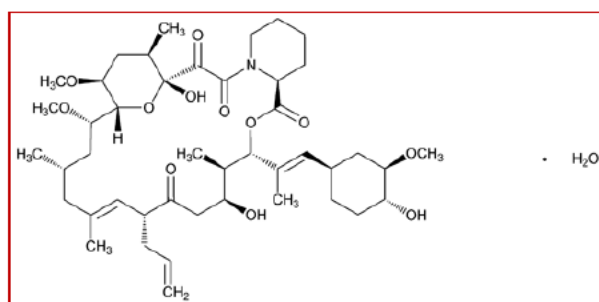
15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-, monohydrate, [3S-[3R*,E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-;

IUPAC Chemical Name:

(-)-(3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)-8-Allyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[(E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylvinyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate

USAN: Tacrolimus

Structural Formula: (as presented in USAN Dictionary)



Molecular Formula: $C_{44}H_{69}NO_{12} \cdot H_2O$.

Molecular Weight: 822.03 [monohydrate]

17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3,4	Adequate	G.J.Kang, OGD 12/19/2013	LoA 11/21/2013
	III			4	N/A	-	LoA 09/05/2013
	III			4	N/A	-	LoA 07/19/2013
	III			4	N/A	-	LoA 09/03/2013
	III			4	N/A	-	LoA 09/04/2013

Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

APPLICATION NUMBER	DESCRIPTION	DOCUMENT
IND 75,250	LCP-Tacro (tacrolimus extended-release tablets); Veloxis (previously dba Lifecycle Pharma)	-

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	na		
EES	Overall ACCEPTABLE recommendation	09/01/2014	See attached EES report
Pharm/Tox	<i>No new non-clinical studies conducted to support this NDA</i>		
ONDQA Biopharmaceutics	Approval	09/25/2014	Banu Zolnik
LNC	na		
Methods Validation	na		
DMEPA	Trademark acceptable Labeling revisions proposed		DMEPA
EA	Categorical exclusion - Acceptable	this review	M.Seggel
Quality Microbiology	Recommended for Approval*	01/13/2014	Bryan Riley
CDER Office of Testing and Research	Recommendations regarding test methods for crystalline tacrolimus	-	Mansoor Khan

* "The Microbial Limits specification for Envarsus is acceptable from a Product Quality Microbiology perspective."

19. GOAL DATES

GRMP Goal:	25-SEP-2014
PDUFA Goal:	30-OCT-2014

The Chemistry Review for NDA 206406

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Veloxis' NDA 206406, Envarsus XR (tacrolimus extended-release tablets), 0.75, 1 and 4 mg, as amended, has in general, provided sufficient information to assure the identity, strength, quality, purity, potency and bioavailability. However, because of the potential for crystallization of (b) (4) tacrolimus in the drug product, and resulting decrease in solubility and bioavailability, and the absence of an analytical procedure sufficiently sensitive and robust to detect such crystallization, the applicant has agreed to develop and implement an X-ray powder diffraction test (XRPD) as a post-marketing commitment (PMC).

The Office of Compliance has issued an overall recommendation of 'Acceptable' based on the satisfactory cGMP status of the manufacturing facilities (see attached EES report).

Minor revisions to the labeling are needed, and will be recommended to the applicant during labeling negotiations.

Therefore, from the CMC perspective, this NDA is recommended for approval pending agreement on PMCs and minor labeling revisions.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Post-marketing commitments to establish a suitable test for conversion of (b) (4) tacrolimus to crystalline form in drug product (e.g., x-ray powder diffraction) and to evaluate the stability of tacrolimus (b) (4) tablets, have been agreed to in principal.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Envarsus XR (tacrolimus extended-release tablets, 0.75, 1 and 4 mg) is a once-daily formulation of the calcineurin-inhibitor, tacrolimus. Approved formulations of tacrolimus include tacrolimus injection, tacrolimus capsules (e.g., Prograf and generic versions), and tacrolimus extended-release capsules (Astagraf XL, 0.5, 1, and 5 mg).

Executive Summary Section

Envarsus XR and Astagraf XL are NOT bioequivalent. Envarsus XR is also not bioequivalent to Prograf Capsules.

The drug product is manufactured in

(b) (4)

The drug product specification includes

(b) (4)

makes detection of crystalline material challenging. Post-marketing commitments to address test methodology and product stability will be established.

When protected from heat, light and moisture, tacrolimus exhibits good chemical stability as demonstrated by little increase in related substances on stability. Originally, the applicant intended to base their calculation of the expiration date on (b) (4). However, the final approved shelf-life of 24 months will begin at the time of (b) (4).

Inactive ingredients include hypromellose, lactose monohydrate, polyethylene glycol, poloxamer, magnesium stearate, tartaric acid, butylated hydroxytoluene, and dimethicone. All excipients meet USP/NF compendial requirements.

Tacrolimus, the active ingredient in Envarsus XR, is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. There is a significant body of literature covering the characterization of tacrolimus. Tacrolimus monohydrate used in the manufacture of Envarsus XR is sourced from (b) (4). Drug substance CMC is documented in DMF (b) (4).

B. Description of How the Drug Product is Intended to be Used

Envarsus XR (tacrolimus extended-release tablets) is indicated for the prophylaxis of organ rejection in patients receiving a kidney transplant.

Envarsus XR is to be taken once daily at the same time, consistently with or without food. It should not be taken with an alcoholic beverage or grapefruit juice. The tablets should not be chewed, divided (split) or crushed. Monitoring of whole blood tacrolimus trough concentrations is recommended.

Envarsus XR tablets are packaged in 30-count and 100-count HDPE bottles with CRC closures. The closures include a (b) (4). Bottles are sealed in (b) (4) overwraps and packaged in cartons.

The drug product is labeled for storage at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature]. An expiration dating period of 24 months, starting from the date that of (b) (4) and including up to 3 months storage of the (b) (4) has been granted.

C. Basis for Approvability or Not-Approval Recommendation

The quality of the drug substance, tacrolimus monohydrate, has been adequately documented (via cross-reference to (b) (4) for Tacrolimus; the open portion of the DMF was included in the NDA application). DMF (b) (4) was recently reviewed for (b) (4) and was found adequate.

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent quality of tacrolimus extended-release tablets.

The NDA, as amended, also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

All facilities have acceptable site recommendations. An overall recommendation of Acceptable was issued by the Office of Compliance on September 1, 2014 (see attached EES Report).

The proposed trademark, Envarsus XR, has been found acceptable by DMEPA. Other labeling recommendations (package insert, container and carton labels) have been provided by DMEPA. The only apparent error in the labeling from the CMC perspective is listing of the manufacturer as (b) (4).

(b) (4) Envarsus XR is manufactured by Rottendorf Pharma GmbH. (b) (4) is only responsible for regulatory oversight of the release of the finished product. References to Veloxis' (b) (4) ®

Executive Summary Section

(b) (4) should be removed from the labeling; it is promotional and provides no useful information to healthcare provider or patient. All labels otherwise appear to be accurate and to have the required information.

III. Lifecycle Knowledge Management

RISK IDENTIFICATION *[note: completed concurrently with review]*

Product attribute/CQA	Factors that can impact the CQA	Probability of Occurrence (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment, if any (+) = considerations that increase risk (-) = considerations that reduce risk
Assay	Raw materials Formulation Scale/Equipment/Site Process parameters Container closure	3	5	1	15	(b) (4)
Related substances	“	3	3	2	18	
Content Uniformity	“	3	3	4	36	
(b) (4)	“	1	5	1	5	
(b) (4) form of drug substance in product (b) (4) / Crystalline Content)	“	3	5	5	75	

Executive Summary Section

Dissolution ^	“	3	5	2	30	(b) (4)
Appearance	“	1	2	1	2	
RPN Values: Low Risk (1-25); Moderate Risk (26-60); High Risk (61-125)						

^ See ONDQA Biopharmaceutics Review

RISK MITIGATION AND LIFECYCLE CONSIDERATIONS

From Initial Quality Assessment			Review Assessment		
Product attribute / CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation Approach / Control Strategy	Risk Evaluation [Acceptable/ Not Acceptable]	Lifecycle Considerations/ Comments**
Assay	Raw materials Formulation Scale/Equipment/Site Process parameters Container closure	L	Manufacturing process controls; container closure system	Acceptable	(b) (4)
Related substances	“	L	Manufacturing process controls (e.g., limit exposure to elevated temperatures); container closure system (with (b) (4) to protect from light and moisture.	Acceptable	
Content Uniformity	“	M	Manufacturing process controls	Acceptable	

Executive Summary Section

(b) (4)	“	L	Manufacturing process controls, environmental controls, and container closure system	Acceptable	(b) (4)
(b) (4) form of drug substance in product (b) (4) / Crystalline Content)	“	H	Conditions potentially contributing to conversion to be evaluated by applicant (PMC); (b) (4) may be critical (crystalline form is the monohydrate)	Acceptable	
Dissolution ^	Potential risk to crystalline conversion can impact the dissolution`	M	XRPD method will be used to monitor crystalline content (b) (4)	Acceptable	
Appearance	“	L	Formulation; manufacturing (tableting controls); packaging	Acceptable	

* Risk ranking applies to product attribute/CQA (L, M, and H)

** For example, post marketing commitment, knowledge management post approval, etc. {e.g. Continue monitoring, especially during stability studies}

IV. Administrative**A. Reviewer's Signature**

{see electronic signature page}
Mark R. Seggel, Chemistry Reviewer

B. Endorsement Block

{see electronic signature page}
Celia Cruz, Ph.D., Secondary Reviewer

C. CC Block

{see DARRTS}

Chemistry Assessment**I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2:
Body of Data****S DRUG SUBSTANCE**

(b) (4)

80 pages have been withheld immediately following this page as b4 (CCI/Trade Secret)

A APPENDICES**A.1 Facilities and Equipment (biotech only)**

Not applicable

A.2 Adventitious Agents Safety Evaluation

Not applicable

A.3 Novel Excipients

Not applicable

R REGIONAL INFORMATION**R1 Executed Batch Records**

Executed batch records for batches (b) (4) are included in Module 3.2.R. These batches of 0.75 mg, 1 mg and 4 mg tacrolimus extended-release tablets were manufactured by Rottendorf Pharma. [It appears that some (b) (4) were used in two batches of a single strength product.]

R2 Comparability Protocols

Not applicable.

R3 Methods Validation Package

Reference is made to NDA sections 3.2.S.4.3 and 3.2.P.5.3

Comments: Because tacrolimus is not an NME and no unusual analytical procedures are currently employed, FDA's St. Louis laboratory (CDER DPA) was not consulted.

Additional testing to verify the suitability of (b) (4) may be necessary (USP, DPA and OTR will be consulted).

OTR has received samples of drug substance, tacrolimus (b) (4) placebo (b) (4) and finished drug product from Veloxis for the purpose of conducting research on the detection of crystallization of tacrolimus by dissolution, XRPD and other methods.

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1**A. Labeling & Package Insert**

Trademark: The proposed trademark, Envarsus, was found acceptable by DMEPA. “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.” [DMEPA email to applicant dated 14-MAR-2014] On 21-MAR-2014, Veloxis proposed use of ‘XR’ as the proprietary name modifier, noting that Envarsus was not interchangeable with Astagraf XL. Use of ‘XR’ as the modifier would help differentiate the products. This was found acceptable by DMEPA and the clinical review team.

Container Labels: (0000)

(b) (4)

3 pages have been withheld immediately following this page as b4 (CCI/TS)

B. Environmental Assessment Or Claim Of Categorical Exclusion

“FDA’s approval of the NDA will not increase the use of the active moiety. LCP-Tacro tablets are supposed to substitute directly for conventional tacrolimus products such as Prograf or Astagraf. In addition, the estimated concentration of the substance at the point of entry into the aquatic environment is below 1 ppb. Therefore, Veloxis Pharmaceuticals A/S hereby claims categorical exclusion from the requirement to submit an Environmental Assessment (EA) according to 21 CFR 25.31(b). According to the applicant’s knowledge no extraordinary circumstances exist (21 CFR 25.21).”

The maximum projected annual sales during the first five is (b) (4) kg (in 2019), which results in an expected introduction concentration (EIC) into the aquatic environment of ca. (b) (4) ppb.

Comments: The categorical exclusion from the preparation of an environmental assessment (EA) is acceptable based the applicant’s analysis and determination of an EIC significantly below 1 ppb. [Note that while the tabulation of projected annual sales on page 2 of Section 1.12.14 referred to amounts of tacrolimus, the page title referred to (b) (4) This has been corrected by the applicant at our request.]

IIIA. List Of Deficiencies To Be Communicated

There are no deficiencies to be communicated to the applicant at this time.

IIIB. Communications with Applicant

Information Requests: Information requests communicated with the applicant during the course of the review are provided here.

08-JAN-2014: Request for manufacturing facility names, FEIs, and contact information.

(b) (4)





(b) (4)

Summary of Other Communications with Applicant:

(b) (4)

Iv. Miscellaneous Attachments

Attachment A. EES Report

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT					
Application:	NDA 209409/000	Action Goal:			
Stamp Date:	30-DEC-2013	District Goal:	31-AUG-2014		
Regulatory:	30-OCT-2014				
Applicant:	VELOXIS PHARMS INC. 499 THORNALL ST 3RD FL EDISON, NJ 08837	Brand Name:	ENVARSUS XR		
		Establish Name:	TACROLIMUS		
		Generic Name:			
Priority:	3	Product Number, Dosage Form, Ingredient, Strengths:			
Org. Code:	500		001: TABLET, EXTENDED RELEASE, TACROLIMUS, 75MG 002: TABLET, EXTENDED RELEASE, TACROLIMUS, 1MG 003: TABLET, EXTENDED RELEASE, TACROLIMUS, 4MG		
Application Comment:					
FDA Contacts:	M. SEGUEL	Prod Qual Reviewer:		3017961455	
	O. SIMAKOVA	Product Quality PM		2404023814	
	L. ALMOZA	Regulatory Project Mgr		2404025146	
	B. SHANMUGAM	Team Leader:		3017961457	
Overall Recommendation:	ACCEPTABLE	on 01-SEP-2014	by R. XU	()	3017961887
	PENDING	on 08-APR-2014	by EES_PROD		
	ACCEPTABLE	on 18-FEB-2014	by J. WILLIAMS	()	3017964186
	PENDING	on 17-FEB-2014	by EES_PROD		
	PENDING	on 03-FEB-2014	by EES_PROD		
	PENDING	on 09-FEB-2014	by EES_PROD		
	PENDING	on 03-FEB-2014	by EES_PROD		

Establishment:	CFN:	FEI:	(b) (4)
DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Establishment Comment:	API SUPPLIER (or (b) (4) by N. BHANDARI (j 2404023815))		
Profile:	(b) (4)	OAI Status:	NONE
Milestone Name	Milestone Date	Request Type	Planned Completion
Comment			
OAI Submit To OC			
Request to Extend Re-eval Date To			
Extension Request Comment			
Reason			
SUBMITTED TO OC	(b) (4)		BHANDARI
OC RECOMMENDATION		ACCEPTABLE	DOBBINE

Establishment:	CFN:	FEI:	(b) (4)
DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER		
Establishment Comment:	DRUG PRODUCT MICROBIOLOGICAL TESTING (or (b) (4) by M. SEGUEL (j 3017961455)) CONTRACT TEST FACILITY FOR VELOXIS. PERFORMS TESTING OF TACROLIMUS DRUG SUBSTANCE. FACILITY APPARENTLY NOT IDENTIFIED ON FORM 306H OR IN 3.2.5.2.1. SITE IDENTIFIED IN APPLICANTS METHOD VALIDATION REPORT (or (b) (4) by M. SEGUEL (j 3017961455))		
Profile:	CONTROL TESTING LABORATORY	OAI Status:	NONE
Milestone Name	Milestone Date	Request Type	Planned Completion
Comment			
OAI Submit To OC			
Request to Extend Re-eval Date To			
Extension Request Comment			
Reason			
SUBMITTED TO OC	(b) (4)		SEGUEL
OC RECOMMENDATION		ACCEPTABLE	R-K

Chemistry Assessment Section

Establishment:	CFR: (b) (4)	FEL: (b) (4)
DMF No:	AADA:	
Responsibilities:	FINISHED DOSAGE OTHER TESTER	
Establishment Comment:	DRUG PRODUCT TESTING. SITE NAME IS LISTED AS (b) (4) ON 350H FORM. (b) (4) by N. BHANDARI (J 2404023815)	
Profile:	CONTROL TESTING LABORATORY	OAI Status: NONE
Milestone Name	Milestone Date	Request Type
Comment		
OAI Submit To OC		
Request to Extend Re-eval Date To		
Extension Request Comment		
Reason		
SUBMITTED TO OC	(b) (4)	BHANDARI
OC RECOMMENDATION	ACCEPTABLE	WITTORFF

Establishment:	CFR: ROTTENDORF PHARMA GMBH OSTENFELDER STR 51 - 01 ENNIERLOH, GERMANY	FEL: 3003732290
DMF No:	AADA:	
Responsibilities:	(b) (4) FINISHED DOSAGE MANUFACTURER (b) (4)	
Establishment Comment:	(b) (4), DRUG PRODUCT MANUFACTURING (b) (4) 14 JAN-2014 by N. BHANDARI (J 2404023815)	
Profile:	TABLETS, EXTENDED RELEASE	OAI Status: NONE
Milestone Name	Milestone Date	Request Type
Comment		
OAI Submit To OC		
Request to Extend Re-eval Date To		
Extension Request Comment		
Reason		
SUBMITTED TO OC	03-FEB-2014	BHANDARI
SUBMITTED TO DO	03-FEB-2014	CAPACODANIC
TTR PROFILE TO EXPIRE BEFORE POUFA (30-OCT-2014)		
DO RECOMMENDATION	05-FEB-2014	ACCEPTABLE
DO RECOMMENDATION	18-FEB-2014	ACCEPTABLE
EXTENSION REQUEST		
OC RECOMMENDATION	18-FEB-2014	ACCEPTABLE
WILLIAMSJU		

Attachment B. Representative Drug Substance Certificate of Analysis

(b) (4)



Attachment C. Related Tacrolimus Product Specifications**Astagraf XL (tacrolimus extended-release capsules)**

Acceptance Criteria for Assay and Related Substances in Astagraf XL (NDA 204096)

(b) (4)

Tacrolimus Capsules, USP (USP37s1)

Acceptance Criteria for Assay and Related Substances in Tacrolimus Capsules, USP

(b) (4)

####

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/s/

MARK R SEGCEL
09/25/2014

CELIA CRUZ
09/25/2014

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre- Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

I. Review Cover Sheet

1. OMPQ Reviewer: Linda Ng, Ph.D.
2. NDA/BLA Number: NDA 206-406
Submission Date: December 30, 2013
21st C. Review Goal Date: August 30, 2014
PDUFA Goal Date: October 30, 2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Envarsus
Established or Non-Proprietary Name (USAN) and strength:	Tacrolimus extended-release tablets, 0.75 mg, 1.0 mg, 4.0 mg
Dosage Form:	Extended release tablets

4. SUBMISSION PROPERTIES:

Review Priority :	STANDARD
Applicant Name:	Veloxis Pharmaceuticals Inc
Responsible Organization (OND Division):	DTOP

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

II. Application Detail

1. INDICATION: Prophylaxis of organ rejection in patients receiving a kidney transplant
2. ROUTE OF ADMINISTRATION: Oral
3. STRENGTH/POTENCY: 0.75 mg, 1.0 mg and 4.0 mg
4. Rx/OTC DISPENSED: X ☐ Rx ☐ OTC
5. ELECTRONIC SUBMISSION (yes/no)? yes
6. PRIORITY CONSIDERATIONS: no

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V		x		
2.	Breakthrough Therapy Designation		x		
3.	Orphan Drug Designation		x		
4.	Unapproved New Drug		x		
5.	Medically Necessary Determination		x		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		x		
7.	Rolling Submission		x		
8.	Drug/device combination product with consult		x		
9.	Complex manufacturing		x		
10.	Other (e.g., expedited for an unlisted reason)		x		

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	Yes	No	Comment
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		
12.	Do all sites indicate they are ready to be inspected (on 356h)?	X		
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	X		
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?		X	Sites stated for a) release testing and b) testing (stability?)
15.	Additional notes (non-filing issue) 1. Are all sites registered or have FEI #?		X	(b) (4) does not have FEI #. See CGMP facilities Assessment below.
	2. Do comments in EES indicate a request to participate on inspection(s)?		X	
	3. Is this first application by the applicant?		X	

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
16.	Have any Comparability Protocols been requested?		X	Did not locate any

IMA CONCLUSION				
	Parameter	Yes	No	Comment
17.	Does this application fit one of the EES Product Specific Categories?		X	
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	X		Two listed testing sites were not added to EES. See CGMP facilities Assessment below for (b) (4) Veloxis, Denmark only reviews results as per CMC reviewer and thus not added
19.	From a CGMP/facilities perspective, is the application fileable? If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements? No			
Nanotechnology ☐	RTRT Proposal ☐	PAT ☐	Drug/Device Combo ☐
PET ☐	Design Space ☐	Continuous Mfg ☐	Naturally derived API ☐
Other (explain):			

Manufacturing Highlights

1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	

Include process flow chart/diagram (see eCTD Section 2.3.S.1)

2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?	X		Possible; (b) (4) When does expiry begin?

Include process flow chart/diagram (see eCTD Section 2.3.P.1)

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

(b) (4)

3. Facility-Related Risks (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc.). Describe any potential 21CFR 211 compliance issues.

Not likely.

4. Drug Product Facility Inspectional History that could impact the manufacturing of this product

No

Additional information not covered above

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

NDA: 206406
Sponsor:
Indication:
PDUFA:
Responsible Organization:
EERS Submitted By:
Chart Generated On:

206406 TACROLIMUS
VELOXIS PHARMACEUTICALS INC
 Prophylaxis of organ rejection in
 patients receiving a kidney transplant
10/30/2014 under STANDARD Review
CDER/OAP/DTOP
SIMAKOVA, OLGA: CDER
3/5/2014

Overall OC Recommendation:
Reevaluation date:

ACCEPTABLE entered into EES on 2/18/2014 11:01:47 PM
10/30/2014

Establishment Name	EER Creation Date	FEI #	District Short	Country Code	Responsibilities	Profile Code	Firm Profiles - Current Status	Inspection History, Dates, Classifications	Most Recent Milestone	Most Recent EER Compliance Status	Comment
(b) (4)									OC Recommendation	AC	The address and FEI are different in 356h and EES;
									OC Recommendation	AC	Also listed as (b) (4)
									OC Recommendation	AC	
ROTTENDORF PHARMA GMBH	1/8/2014	3003732290	EEU	DEU	(b) (4) drug product manufacturing, (b) (4)	TTR	pps.fda.gov/scrpts/mpqa/profile.cfm?FEI=3003732290	Based on profile Feb 18, 2014	OC Recommendation	AC	

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

For each EER, indicate PAI recommendation on the Manufacturing Facilities Chart above (e.g., PS, GMP, 10 Day, AC based on file review). This is the recommendation that will be entered into EES. **For PAI, include the reason for the PAI (i.e. PAI Trigger) in the comment section of the facilities chart.**

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no, Yes to questions 11-12) Yes
Based on Section IV, is a KTM warranted for any PAI? (yes/no). If yes, please identify the sites in the above chart. (b) (4) However, this site has been found acceptable based on profile. The comment on the expiry dating period can be addressed by the quality reviewer.
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no) No
Comments for 74 Day Letter
1.
2.
3.

REVIEW AND APPROVAL (DARRTS)

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

/s/

LINDA L NG
03/14/2014

MAHESH R RAMANADHAM
03/17/2014

Initial Quality Assessment (IQA) and Filing Review for Pre-Marketing Applications CMC and Biopharmaceutics

Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 206406
2. SUBMISSION TYPE : Original
3. SUBMISSION NUMBER: 0
4. PRODUCT PROPERTIES: Extended-release tablets

Trade or Proprietary Name:	Envarsus
Established or Non-Proprietary Name (USAN):	Tacrolimus
Dosage Form:	Extended-release tablets

5. NAME & ADDRESS OF APPLICANT:

Name:	Veloxis Pharmaceuticals
Address:	499 Thornall Street, Edison, NJ 08837
Representative:	NA

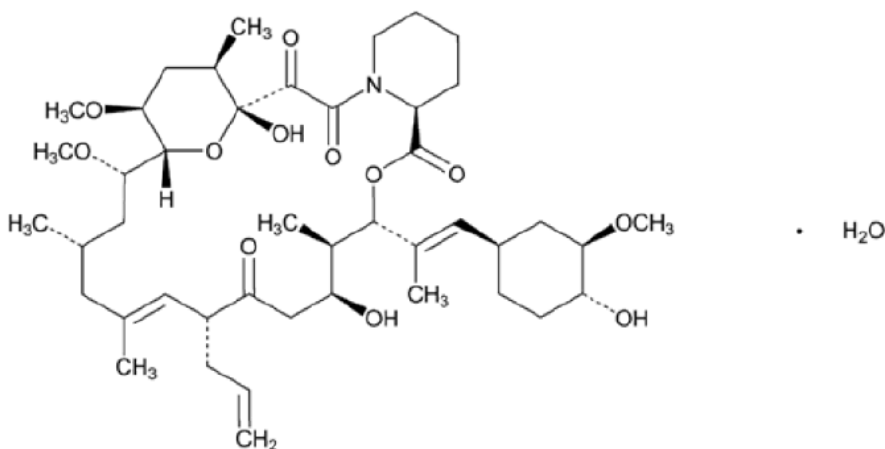
6. SUBMISSION PROPERTIES:

Review Priority :	Standard
Classification (Chem. Code and Type):	3
Property (Legal Basis):	505 (b) (2)
Responsible Organization:	CDER

Review Information

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOLECULAR WEIGHT:

[3*S* – [3*R**[*E*(1*S**, 3*S**, 4*S**), 4*S**, 5*R**, 8*S**, 9*E*, 12*R**, 14*R**, 15*S**, 16*R**, 18*S**, 19*S**, 26*aR**]] – 5, 6, 8, 11, 12, 13, 14, 15, 16, 17, 18, 19, 24, 25, 26, 26*a* – hexadecahydro – 5, 19 – dihydroxy – 3 – [2 – (4 – hydroxy – 3 – methoxycyclo – hexyl) – 1 – methylethenyl] – 14, 16 – dimethoxy – 4, 10, 12, 18 – tetramethyl – 8 – (2 – propenyl) – 15, 19 – epoxy – 3*H* – pyrido[2, 1 – *c*][1, 4]oxaazacyclotricosine – 1, 7, 20, 21(4*H*, 23*H*) – tetrone, monohydrate



C₄₄H₆₉NO₂
822.03

2. INDICATION: Prophylaxis of organ rejection in patients receiving a kidney transplant.

3. PHARMACOLOGICAL CATEGORY: Immunosuppressant

4. ROUTE OF ADMINISTRATION: Oral

5. STRENGTH/POTENCY: 0.75 mg, 1.0 mg and 4.0 mg

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications
NDA #: 206406

6. Rx/OTC DISPENSED: ☒Rx ☐OTC

7. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

Is this a SPOTS product? ☐Yes ☒No ☐ Not evaluated at time of IQA.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

NDA #: 206406

RELATED REVIEW DOCUMENTS:

a. Drug Master Files listed on 356h form:

DMF	TYPE	ITEM	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	Nov-21-2013	
	III		Sep-5-2013	
	III		July-19-2013	
	III		Sep-9-2013	
	III		Apr-9-2013	

b. Consults Recommended by CMC and Biopharmaceutics

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	☐	☒	
Clin Pharm	☐	☐	
EES	☐	☐	
Pharm/Tox	☐	☐	
Methods Validation	☐	☐	
EA	☐	☐	
New Drug Micro	☒	☐	
CDRH	☐	☐	
Other	☐	☐	

c. Other Applications or Submissions to note (if any):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION

d. Previous Communications with the Applicant to note (if any):

		APPLICATION	
(b) (4)			

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications
NDA #: 206406**

(b) (4)

Overall Conclusions and Recommendations

Is the Product Quality Section of the application fileable from a CMC perspective?

Yes	No	CMC Filing Issues
☒	☐	1.

Are there potential CMC review issues to be forward to the Applicant with the 74 day letter?

Yes	No	CMC Comments for 74 Day Letter
☐	☒	1.

Is the Product Quality Section of the application fileable from a biopharmaceutics perspective?

Yes	No	Biopharmaceutics Filing Issues
☒	☐	1. None

Are there potential biopharmaceutics review issues to be forward to the Applicant with the 74 day letter?

Yes	No	Biopharmaceutics Comments for 74 Day Letter
☒	☐	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. In consistency with the ICH Q6A guidance, we recommend the use of dissolution testing to monitor for the amount of crystalline content at release and on stability. For this purpose, provide information/data showing that your dissolution testing methodology and selected criteria are able to reject batches with inadequate amounts of crystalline form. Submit dissolution profiles as a function of crystalline content (e.g. 0%, 2%, 5%, 8%, 10%, 20%). In addition, the setting of the acceptable amount of crystalline form allowed by dissolution should be supported by clinical information (i.e., bioavailability, exposure-response, etc.). Alternatively, monitor crystalline content at release and on stability using a sensitive analytical method (e.g. XRPD with adequate sensitivity, e.g. (b) (4) sensitivity). In addition, the setting of the acceptable amount of the crystalline form

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

NDA #: 206406

		allowed by XRPD specification should be supported by clinical information (i.e., bioavailability, exposure-response, etc.). Note that an additional dissolution acceptance criterion may need to be implemented to monitor crystalline content, in addition to the QC acceptance criteria. 3. 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. 4. Submit the following PK data from all the BE Studies 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 (.).
--	--	--

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications
NDA #: 206406**

CMC Summary: Critical Issues and Complexities

CMC Critical Issues or Complexities

Tacrolimus, a macrolide lactone has been approved as Prograf® for the prophylaxis of organ rejection and more recently an extended-release formulation, Astagraf XL (tacrolimus extended-release capsule) was approved for prophylaxis of organ rejection in adult patients receiving kidney transplants. Veloxis' s product which is also an extended-release formulation uses a proprietary Meltdose® drug-delivery technology (b) (4)

The non-critical quality issues are mentioned below for further evaluation during review of the NDA.

Does the submission contain any of the following elements?

Nanotechnology	QbD Elements	PET	Other, please explain
☐	☐	☐	

Is a team review recommended?

Yes	No	Suggested expertise for team
☒	☐	Evaluation of (b) (4)

Summary or Highlights of the Application *(not already mentioned in other sections)*

- Drug substance CMC information is referenced to DMF (b) (4). This DMF was last reviewed by (b) (4) and found adequate in the review dated (b) (4). There are no further submissions (quality amendments or annual reports) for this DMF since the last review.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

NDA #: 206406

- *It appears that some of the drug substance batches were tested per (b) (4) specification while other batches were tested per USP monograph. Please verify that (b) (4) specification is aligned with the USP monograph and that the in-coming material is accordingly qualified by Veloxis.*

(b) (4)

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

(b) (4)

- *It is not clear how Veloxis calculates the start date for stability (typically when the API is mixed with the excipient). Needs to be clarified.*
- *Considering the amount of stability data available, statistical analysis will be helpful in evaluating the stability information and in determining the appropriateness of the expiration date requested. Veloxis can be requested to provide statistical analysis, if available.*
- *Stability results indicate observable trends for most impurities but remains within the proposed specification. There is a corresponding increase in total impurities. Does this increasing trend correlate with change in (b) (4)*
- *Section 16 on How Supplied/Storage and Handling in the PI may need revision (example, “Envarsus is supplied in round bottles”) to provide more accurate description.*
- *The PI has no reference to the 100 count packaging in the PI. Is this packaging configuration meant for (b) (4)*

Description of Facility Related Risks or Complexities (i.e. number of foreign sites, large number of sites involved, etc.)

See EES for complete list of facilities related to this application.

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications
NDA #: 206406

Biopharmaceutics Initial Assessment

Critical Issues or Complexities

Submission: This 505(b)(2) NDA submission contains tacrolimus, an approved drug in a new extended release formulation. FDA's approved tacrolimus products include, Prograf® (NDA 50708 0.5 mg, 1 mg, and 5 mg, Approval Date April 8, 1994) and Astagraf XL (NDA 204096, 0.5 mg, 1 mg, and 5 mg, Approval date: July 19 2013).

Product Development: The Applicant developed several formulations of LCP-Tacro ER

(b) (4)

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

(b) (4)

Review:

The Biopharmaceutics review will be focused on 1) the evaluation and acceptability of the bridging bioequivalence studies supporting the approval of the proposed drug product, 2) the evaluation of the proposed acceptance criteria, 3) the evaluation of the (b) (4), 4) the evaluation of the dissolution data included in the in vitro alcohol induced dose dumping study, and 5) evaluation of the data supporting the extended release claim.

The dissolution method was accepted during the IND stage. For further information refer to the reviews by Dr. John Duan for IND 75-250/SDN029, SDN038 and SDN064 in DARRTS. The following table lists the dissolution method and proposed acceptance criteria.

Dissolution Method and Proposed Acceptance Criteria for Tacrolimus					
USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criteria (% of the labeled amount dissolved)
USP II (paddles)	100 rpm	900 mL	37°C ± 0.5°C	Water + 0.005% hydroxypropyl cellulose (HPC) + 0.50% SLS adjusted to pH 4.5 ± 0.2 (2N Acetic Acid	2½ hours: (b) (4) 6½ hours: (b) (4) 12 hours: (b) (4)

There is a concern about the possibility of the crystallization of (b) (4) tacrolimus. During Pre-NDA meeting dated August 7, 2013, FDA communicated this concern and informed them that dissolution could be used to monitor crystal content. However, the Applicant did not address this issue in the submission. The assessment of crystal content will be requested in the 74-day letter.

Consult Request:

The Division of Scientific Investigations (DSI) has been consulted for the inspections of the analytical and clinical sites of BE studies LCP-Tacro 1020 (fasted) and LCP-Tacro 1023 (fed).

Recommendation:

The NDA is fileable from a Biopharmaceutics perspective. However, there are potential issues for review and Biopharmaceutics has comments to be sent to the Applicant in the 74 day letter. These comments are included in pages 5 and 6 of this IQA and filing review.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications
NDA #: 206406**

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	☒	☐	
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	☒	☐	
3.	Are all the pages in the CMC section legible?	☒	☐	
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	☒	☐	

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	☒	☐	
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.	☐	☒	

ONDQA Initial Quality Assessment (IQA) and Filing Review
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7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	☒	☐	
8.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	☒	☐	

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9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	☒	☐	
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	☒	☐	

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	

D. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
12.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	☒	☐	See table on cover page.

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E. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
13.	Does the section contain a description of the DS manufacturing process?	☒	☐	Referenced to DMF (b) (4)
14.	Does the section contain identification and controls of critical steps and intermediates of the DS(in process parameters?	☒	☐	
15.	Does the section contain information on impurities?	☒	☐	
16.	Does the section contain information regarding the characterization of the DS?	☒	☐	
17.	Does the section contain controls for the DS?	☒	☐	
18.	Has stability data and analysis been provided for the drug substance?	☒	☐	
19.	Does the application contain Quality by Design (QbD) information regarding the DS?	☐	☒	
20.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?	☐	☒	
21.	Does the section contain container and closure information?	☒	☐	The DMFs referenced for container closure are: a) (b) (4) b) (b) (4) c) (b) (4) d) (b) (4) LOA's have been provided in the NDA.

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F. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
22.	Does the section contain quality controls of excipients?	☒	☐	
23.	Does the section contain information on composition?	☒	☐	
24.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	☒	☐	
25.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	☒	☐	
26.	Is there a batch production record and a proposed master batch record?	☒	☐	
27.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	☒	☐	
28.	Have any biowaivers been requested?	☒	☐	
29.	Does the section contain description of to-be-marketed container/closure system and presentations?	☒	☐	
30.	Does the section contain controls of the final drug product?	☒	☐	
31.	Has stability data and analysis been provided to support the requested expiration date?	☒	☐	
32.	Does the application contain Quality by Design (QbD) information regarding the DP?	☐	☒	
33.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?	☐	☒	

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G. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
34.	Is there a methods validation package?	☒	☐	

H. MICROBIOLOGY				
	Parameter	Yes	No	Comment
35.	If appropriate, is a separate microbiological section included discussing sterility of the drug product?	☒	☐	

I. LABELING				
	Parameter	Yes	No	Comment
36.	Has the draft package insert been provided?	☒	☐	
37.	Have the immediate container and carton labels been provided?	☒	☐	
38.	Does section contain tradename and established name?	☒	☐	

ONDQA-BIOPHARMACEUTICS				
A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	Yes	No	Comment
39.	Does the application contain dissolution data?	X		USP II (paddles), 100 rpm, Water containing 0.005 % hydroxypropyl cellulose (HPC) with 0.5% Sodium Lauryl Sulfate (SLS), 900 mL pH 4.5
40.	Is the dissolution test part of the DP specifications?	X		The following acceptance criteria are proposed; 2½ hours: (b) (4) 6½ hours: (b) (4) 12 hours: (b) (4)
41.	Does the application contain the dissolution method development report?		X	No, However, the dissolution method was accepted during the IND stage. For further information refer to the Biopharmaceutics reviews by Dr. John Duan for IND 75250/SDN-029, SDN-038 and SDN-064) in DARRTS.
42.	Is there any data submitted to support the proposed dissolution specification?		X	Dissolution information from primary stability batches includes only dissolution data from three time point (2 hours, 5 hours and 9 hours). The complete multipoint dissolution profile data supporting the proposed acceptance criteria will be requested in the 74-Day letter.
43.	Is there a validation package for the analytical method and dissolution methodology?	X		

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44.	Does the application contain in vitro alcohol induced dose dumping studies?	X		
45.	Does the application include a biowaiver request?	X		The Applicant requested a biowaiver for the lower 0.75 mg and 1 mg strengths.
46.	Is there information provided to support the biowaiver request?		X	The Applicant provided comparative dissolution data with between 0.75 mg, 1 mg and 4 mg with Formulation G. And bioequivalence data between 4 mg and 1 mg with Formulation F. It should be noted that 4 mg strength uses different (b) (4) The data supporting the biowaiver request will be reviewed.
47.	Does the application include an IVIVC model?		X	
48.	Is information such as BCS classification mentioned, and supportive data provided?	X		The Applicant stated that tacrolimus is a BCS Class II (low solubility and high permeability drug) but did not provide any supportive data.
49.	Is information on mixing the product with foods or liquids included?			Per draft label, Envarsus tablets should be preferably taken consistently either with food or without food.
50.	Is there any in vivo BA or BE information in the submission?	X		The following bridging PK studies were submitted. See Schematic Clinical Overview in page 10 for more details. BE# 1018: Bridging Formulation C and D BE# 1020 for 1 mg: Bridging Formulation D and F BE# 1023 for 4 mg: Bridging Formulation F and G BE# 1024: Bridging between 4 mg and 1 mg Formulation F. BE studies will be reviewed by ONDQA-Biopharmaceutics.
51.	Has the Applicant submitted validation of bioanalytical assay?	X		
52.	Has the Applicant provided IRB approval, Informed Consent forms?	X		

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53.	Has the Applicant provided appropriate pharmacokinetic information?		X	The Applicant did not provide the raw data for BE analysis. Therefore, the Applicant will be requested in the 74-day letter to provide the raw data in SAS format.
54.	Are there any manufacturing changes implemented to the clinical trial and bio batch formulations?	X		See Schematic Clinical Overview in page 10 for more details
55.	Are there any data submitted to support the manufacturing changes?	X		Evaluation of the bridging studies between Formulation B used for food effect study and Formulation G is a review issue.
56.	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		

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REVIEW AND APPROVAL

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

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/s/

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