

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210115Orig1s000

PRODUCT QUALITY REVIEW(S)



Recommendation: Approval

**NDA 210115
Review # 1
Apr 10, 2018**

Drug Name/Dosage Form	<i>Prograf (Tacrolimus for suspension)</i>
Strength	<i>0.2 mg and 1mg</i>
Route of Administration	<i>Oral</i>
Rx/OTC Dispensed	<i>Rx</i>
Applicant	<i>Astellas Pharma US, Inc.</i>
US agent, if applicable	<i>NA</i>

SUBMISSION(S) REVIEWED	DOCUMENT DATE
<i>Original</i>	<i>7/26/2017</i>
<i>Amendment</i>	<i>10/2/2017</i>
<i>Amendment</i>	<i>11/22/2017</i>
<i>Amendment</i>	<i>12/19/2017</i>
<i>Amendment</i>	<i>1/4/2018</i>
<i>Amendment</i>	<i>2/15/2018</i>
<i>Amendment</i>	<i>3/8/2018</i>
<i>Amendment</i>	<i>3/19/2018</i>

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Application Technical Lead	Chunchun Zhang	NA
Drug Substance	Sharon Kelly	Charles Jewell
Drug Product	Yushi Feng	Bala Shanmugam
Microbiology	Nancy Waites	Dan Obrzut
Biopharmaceutics	Joan Zhao	Jing Li
Process	Nancy Waites	Dan Obrzut
Facility	Ebern Dobbin	Derek Smith
Regulatory Business Process Manager	Kristine Leahy	NA
ORA Lead	Caryn McNabb	NA
Laboratory (OTR)	NA	NA
Environmental Assessment (EA)	Yushi Feng	Balajee Shanmugam

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status ¹	Date Review Completed	Comments
16683	Type II	Astellas Pharma Inc.	Tacrolimus drug substance	Adequate	11/1/2017	LoA: 7/7/2017 Reviewed by Srinivasa Murthy
(b) (4)	Type III	(b) (4)	(b) (4)	NA		LoA: 1/26/2016

¹NA (There is enough data in the application, therefore the DMF did not need to be reviewed).

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	(b) (4)	This product during IND development

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	Adequate		1/26/2017	Aaron Ruhland
CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations and Conclusion on Approvability

The NDA, as amended, has provided sufficient product quality information to assure the identity, strength, purity, and quality of the proposed drug product tacrolimus for oral suspension. All information requests and review issues have been addressed.

The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities on 4/6/2018.

Therefore, NDA 210115 is recommended for approval from Product Quality perspective.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling discussion.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	For the treatment of pediatric patients with liver, heart or ^{(b) (4)} transplant.
Duration of Treatment	The required dose is calculated based on the weight of the patient. See package insert for the recommended dosage in patients.
Maximum Daily Dose	As above (see the package insert for details).
Alternative Methods of Administration	NA

B. Quality Assessment Overview

i. Drug Substance Quality Summary

The drug substance is tacrolimus, a white crystals or crystalline powder. It is manufactured by Astellas Pharma Inc. The drug substance referenced in DMF 16833 was found adequate by Dr. Srinivasa Murthy on 11/01/2017.

ii. Drug Product Quality Summary

Prograf (tacrolimus) for oral suspension is intended for the pediatric patients with liver, heart or (b) (4) transplant. The drug product is provided in packets (b) (4) with two strengths: 0.2 mg and 1 mg.

All excipients used in the formulation are adequately qualified. No novel excipients are used in the formulation. The drug product specification includes tests for appearance, identity, assay, impurities, dissolution, content uniformity, and microbial limits. The proposed specification is acceptable to ensure quality of the product over its expiration period. All analytical methods are described in reasonable detail and have been adequately validated.

Batch analyses are provided for 6 batches for each strength on commercial scales (b) (4) which were manufactured by Astellas Pharma Inc. All batches complied with the proposed specification.

Drug product stability data is available to 36 months at long term storage 25°C/60%RH and 6 months at accelerated conditions 40°C/75%RH for two strengths with 6 registration batches. There is no trend observed for all tests when the drug products were stored at long term or accelerated condition. The shelf life of 36 months when stored at 20°C-25°C is granted.

The storage statement is “Store at 20°C to 25°C (68°F to 77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

The proposed drug product manufacturing process includes (b) (4)

(b) (4) During the NDA review several information requests regarding (b) (4) controls, process yields, and the executed batch records were conveyed to and addressed by the applicant. Microbial limits will be performed at release and on stability for both strength. The overall information regarding the manufacturing process provided in the NDA submission and subsequent amendments was found acceptable.

The biopharmaceutics review has found the proposed dissolution method and acceptance criterion (NLT (b) (4) % (Q) in 45 minutes) acceptable. The formulation of the commercial tacrolimus for oral suspension is the same as the clinical batches, except for the manufacturing site and scale. The bridge between the clinical batches and the commercial product is supported by the comparative dissolution in profile.

A pre-approval inspection of Astellas Pharma Tech Co., Ltd (FEI 3002807003) was conducted to support the manufacturing of the drug substance and drug product. The facility adequately addressed the deficiencies identified during the pre-approval inspection. Therefore, the overall recommendation of “Approve” was entered for the NDA into Panorama by OPF on 4/6/2018.

C. Special Product Quality Labeling Recommendations (NDA only)

NA

D. Final Risk Assessment (see Attachment)

I. From Initial Risk Identification			Review Assessment		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations Comments
Assay (API), stability	Formulation Container closure ¹ Raw materials	L	Robust analytical method validated for assay; no trend on stability; levels remain within the proposed specification. Label claim will be delivered.	L	
Uniformity of Dose	Formulation Container closure ¹ (b) (4) Scale/equipment	M	Complies with USP <905>	L	
Related Substances	Formulation Raw material (b) (4) Container closure ¹	M	(b) (4) not more than (b) (4) %; (b) (4) not more than (b) (4) %; (b) (4) not more than (b) (4) %; Not identified single peaks: (b) (4) not more than (b) (4) %; Total not more than: (b) (4) %.	L	
Dissolution	Formulation (b) (4)	M	NMT (b) (4) % in 45 minutes. Acceptable by biopharmaceutics reviewer.	L	
Microbial limits	Formulation (b) (4) Container closure ¹	M	The proposed limits found acceptable by the quality micro reviewer.	L	

¹ Stability studies demonstrate container closure compatibility with the drug product for all quality attributes.

BIOPHARMACEUTICS

Product Background:

NDA: 210115 (505(b)(1))

Drug Product Name / Strength: Prograf (tacrolimus) granules for oral suspension, 0.2 and 1 mg

Route of Administration: Oral

Applicant Name: Astellas Pharma US, Inc.

Review Summary:

NDA 210115 is a granule formulation for oral suspension of tacrolimus, a calcineurin inhibitor immunosuppressant. The proposed strengths are 0.2 and 1 mg in individual packet. The Applicant, Astellas, also holds other approved tacrolimus product, i.e., Prograf[®] Capsules (NDA 50708), Prograf[®] Injection (NDA 50709) and Astagraf XL[®] Capsules (NDA 204096).

The Biopharmaceutics review is focused on the evaluation and acceptability of the proposed dissolution method and acceptance criterion and the evaluation of the need for formulation bridging.

Based on the provided dissolution data, the following dissolution methods and acceptance criteria are acceptable and agreed upon for single packet of the proposed drug product:

Acceptable Dissolution Methods and Acceptance Criteria					
Strength	USP Apparatus	Speed	Medium	Volume (mL)	Cumulative % of Drug Dissolved (Label Claim)
0.2 mg	II (Paddle)	50 RPM	Hydroxypropyl Cellulose Solution (1 g in 20,000 mL). Adjust to pH 4.5 by Phosphoric Acid	500	NLT ^(b) ₍₄₎ % (Q) in 45 minutes
1 mg				900	

The formulation of the commercial Prograf[®] (tacrolimus) granules for oral suspension is the same as the clinical batches, except for the manufacturing site and scale. The comparative dissolution profiles support the bridging between the clinical batches and the commercial product.

From the Biopharmaceutics perspective, NDA 210115 for tacrolimus granules for oral suspension, 0.2 and 1 mg is recommended for **APPROVAL**.

List of Submissions being reviewed:

Submissions Reviewed	Document Date
Original Submission	07/26/2017
IR Response	10/02/2017 and 1/4/2018

BCS Designation

Reviewer’s Assessment: The Sponsor did not request an official BCS designation.

Solubility: Tacrolimus is a lipophilic molecule, practically insoluble in water and hexane.

Permeability: Not provided

Drug Substance

The active pharmaceutical ingredient (API) for the proposed tacrolimus granules for oral suspension, 0.2 and 1 mg, is the same as the API in the Applicant’s approved Prograf® Capsules (NDA 50708, approved on April 8, 1994), Prograf® Injection (NDA 50709, approved on April 8, 1994) and Astagraf XL® Capsules (NDA 204096, approved on July 19, 2013).

Table 1. General Properties of Tacrolimus Drug Substance¹

Attribute	Results	
Appearance	White crystalline solid	
Specific Rotation $[\alpha]_D^{25}$	-111.4° to -113.8°	
Partition Coefficient (cLog P)	>1,000	
Solubility Profile	Methanol	Very soluble
	Chloroform	Very soluble
	Acetone	Very soluble or freely soluble
	N,N-Dimethylformamide	Freely soluble
	Acetonitrile	Freely soluble
	Ethanol (95%)	Freely soluble
	Ethyl ether	Soluble
	Water	Practically insoluble
Hexane	Practically insoluble	
Hygroscopicity	Not hygroscopic	
Melting Point (USP <741>)	124 to 132°C	
Polymorph	One crystalline form	

Formulation:

The unit dose composition and components of tacrolimus 0.2 mg and 1 mg granules as well as the function of the components and the quality standards are summarized in Table 2 below:

Table 2. Composition of Tacrolimus Granules 0.2 mg and 1 mg Granules

Name of Ingredients	Tacrolimus Granules 0.2 mg [mg/packet] ^{*3)}	Tacrolimus Granules 1 mg [mg/packet]	Rationale	Reference to Quality Standard
Tacrolimus ^{*1)}	0.2	1.0	Active ingredient	USP, US DMF#16833
Hypromellose				(b) (4) USP
Croscarmellose Sodium				NF
Lactose Monohydrate				NF
Total				-

*1): (b) (4)

(b) (4) Tacrolimus USP is used for the drug product, however, the specifications are the same as in the current DMF No. 16833.

*2): (b) (4)

*3): An overfill (b) (4) added to ensure the withdrawal of the labeled amount content of tacrolimus 0.2 mg from the packet.

¹ <\\cdsesub1\evsprod\nda210115\0004\m3\32-body-data\32s-drug-sub\tacrolimus-astellas\32s1-gen-info\3-2-s-1-3-general-properties-nov-2017.pdf>

Table 3 shows the composition of the intermediate granules (also named Solid Dispersion Formulation, abbreviated as SDF). The same SDF is currently used in the approved Prograf® capsules 0.5 mg, 1 mg and 5 mg (NDA 50708)².

Table 3. Composition of SDF and Tacrolimus 0.2 mg and 1 mg Granules in Packets

Name of Ingredients	SDF	Name of Ingredients	Tacrolimus 0.2 mg [mg/packet]	Tacrolimus 1 mg [mg/packet]
Tacrolimus ^{*1)}	(b) (4)	Intermediate Granules (SDF)	(b) (4)	(b) (4)
Hypromellose		Lactose Monohydrate		
Croscarmellose Sodium		Total		
Lactose Monohydrate				
Total				

*1):

(b) (4)

(b) (4)

6 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reviewer's Assessment:

Based on the provided information, the revised dissolution method is adequate for quality control for the proposed Tacrolimus Granules 0.2 and 1 mg. The selection of the dissolution conditions (e.g., apparatus, medium, rotation speed) were adequately justified. The dissolution method's discriminating power (b) (4) has been demonstrated.

Dissolution Acceptance Criterion:

The Applicant initially proposed a dissolution acceptance criterion of NLT (b) (4)% (Q) at (b) (4) minutes, and provided in the submission the statistical summary for the dissolution data only at the (b) (4) min time point.

Reviewer's Assessment:

The Applicant provided only the statistical summary for the dissolution data at (b) (4) min time point to supported the proposed acceptance criterion of $Q = \frac{(b) (4)}{(b) (4)}\%$ at (b) (4) min. However, based on the provided dissolution data in Tables 5, 7, 8, and 9 ([Appendix 1](#)) and Figures 4, 6, 7 and 8 ([Appendix 2](#)), a tighter dissolution acceptance criterion of $Q = \frac{(b) (4)}{(b) (4)}\%$ in 45 minutes was supported and was recommended in IR request dated December 15, 2017 ([Appendix 3](#)). In addition, the discrimination study suggests that the proposed dissolution method is discriminating (b) (4) through the 45 minutes, but not at (b) (4) minutes.

The Applicant accepted the recommended dissolution acceptance criterion in the IR response dated January 4, 2018 ([Appendix 3](#)).

Bridging of Formulations:

In the IR response dated October 2, 2017 ([Appendix 2](#)), the Applicant states that there is no difference in the manufacturing process between the clinical batches in studies (FG-506-01-13 and FG 506-01-08) and the proposed commercial product, except of the manufacturing site and scale (b) (4) and provided the comparative dissolution profiles between clinical batches and the commercial product (see Figure 8 in [Appendix 2](#)).

Reviewer's Assessment:

The comparative dissolution profiles support the bridging between the clinical and the commercial batches.

Biowaiver Request: N/A

No biowaiver is requested or required for this NDA.

R Regional Information

Comparability Protocols: None

Lifecycle Management Considerations: None

List of Deficiencies: None

Recommendations:

From the Biopharmaceutics perspective, NDA 210115 for tacrolimus granules for oral suspension, 0.2 and 1 mg is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer Name and Date: Zhuojun Zhao, Ph.D. 3/9/2018

I concur with Dr. Zhao's recommendation.

Secondary Reviewer Name and Date: Jing Li, Ph.D. 3/20/2018

(b) (4)



Appendix 2: IR Request Sent on September 19, 2017 and Response on October 2, 2017**FDA IR Comment:**

Clarify whether there is any difference in manufacturing site or process for the proposed drug product between the former Fujisawa Pharmaceutical Co. Ltd and the current manufacturer. Provide supportive data to bridge the clinical batches and the proposed commercial product if differences exist.

Response to IR 1:

Clinical batches as shown in Table 10 were manufactured by Fujisawa Pharmaceutical Co., Ltd at the Kashima plant located in Osaka, Japan, except for the bulk granule process for batches No. 701291K, 704989K, 701191K, and 705089K (used in Clinical Study No. FG-506-01-13). These clinical batches were manufactured by Fujisawa Pharmaceutical Co., Ltd at Toyama plant. There is no difference in the manufacturing process between the clinical batches and the proposed commercial product, except of the manufacturing site and scale (b) (4)⁷. Since commercial launch of the product in Japan in 2001, Tacrolimus granules have been manufactured at Toyama plant (former Fujisawa Pharmaceutical Co., Ltd. and current Astellas Pharma Tech Co., LTD.).

⁷ The proposed commercial production scale is (b) (4).

Table 12. Summary of Granule Drug Product Batch in Clinical Studies

Clinical Study Number	Drug Product Strength	Drug product Lot No.	Primary Packaging Lot No.	Bulk granules Lot No.	Manufacturing scale of bulk granules (b) (4)	Manufacturing site of bulk granules		
95-0-00 ¹	1 mg	702153K	206352K	205652K				
		FG-506-01-08 ²	0.2 mg	700361K			259950K	238257K
				700481K			200381K	26237XK
				705376K			225075K	205872K
				709867K			901750K	900258K
				71345XK			259950K	238257K
		1 mg	901850K	901850K			900358K	
			26926XK	26926XK			263360K	
			700381K	200481K			26237XK	
			700461K	260050K			238257K	
			702272K	204372K			200171K	
		FG-506-01-13 ³	0.2 mg	705276K			224575K	205772K
				705476K			224675K	205872K
				71335XK			260050K	238257K
902150K	902150K			900358K				
700481K	200381K			26237XK				
701291K	300291K			26267XK				
1 mg	704989K		324987K	26267XK				
	705376K		225075K	205872K				
	709867K		901750K	900258K				
	901850K		901850K	900358K				
	26926XK		26926XK	263360K				
	700381K		200481K	26237XK				
	701191K		300191K	26267XK				
	702272K		204372K	200171K				
705089K	324887K	26267XK						
705276K	224575K	205772K						
705476K	224675K	205872K						
706277K	26926XK	263360K						

1: Bioequivalence Study of Tacrolimus Granular and Capsule Formulations in Normal Healthy Volunteers.
 2: A two center clinical pilot study in children with tacrolimus (FK506) fine granule formulation as immunosuppressive therapy in liver allograft transplantation.
 3: An open, randomised, comparative, multicentre paediatric clinical trial comparing the efficacy and safety of a dual regimen with oral tacrolimus (FD506) Versus a triple regimen with oral cyclosporin-microemulsion in primary liver allograft transplantation.

Comparative dissolution profiles between clinical batches and proposed commercial product are shown in Figure 10. These data support the bridging of the clinical batches and the proposed commercial product.

(b) (4)



Appendix 3: IR Request Sent on December 15, 2017 and Response on January 4, 2018**FDA IR Comment:**

1. *Based on the provided dissolution data, the FDA recommends you use 1 packet of 0.2 mg Tacrolimus Granules per vessel for dissolution testing, as the intra-unit variability of the data obtained using 1 packet of 0.2 mg in 500 and 900 mL appears acceptable, and single-unit dissolution testing will allow for the evaluation of inter-unit variability. Provide an updated analytical procedure for dissolution with the revised sampling amount for your proposed Tacrolimus Granules, 0.2 mg.*
2. *Based on the submitted dissolution data, a dissolution acceptance criterion of NLT $\frac{(b)(4)}{(4)}\%$ (Q) in 45 minutes is recommended for your proposed drug product. Please note that the results of your $\frac{(b)(4)}{(4)}$ study provided in Section 3.2.P.2.2.3.2 also supports the discriminating ability of your proposed dissolution method at the recommended 45-minute time point.*

Be aware that setting of the dissolution acceptance criterion is based on stage 2 testing (n=12), and therefore sometimes stage 2 testing and occasional stage 3 testing may be needed.

3. *Provide an updated Specifications table for the Drug Product with the revised acceptance criterion for the dissolution test. Provide the dissolution data at the 45-min time point thereafter.*

Response to IR 1:

In accordance with the comment, Astellas adopts the dissolution procedure using 1 packet of tacrolimus 0.2 mg granules in 500 mL. Updated [\[Section 3.2.P.5.2\]](#) and [\[Section 3.2.P.5.3\]](#) are provided.

Reviewer Note:

The Applicant's response is satisfactory.

Response to IR 2:

In accordance with the comment, Astellas adopts a dissolution acceptance criterion of "NLT $\frac{(b)(4)}{(4)}\%$ (Q) in 45 minutes". Updated [\[Section 3.2.P.5.1\]](#), [\[Section 3.2.P.5.2\]](#), [\[Section 3.2.P.5.3\]](#) and [\[Section 3.2.P.5.6\]](#) are provided.

Reviewer Note:

The Applicant's response is satisfactory.

Response to IR 3:

Astellas is revising the dissolution specification and providing the respective update in [[Section 3.2.P.5.1](#)]. Astellas commits to generating and providing dissolution data that supports the revised specification (NLT ^(b)₍₄₎% (Q) at 45 minutes) in a future update to this request.

Reviewer Note:

The Applicant's response is satisfactory.



Zhuojun
Zhao

Digitally signed by Zhuojun Zhao

Date: 3/23/2018 11:55:49AM

GUID: 508da6fd000284770cf4eecbae074722



Jing
Li

Digitally signed by Jing Li

Date: 3/23/2018 12:40:01PM

GUID: 508da7420002bb05ac913303b23c39bb

6 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page