CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204096Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

MICROBIOLOGY/IMMUNOLOGY REVIEW
DIVISION OF TRANSPLANT AND OPTHALMOLOGY PRODUCTS
(Addendum)

NDA # 204096
(Original; SDN-001 and -039)

REVIEWER: Shukal Bala
REVIEW COMPLETE DATE: 07/17/2013

APPLICANT: Astellas Pharma US INC
1 Astellas Way
Northbrook, Illinois 60062

DRUG CATEGORY: Immunosuppressive agent

INDICATION: Prophylaxis of organ rejection in adult patients receiving kidney transplants

DOSAGE FORM: Capsules for oral administration

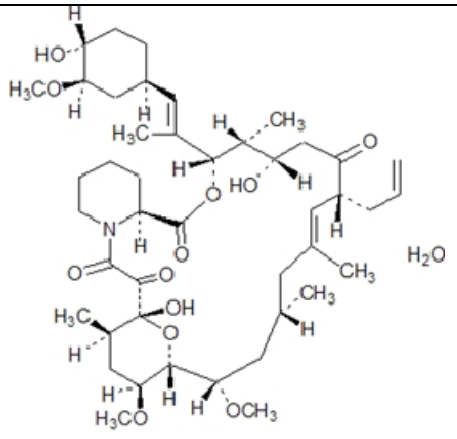
PRODUCT NAMES:

a. PROPRIETARY: ASTAGRAF XL (name requested)

b. NONPROPRIETARY: Tacrolimus; FK506

c. CHEMICAL: [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**, 26a*R**]] – 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 – methoxycyclo – hexyl) – 1 – methylethenyl] – 14, 16 – dimethoxy – 4, 10, 12, 18 – tetramethyl – 8 – (2 – propenyl) – 15, 19 – epoxy – 3H – pyrido[2, 1 – *c*][1, 4] oxaazacyclotricosine – 1, 7, 20, 21(4H, 23H) – tetrone, monohydrate.

STRUCTURAL FORMULA:



Molecular Weight: 822.03
Molecular Formula: $C_{44}H_{69}NO_{12}\bullet H_2O$

SUPPORTING DOCUMENTS: NDA 50-708

Introduction
The subject of this NDA is tacrolimus extended-release (ASTAGRAF XL) capsules, once daily, for the prophylaxis of organ rejection in adult patients receiving kidney transplants; the applicant has withdrawn the indication for prophylaxis of organ rejection in adult male patients receiving liver transplants. Immediate-release capsules of tacrolimus (Prograf®) are approved in the United States for prophylaxis of organ rejection in patients receiving allogeneic liver, kidney or heart transplants and require twice daily oral dosing.

A nonclinical study showing no significant differences in median skin allograft survival times between rats administered tacrolimus by daily intramuscular bolus injections (comparable with immediate release) and those receiving continuous intravenous infusion (sustained-release profile somewhat representative of the extended-release formulation), was reviewed previously (for details see Microbiology/Immunology review dated 5/10/2013).

The Labeling
Section 12.1 of the labeling summarizes “Mechanism of Action” of tacrolimus extended release which is same as that for immediate-release capsules of tacrolimus (Prograf®) and reads as follows:.

12.1 Mechanism of Action
Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. Experimental evidence suggests that tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin inhibited. This effect may prevent the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (such as interleukin-2, gamma interferon). The net result is the inhibition of T-lymphocyte activation (i.e., (b) (4)

(b) (4)

Comments:

- (b) (4)
-

(b) (4)

The applicant has agreed to the changes proposed by the Division.

Recommendations

With respect to Immunology/Microbiology, this NDA should be approved

Shukal Bala
Shukal Bala, Ph.D.
Microbiologist/Immunologist

CONCURRENCE:
Division Director/Dr Renata Albrecht
CC:
DTOP/NDA 204096
DTOP/PM/Jacquelyn Smith

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/s/

SHUKAL BALA
07/17/2013

RENATA ALBRECHT
07/17/2013

MICROBIOLOGY/IMMUNOLOGY REVIEW
DIVISION OF TRANSPLANT AND OPTHALMOLOGY PRODUCTS

NDA # 204096	**REVIEWER**	**:** Shukal Bala
(SDN-001; Original)	**CORRESPONDENCE DATE**	**:** 9/20/2012
	CDER RECEIPT DATE	**:** 9/21/2012
	REVIEW ASSIGN DATE	**:** 9/26/2012
	REVIEW COMPLETE DATE	**:** 05/10/2013

APPLICANT: Astellas Pharma US INC
1 Astellas Way
Northbrook, Illinois 60062

DRUG CATEGORY: Immunosuppressive agent

INDICATION: Prophylaxis of organ rejection in adult patients receiving kidney transplants

DOSAGE FORM: Capsules for oral administration

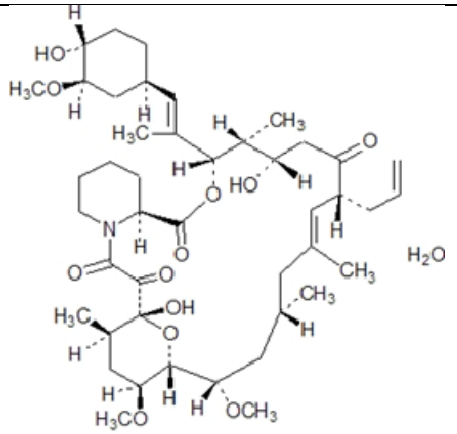
PRODUCT NAMES:

a. PROPRIETARY: ASTAGRAF XL (name requested)

b. NONPROPRIETARY: Tacrolimus; FK506

c. CHEMICAL: [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**, 26a*R**]] – 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 – methoxycyclo – hexyl) – 1 – methylethenyl] – 14, 16 – dimethoxy – 4, 10, 12, 18 – tetramethyl – 8 – (2 – propenyl) – 15, 19 – epoxy – 3H – pyrido[2, 1 – *c*][1, 4]oxaazacyclotricosine – 1, 7, 20, 21(4H, 23H) – tetrone, monohydrate.

STRUCTURAL FORMULA:



Molecular Weight: 822.03
Molecular Formula: $C_{44}H_{69}NO_{12}\cdot H_2O$

SUPPORTING DOCUMENTS: NDA 50-708

Introduction

The subject of this NDA is Advagraf® (tacrolimus) extended-release capsules, once daily, for the prophylaxis of organ rejection in adult patients receiving kidney transplants; the applicant has withdrawn the indication for prophylaxis of organ rejection in adult male patients receiving liver transplants. Immediate-release capsules of tacrolimus (Prograf®) are approved in the United States for prophylaxis of organ rejection in patients receiving allogeneic liver, kidney or heart transplants and require twice daily oral dosing.

Activity of tacrolimus

Tacrolimus is known to inhibit T-lymphocyte activation by tacrolimus binding to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin inhibited. This effect may prevent the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines such as interleukin-2, gamma interferon (for details see Prograf® package insert).

In this submission, the applicant included a study report (Report no. CRR980201) comparing the activity of bolus intramuscular administration and continuous intravenous infusion of tacrolimus on skin allograft rejection in rats; the study is summarized below:

The donor (Male Fisher rats) ear skin grafts were transplanted to the lateral thoraxes of the recipients (MHC-incompatible male WKAH rats), and the grafts were inspected daily until rejection, which was defined as more than 90% necrosis of the graft epithelium. Intramuscular administration of tacrolimus (injectable formulation; 0.01, 0.1, and 1 mg/kg) or placebo was performed once a day for 14 days from the grafting day. Continuous intravenous infusion of tacrolimus (powdered tacrolimus dissolved in propylene glycol containing hydrogenated castor oil-60 (HC0-60) and ethanol; 0.01, 0.1, 1 mg/kg/day) or placebo was performed for the same period by using the Alzet® mini-osmotic pumps, which were connected to femoral veins and implanted in abdominal subcutis. The mini-osmotic pumps were taken out of the animal on day 14. The pumps were pre-conditioned by placing in physiological saline at 37^{o}C for about 24 hours before the implantation.

The median survival time (MST) of rats in the placebo group, administered intramuscularly or by intravenous infusion was 5 and 6 days, respectively. Administration of tacrolimus either as intramuscular bolus injection (comparable with immediate release) or as continuous infusion (comparable with sustained-release) showed similar activity; tacrolimus dose of 1 mg/kg was most effective and improved graft survival in all animals compared to controls and those treated with lower doses of tacrolimus (Table 1).

Table 1: Effect of tacrolimus (FK506) on allograft skin survival in rats

	IM Dose		IV Dose	
	n	MST (days)	n	MST (days)
Control (placebo)	7	5	7	6
FK506 0.01 mg/kg	7	6	7	7
FK506 0.1 mg/kg	8	10	8	10*
FK506 1.0 mg/kg	8	20**	8	22**

a) Intermittent intramuscular administration

	n	Graft survival (days after transplantation)	MST (day)
Control	7	(5、5、5、5、6、6、6)	5
FK506 0.01mg/kg	7	(5、6、6、6、6、6、6)	6
0.1mg/kg	8	(7、7、8、10、10、10、10、10)	10
1.0mg/kg	8	(19、19、20、20、20、20、21、21)	20**

b) Continuous intravenous infusion

	n	Graft survival (days after transplantation)	MST (day)
Control	7	(5、6、6、6、6、6、6)	6
FK506 0.01mg/kg	7	(6、6、7、7、7、7、7)	7
0.1mg/kg	8	(10、10、10、10、10、10、12、12)	10*
1.0mg/kg	8	(17、20、21、22、22、22、22、22)	22**

MST: Median survival time in days after transplantation
* P < 0.05; ** P < 0.01 versus each control
Statistical significance was determined by Peto test.
Source: Study CRR980201

The applicant states that in other experiments, intramuscular administration of tacrolimus (1 mg/kg/day) produced the trough concentration of 5-10 ng/mL and the Cmax of about 60 ng/mL; continuous intravenous infusion (1 mg/kg/day) yielded the trough concentration of 25-35 ng/mL. The Cmax of intramuscular administration was about twice as much as that of continuous intravenous infusion and is almost equal to the trough concentration in the infusion. Therefore, the results suggest that the activity of tacrolimus as measured by prolongation of skin graft survival may depend on the total dose (AUC), and not on its Cmax. It is unclear whether the pharmacokinetic evaluations were performed in healthy volunteers or transplanted animals.

Comments:

- *The study shows no significant differences in median skin allograft survival times between rats administered tacrolimus by daily intramuscular bolus injections (comparable with immediate release) and those receiving continuous intravenous infusion (sustained-release profile somewhat representative of the extended-release formulation), at the dose tested. However, the Advagraf formulation was not tested.*

- *The results suggest that the activity of tacrolimus as measured by prolongation of skin graft survival may depend on the AUC levels and not on its Cmax.*

The Labeling
The applicant's version of the labeling:

12.1 Mechanism of Action
Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. Experimental evidence suggests that tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin inhibited. This effect may prevent the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (such as interleukin-2, gamma interferon). The net result is the inhibition of T-lymphocyte activation (i.e., immunosuppression).

(b) (4)

Comments:

- (b) (4)
-

Recommendations

This NDA should be approved with respect to Immunology/Microbiology.

Shukal Bala
Shukal Bala, Ph.D.
Microbiologist/Immunologist

CONCURRENCE:
Division Director/Dr Renata Albrecht

CC:
DTOP/NDA 204096
DTOP/PM/Jacquelyn Smith and Hyun Son

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/s/

SHUKAL BALA
05/10/2013

RENATA ALBRECHT
05/10/2013

Product Quality Microbiology Review

December 7, 2012

NDA: 204096

Drug Product Name
Proprietary: Advagraf
Non-proprietary: tacrolimus extended-release capsules

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
20 SEP 2012	21 SEP 2012	25 OCT 2012	27 OCT 2012

Applicant/Sponsor
Name: Astellas Pharma US, Inc.
Address: 1 Astellas Way, Northbrook, IL 60062
Representative: Glen W. Spears, Ph.D.
Telephone: 224-205-5935

Name of Reviewer: Erika Pfeiler, Ph.D.

Conclusion: Recommend Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: 505(b)(1)

2. SUBMISSION PROVIDES FOR: Initial marketing of a drug product

3. MANUFACTURING SITE:
Astellas Pharma Tech. Co., Ltd., Toyama Technology Center
2-178 Kojin-machi,
Toyama city,
Toyama 930-0809, Japan

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:
0.5 mg, 1 mg, and 5 mg solid oral capsules

5. METHOD(S) OF STERILIZATION: Drug product is nonsterile.

6. PHARMACOLOGICAL CATEGORY: Prophylaxis of organ rejection in adult patients receiving kidney transplants and in male patients receiving liver transplants.

B. SUPPORTING/RELATED DOCUMENTS: N/A

C. REMARKS: This application was submitted in the eCTD format.

filename: N204096R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommend approval on the basis of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – Drug product is a nonsterile oral dosage form with microbial limits.

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____
Erika Pfeiler, Ph.D.

B. Endorsement Block_____
Bryan Riley, Ph.D.
Microbiology Team Leader

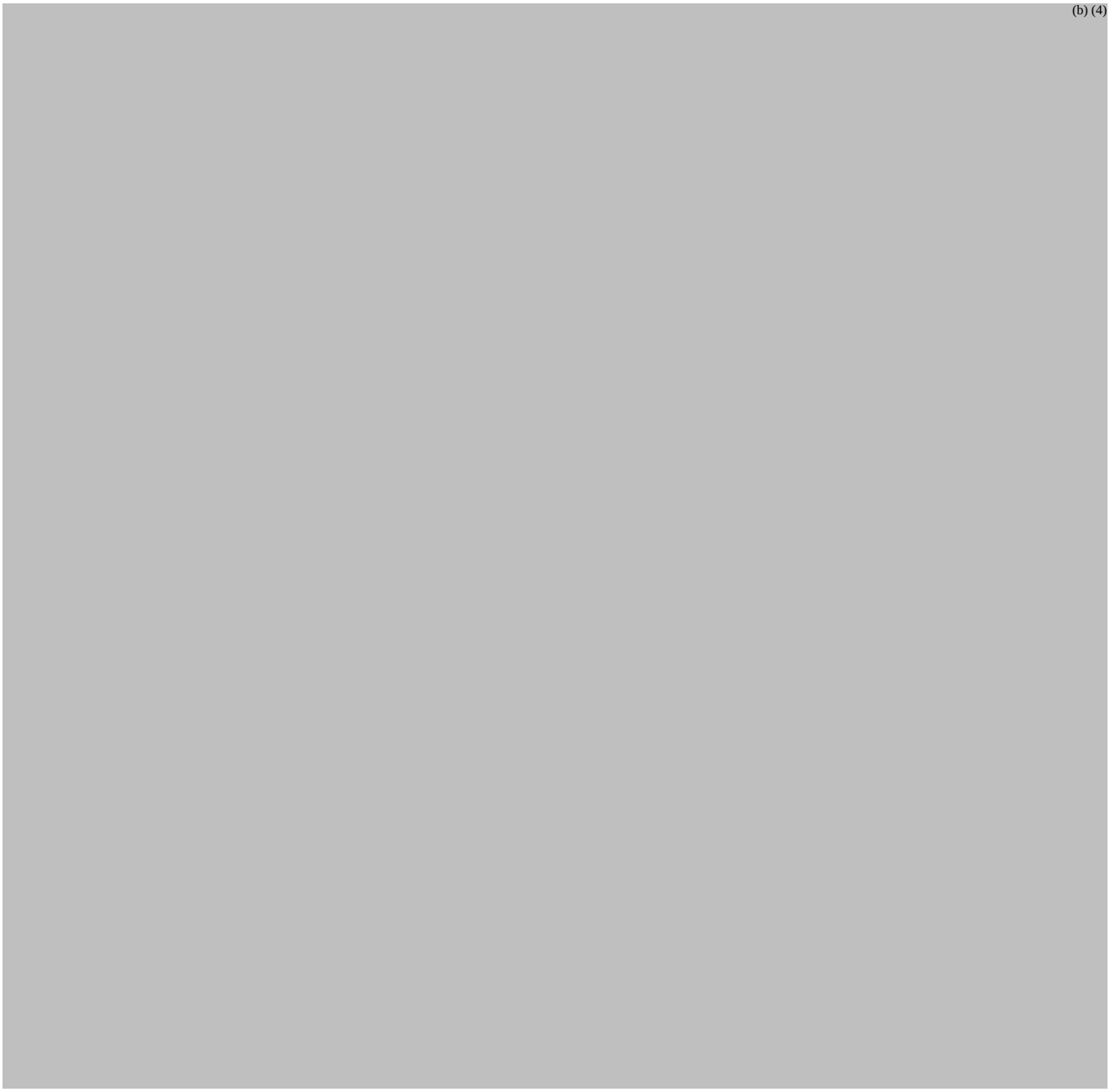
C. CC Block
N/A

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

P DRUG PRODUCT

(b) (4)



-Adequate-

-Adequate-

(b) (4)

-Adequate-

A APPENDICES

N/A

R REGIONAL INFORMATION

R.1 Executed Batch Record

The application contains executed batch records for one batch of 1 mg capsules, as well as for the drug substance (b) (4) process.

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT

N/A

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

N/A

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/s/

ERIKA A PFEILER
12/07/2012

BRYAN S RILEY
12/07/2012
I concur.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 204096 **Applicant:** Astellas **Letter Date:** 9/20/2012

Drug Name: Advagraf **NDA Type:** 505(b)(1) **Stamp Date:** 9/21/2012

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?			N/A, product is nonsterile with microbial limits.
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?			N/A, the submission is in English.
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?			N/A, the drug product is non-sterile.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		
7	Has the applicant submitted the results of analytical method verification studies?	X		
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			N/A
9	If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data?			N/A
10	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: Product is a non-sterile oral dosage form (tablet.)

Erika Pfeiler, Ph.D. Date

Bryan Riley, Ph.D. Date
Microbiology Team Leader

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/s/

ERIKA A PFEILER
11/19/2012

BRYAN S RILEY
11/19/2012
I concur.

IMMUNOLOGY/MICROBIOLOGY FILING CHECKLIST FOR NDA 204684

NDA Number: 204096 **Applicant:** Astellas Pharma US, Inc. **Stamp Date:** 9/21/ 2012

Drug Name: Tacrolimus extended release **NDA Type:** NME (1)

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comments
1	Is the immunology/microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA organized in a manner to allow substantive review to begin?	X		
2	Is the immunology/microbiology information (preclinical/nonclinical and clinical) indexed, paginated and/or linked in a manner to allow substantive review to begin?	X		
3	Is the immunology/microbiology information (preclinical/nonclinical and clinical) legible so that substantive review can begin?	X		
4	On its face, has the applicant submitted *in vitro* data in necessary quantity, using necessary clinical and non-clinical strains/isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?			N/A
5	Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?	X		
6	Has the applicant submitted all special/critical studies/data requested by the Division during pre-submission discussions?	X		
7	Has the applicant submitted the clinical microbiology datasets in a format which intents to correlate baseline pathogen with clinical and microbiologic outcome?			N/A
8	Has the applicant submitted draft/proposed interpretive criteria/breakpoint along with quality control (QC) parameters and interpretive criteria, if applicable, in a manner consistent with contemporary standards, which attempt to correlate criteria with clinical results of NDA/BLA studies, and in a manner to allow substantive review to begin?			N/A
9	Has the applicant submitted a clinical microbiology dataset in an appropriate/standardized format which intents to determine resistance development by correlating changes in the phenotype (such as *in vitro* susceptibility) and/or genotype (such as mutations) of the baseline pathogen with clinical and microbiologic outcome?			N/A

IMMUNOLOGY/MICROBIOLOGY FILING CHECKLIST FOR NDA 204684

	Content Parameter	Yes	No	Comments
10	Has the applicant used standardized or nonstandardized methods for measuring microbiologic outcome? If nonstandardized methods were used, has the applicant included complete details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?			N/A
11	Has the applicant submitted draft labeling consistent with current regulation, divisional and Center policy, and the design of the development package?	X		
12	Has the applicant submitted annotated immunology/microbiology draft labeling consistent with current divisional policy, and the design of the development package?	X		
13	Have all the study reports, published articles, and other references been included and cross-referenced in the annotated draft labeling or summary section of the submission?	X		
14	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	X		

IS THE MICROBIOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA is not fileable from the microbiology perspective, state the reasons and provide comments to be sent to the Applicant. N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None

Shukal Bala *11/5/12*

Reviewing Microbiologist Date

Renata Albrecht *11/5/12*

Division Director Date

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/s/

SHUKAL BALA
11/05/2012

RENATA ALBRECHT
11/05/2012