CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 65-461

Name: Tracolimus Capsules

Sponsor: Sandoz, Inc.

Approval Date: August 10, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-461

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Tentative Approval Letter	
Labeling	
Labeling Reviews	**X**
Medical Reviews	
Chemistry Reviews	**X**
Bioequivalence Reviews	**X**
Statistical Reviews	
Microbiology Reviews	
Administrative & Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-461

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 65-461

Sandoz Inc.
Attention: Srinivasa S. Rao,
Director, Regulatory Affairs
506 Carnegie Center
Suite 400
Princeton, NJ 08540

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 28, 2006, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Tacrolimus Capsules, 0.5 mg, 1 mg, and 5 mg.

Reference is also made to your amendments dated July 25, October 23, and December 31, 2007; January 4, March 7, June 20, June 27, July 21, August 8, August 25, October 21, and December 8, 2008; and January 30, February 25, and June 3, 2009.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Tacrolimus Capsules, 0.5 mg, 1 mg, and 5 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Prograf Capsules, 0.5 mg, 1 mg, and 5 mg, respectively, of Astellas Pharma US, Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

We note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Within 14 days of the date of this letter, submit updated content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the approved labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission as "***Miscellaneous Correspondence - SPL for Approved ANDA 65-461***".

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

GARY J BUEHLER
08/10/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-461

LABELING REVIEWS

APPROVAL SUMMARY #2
LABELING REVIEW BRANCH

1. APPLICANT INFORMATION:

ANDA Number	65-461
Date of Submission	03 June 2009
Applicant	Sandoz
Drug Name	Tacrolimus Capsules
Strength(s)	0.5 mg,1 mg, and 5 mg

LABELS AND LABELING SUMMARY-

Containers- 100s
Satisfactory in Jan. 4, 2008
\\Fdswa150\nonectd\N65461\N_000\2008-01-04\ Revised Tacrolimus 0.5 mg.pdf
\\Fdswa150\nonectd\N65461\N_000\2008-01-04\Revised Tacrolimus1 mg.pdf
Satisfactory in Oct. 23, 2007
\\Fdswa150\nonectd\N65461\N_000\2007-10-23\Container labels\Tacrolimus 5 mg 100s for FDA.pdf

Satisfactory in June 3, 2009
\\Fdswa150\nonectd\N65461\N_000\2009-06-03\Labels\Final printed labeling PI.pdf
Patient Leaflet- \\Fdswa150\nonectd\N65461\N_000\2009-06-03\Labels\FPL Patient information leaflet.pdf

2. NOTE TO CHEMIST: None

3. MODEL LABELING-This review was based on the labeling NDA- See below.

Reference Listed Drug

RLD on the 356(h) form	Prograf®
NDA Number	50-708
RLD established name	Tacrolimus Capsules 0.5 mg, 1 mg and 5 mg (equivalent to anhydrous)
Firm	Astellas
Currently approved PI	SE-8/S-027 ----------Patient leaflet S-026
AP Date	May 19, 2009

Note: This insert is a combined IV and PO insert. The generic will have only limited information regarding the IV dosage form in the labeling.

4. PATENTS/EXCLUSIVITIES: [Vol. A1.1 pg.] REFERENCE LISTED DRUG:

Patent Data For NDA 50-708

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None				PII	

Exclusivity Data - 50-708

Code/sup	Expiration	Use Code	Description		Labeling Impact
ODE	3-29-13		Prophylaxis of Organ Rejection in Patients Receiving Heart Transplants		Firm carved out information.

5. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM - Sandoz Private Limited – INDIA

6. INACTIVE INGREDIENTS

RLD 50-708 Prograf is available for oral administration as capsules (tacrolimus capsules) containing the equivalent of 0.5 mg, 1 mg or 5 mg of anhydrous tacrolimus. Inactive ingredients include lactose, (b) (4), croscarmellose sodium, and magnesium stearate. The 0.5 mg capsule shell contains gelatin, titanium dioxide and ferric oxide, the 1 mg capsule shell contains gelatin and titanium dioxide, and the 5 mg capsule shell contains gelatin, titanium dioxide and ferric oxide. Prograf is also available as a sterile solution (tacrolimus injection) containing the equivalent of 5 mg anhydrous tacrolimus in 1 mL for administration by intravenous infusion only. Each mL contains polyoxyl 60 hydrogenated castor oil (HCO-60), 200 mg, and dehydrated alcohol, USP, 80.0% v/v. Prograf injection must be diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection before use.
Tacrolimus, previously known as FK506,

ANDA 65-461- The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition. Tacrolimus capsules are available for oral administration containing the equivalent of 0.5 mg, 1 mg or 5 mg of anhydrous tacrolimus. In addition, each capsule contains the following inactive ingredients: croscarmellose sodium, hypromellose, lactose monohydrate, and magnesium stearate. The tacrolimus capsule shell for 0.5 mg strength consists of gelatin, titanium dioxide and yellow iron oxide. The tacrolimus capsule shell for 1 mg strength consists of black iron oxide, gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The tacrolimus capsule shell for 5 mg strength consists of red iron oxide, gelatin, and titanium dioxide. Tacrolimus capsules 0.5 mg, 1 mg and 5 mg are printed with edible black ink. The black ink is comprised of ammonia, black iron oxide, butyl alcohol, potassium hydroxide, propylene glycol, and shellac.

7. CONTAINER/CLOSURE

The containers are made of HDPE – the 100s have CRC caps.

8. PACKAGING CONFIGURATIONS
NDA: 100s (all three strengths) and Blister Packs of 100s 1 mg and 5 mg only]
ANDA: 100s

9. STORAGE AND DISPENSING STATEMENT
USP: not USP
NDA: Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).
ANDA: Store at 20° - 25°C (68° - 77°F) [see USP Controlled Room Temperature]. (b) (4).

10. The inactive ingredients in the DESCRIPTION section are the same as those listed in the Components and Composition statement.

11. FOR THE RECORD:

Review based on the labeling of Prograf® Capsules (Astellas- NDA 50-708/S-0), approved. The RLD has a shared insert with Prograf® Injection. Some of the information relating to the IV has been retained – see REVIEW NOTES below:

Some of the information relating to the IV has been retained as follows:

a. CLINICAL PHARMACOLOGY, (1) Pharmacokinetics table – leave in IV – (2) Excretion – leave in IV (65-461 was excluded- will need to revisit) (3) Special Populations – (a) Pediatric – leave in IV (change 65-461) – (b) Renal and Hepatic Insufficiency table – include IV

b. INDICATIONS AND USAGE- Delete sentence (relating to IV)

c. CONTRAINDICATIONS – Retain second sentence IV (need to revisit 65-461).

d. WARNINGS (1) Include the last two paragraph regarding the injection. It is important information.

f. DOSAGE AND ADMINISTRATION (1) Leave out IV dosing text (2) Retain "NOTE: Anaphylactic reactions….(See WARNINGS)" (3) Pediatric Patients – (a) Do include the

---

Date of Review: 6-09-09	Date of Submission: 03 JUN 2009
Primary Reviewer: Angela Payne	Date:
Team Leader: John Grace	Date:

---

cc: ANDA 65-461
DUP/DIVISION FILE
HFD-613/APayne/JGrace
V:\FIRMSNZ\SANDOZ\LTRS&REV\65461AP2labdfsreview.doc
Review

SANDOZ
Tacrolimus
Capsules
Rx only
XXXXXX

Tacrolimus Capsules

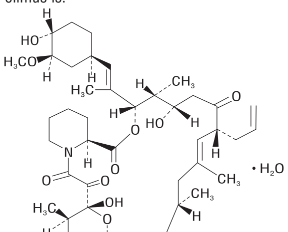
Rx Only

WARNING

Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe tacrolimus capsules. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

DESCRIPTION

Tacrolimus capsules are available for oral administration containing the equivalent of 0.5 mg, 1 mg or 5 mg of anhydrous tacrolimus. In addition, each capsule contains the following inactive ingredients: croscarmellose sodium, hypromellose, lactose monohydrate, and magnesium stearate.
The tacrolimus capsule shell for 0.5 mg strength consists of gelatin, titanium dioxide and yellow iron oxide.
The tacrolimus capsule shell for 1 mg strength consists of black iron oxide, gelatin, red iron oxide, titanium dioxide, and yellow iron oxide.
The tacrolimus capsule shell for 5 mg strength consists of red iron oxide, gelatin, and titanium dioxide.
Tacrolimus capsules 0.5 mg, 1 mg and 5 mg are printed with edible black ink. The black ink is comprised of ammonia, black iron oxide, butyl alcohol, potassium hydroxide, propylene glycol, and shellac.
Tacrolimus, previously known as FK506, is the active ingredient in tacrolimus capsules. Tacrolimus is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. Chemically, tacrolimus is designated as [3*S*-[3*R**[E(*1S*,3S*,4S**)],*4S*,5R*,8S*,9E,12R**,14*R**, *15S*,16R*,18S*,19S*,26aR**]]-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)-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate.
The chemical structure of tacrolimus is:



Tacrolimus has a molecular formula of $C_{44}H_{69}NO_{12}\cdot H_2O$ and a formula weight of 822.03. Tacrolimus appears as white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform.

CLINICAL PHARMACOLOGY

Mechanism of Action

Tacrolimus prolongs the survival of the host and transplanted graft in animal transplant models of liver, kidney, bone marrow, small bowel and pancreas, lung and trachea, skin, cornea, and limb.
In animals, tacrolimus has been demonstrated to suppress some humoral immunity and, to a greater extent, cell-mediated reactions such as allograft rejection, delayed type hypersensitivity, collagen-induced arthritis, experimental allergic encephalomyelitis, and graft versus host disease.
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).

Pharmacokinetics

Tacrolimus activity is primarily due to the parent drug. The pharmacokinetic parameters (mean±S.D.) of tacrolimus have been determined following intravenous (IV) and/or oral (PO) administration in healthy volunteers, and in kidney transplant, and liver transplant patients. (See table below.)

Population	N	Route (Dose)	Parameters					
			C_{max} (ng/mL)	T_{max} (hr)	AUC (ng•hr/mL)	$t_{1/2}$ (hr)	Cl (L/hr/kg)	V (L/kg)
Healthy Volunteers	8	IV (0.025 mg/kg/4hr)	*	*	598‡ ± 125	34.2 ± 7.7	0.04 ± 0.009	1.91 ± 0.31
	16	PO (5 mg)	29.7 ± 7.2	1.6 ± 0.7	243§ ±73	34.8 ± 11.4	0.041† ± 0.008	1.94† ± 0.53
Kidney Transplant Pts	26	IV (0.02 mg/kg/12hr)	*	*	294¶ ±262	18.8 ± 16.7	0.083 ± 0.05	1.41 ± 0.66
		PO (0.2 mg/kg/day)	19.2 ± 10.3	3	203¶ ± 42	#	#	#
		PO (0.3 mg/kg/day)	24.2 ± 15.8	1.5	288¶ ± 93	#	#	#
Liver Transplant Pts	17	IV (0.05 mg/kg/12hr)	*	*	3300¶ ± 2130	11.7 ± 3.9	0.053 ± 0.017	0.85 ± 0.30
		PO (0.3 mg/kg/day)	68.5 ± 30	2.3 ± 1.5	519¶ ± 179	#	#	#

* not applicable; †Corrected for individual bioavailability; ‡AUC_{0-120}; §AUC_{0-72}; ¶AUC_{0-inf}; # not available

Due to intersubject variability in tacrolimus pharmacokinetics, individualization of dosing regimen is necessary for optimal therapy. (See **DOSAGE AND ADMINISTRATION**). Pharmacokinetic data indicate that whole blood concentrations rather than plasma concentrations serve as the more appropriate sampling compartment to describe tacrolimus pharmacokinetics.

Absorption

Absorption of tacrolimus from the gastrointestinal tract after oral administration is incomplete and variable. The absolute bioavailability of tacrolimus was 17± 10% in adult kidney transplant patients (N=26), 22 ± 6% in adult liver transplant patients (N=17) and 18 ± 5% in healthy volunteers (N=16).
A single dose study conducted in 32 healthy volunteers established the bioequivalence of the 1 mg and 5 mg capsules. Another single dose study in 32 healthy volunteers established the bioequivalence of the 0.5 mg and 1 mg capsules. Tacrolimus maximum blood concentrations (C_{max}) and area under the curve (AUC) appeared to increase in a dose-proportional fashion in 18 fasted healthy volunteers receiving a single oral dose of 3, 7, and 10 mg.
In 18 kidney transplant patients, tacrolimus trough concentrations from 3 to 30 ng/mL measured at 10 to 12 hours post-dose (C_{min}) correlated well with the AUC (correlation coefficient 0.93). In 24 liver transplant patients over a concentration range of 10 to 60 ng/mL, the correlation coefficient was 0.94.

Food Effects

The rate and extent of tacrolimus absorption were greatest under fasted conditions. The presence and composition of food decreased both the rate and extent of tacrolimus absorption when administered to 15 healthy volunteers.
The effect was most pronounced with a high-fat meal (848 kcal, 46% fat): mean AUC and C_{max} were decreased 37% and 77%, respectively; T_{max} was lengthened 5-fold. A high-carbohydrate meal (668 kcal, 85% carbohydrate) decreased mean AUC and mean C_{max} by 28% and 65%, respectively.
In healthy volunteers (N=16), the time of the meal also affected tacrolimus bioavailability. When given immediately following the meal, mean C_{max} was reduced 71%, and mean AUC was reduced 39%, relative to the fasted condition. When administered 1.5 hours following the meal, mean C_{max} was reduced 63%, and mean AUC was reduced 39%, relative to the fasted condition.
In 11 liver transplant patients, tacrolimus capsules administered 15 minutes after a high fat (400 kcal, 34% fat) breakfast, resulted in decreased AUC (27 ± 18%) and C_{max} (50 ± 19%), as compared to a fasted state.

Distribution

The plasma protein binding of tacrolimus is approximately 99% and is independent of concentration over a range of 5-50 ng/mL. Tacrolimus is bound mainly to albumin and alpha-1-acid glycoprotein, and has a high level of association with erythrocytes. The distribution of tacrolimus between whole blood and plasma depends on several factors, such as hematocrit, temperature at the time of plasma separation, drug concentration, and plasma protein concentration. In a U.S. study, the ratio of whole blood concentration to plasma concentration averaged 35 (range 12 to 67).

Metabolism

Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily the cytochrome P-450 system (CYP3A). A metabolic pathway leading to the formation of 8 possible metabolites has been proposed. Demethylation and hydroxylation were identified as the primary mechanisms of biotransformation *in vitro*. The major metabolite identified in incubations with human liver microsomes is 13-demethyl tacrolimus. In *in vitro* studies, a 31-demethyl metabolite has been reported to have the same activity as tacrolimus.

Excretion

The mean clearance following IV administration of tacrolimus is 0.040, 0.083, and 0.053, in healthy volunteers, adult kidney transplant patients, adult liver transplant patients, respectively. In man, less than 1% of the dose administered is excreted unchanged in urine.
In a mass balance study of IV administered radiolabeled tacrolimus to 6 healthy volunteers, the mean recovery of radiolabel was 77.8±12.7%. Fecal elimination accounted for 92.4±1% and the elimination half-life based on radioactivity was 48.1±15.9 hours whereas it was 43.5±11.6 hours based on tacrolimus concentrations. The mean clearance of radiolabel was 0.029±0.015 L/hr/kg and clearance of tacrolimus was 0.029±0.009 L/hr/kg. When administered PO, the mean recovery of the radiolabel was 94.9±30.7%. Fecal elimination accounted for 92.6±30.7%, urinary elimination accounted for 2.3±1.1% and the elimination half-life based on radioactivity was 31.9±10.5 hours whereas it was 48.4± 12.3 hours based on tacrolimus concentrations. The mean clearance of radiolabel was 0.226±0.116 L/hr/kg and clearance of tacrolimus 0.172± 0.088 L/hr/kg.

Special Populations

Pediatric

Pharmacokinetics of tacrolimus have been studied in liver transplantation patients, 0.7 to 13.2 years of age. Following oral administration to 9 patients, mean AUC and C_{max} were 337 ± 167 ng±hr/mL and 48.4 ± 27.9 ng/mL, respectively. The absolute bioavailability was 31 ± 24%.
Whole blood trough concentrations from 31 patients less than 12 years old showed that pediatric patients needed higher doses than adults to achieve similar tacrolimus trough concentrations. (See **DOSAGE AND ADMINISTRATION**).

Renal and Hepatic Insufficiency

The mean pharmacokinetic parameters for tacrolimus following single administrations to patients with renal and hepatic impairment are given in the following table.

Population (No. of Patients)	Dose	AUC_{0-t} (ng·hr/mL)	$t_{½}$ (hr)	V (L/kg)	Cl (L/hr/kg)
Renal Impairment (n=12)	0.02 mg/kg/4hr IV	393 ± 123 (t = 60 hr)	26.3 ± 9.2	1.07 ±0.20	0.038 ± 0.014
Mild Hepatic Impairment (n=6)	0.02 mg/kg/4hr IV	367 ± 107 (t = 72 hr)	60.6 ± 43.8 Range: 27.8-141	3.1±1.6	0.042 ± 0.02
	7.7 mg PO	488 ± 320 (t = 72 hr)	66.1 ± 44.8 Range: 29.5-138	3.7 ± 4.7*	0.034 ± 0.019*
Severe Hepatic Impairment (n=6, IV)	0.02 mg/kg/4hr IV (n=2)	762 ± 204 (t = 120 hr)	198 ± 158 Range: 81-436	3.9 ± 1	0.017 ± 0.013
(n=5, PO)†	0.01 mg/kg/8hr IV (n=4) 8 mg PO (n=1)	289 ± 117 (t = 144 hr) 658 (t =120 hr)	119 ± 35 Range: 85-178	3.1 ± 3.4*	0.016 ± 0.011*
	5 mg PO (n=4) 4 mg PO (n=1)	533 ± 156 (t = 144 hr)			

*corrected for bioavailability; †1 patient did not receive the PO dose

Renal Insufficiency

Tacrolimus pharmacokinetics following a single IV administration were determined in 12 patients (7 not on dialysis and 5 on dialysis, serum creatinine of 3.9 ± 1.6 and 12 ± 2.4 mg/dL, respectively) prior to their kidney transplant. The pharmacokinetic parameters obtained were similar for both groups.
The mean clearance of tacrolimus in patients with renal dysfunction was similar to that in normal volunteers (see previous table).

Hepatic Insufficiency

Tacrolimus pharmacokinetics have been determined in six patients with mild hepatic dysfunction (mean Pugh score: 6.2) following single IV and oral administrations. The mean clearance of tacrolimus in patients with mild hepatic dysfunction was not substantially different from that in normal volunteers (see previous table). Tacrolimus pharmacokinetics were studied in 6 patients with severe hepatic dysfunction (mean Pugh score: >10). The mean clearance was substantially lower in patients with severe hepatic dysfunction, irrespective of the route of administration.

Race

A formal study to evaluate the pharmacokinetic disposition of tacrolimus in Black transplant patients has not been conducted. However, a retrospective comparison of Black and Caucasian kidney transplant patients indicated that Black patients required higher tacrolimus doses to attain similar trough concentrations. (See **DOSAGE AND ADMINISTRATION**).

Gender

A formal study to evaluate the effect of gender on tacrolimus pharmacokinetics has not been conducted, however, there was no difference in dosing by gender in the kidney transplant trial. A retrospective comparison of pharmacokinetics in healthy volunteers, and in kidney and liver transplant patients indicated no gender-based differences.

CLINICAL STUDIES

Liver Transplantation

The safety and efficacy of tacrolimus-based immunosuppression following orthotopic liver transplantation were assessed in two prospective, randomized, non-blinded multicenter studies. The active control groups were treated with a cyclosporine-based immunosuppressive regimen. Both studies used concomitant adrenal corticosteroids as part of the immunosuppressive regimens. These studies were designed to evaluate whether the two regimens were therapeutically equivalent, with patient and graft survival at 12 months following transplantation as the primary endpoints. The tacrolimus-based immunosuppressive regimen was found to be equivalent to the cyclosporine-based immunosuppressive regimens.
In one trial, 529 patients were enrolled at 12 clinical sites in the United States; prior to surgery, 263 were randomized to the tacrolimus-based immunosuppressive regimen and 266 to a cyclosporine-based immunosuppressive regimen (CBIR). In 10 of the 12 sites, the same CBIR protocol was used, while 2 sites used different control protocols. This trial excluded patients with renal dysfunction, fulminant hepatic failure with Stage IV encephalopathy, and cancers; pediatric patients (≤ 12 years old) were allowed.
In the second trial, 545 patients were enrolled at 8 clinical sites in Europe; prior to surgery, 270 were randomized to the tacrolimus-based immunosuppressive regimen and 275 to CBIR. In this study, each center used its local standard CBIR protocol in the active-control arm. This trial excluded pediatric patients, but did allow enrollment of subjects with renal dysfunction, fulminant hepatic failure in Stage IV encephalopathy, and cancers other than primary hepatic with metastases.
One-year patient survival and graft survival in the tacrolimus -based treatment groups were equivalent to those in the CBIR treatment groups in both studies. The overall 1-year patient survival (CBIR and tacrolimus-based treatment groups combined) was 88% in the U.S. study and 78% in the European study. The overall 1-year graft survival (CBIR and tacrolimus-based treatment groups combined) was 81% in the U.S. study and 73% in the European study. In both studies, the median time to convert from IV to oral tacrolimus capsules dosing was 2 days.
Because of the nature of the study design, comparisons of differences in secondary endpoints, such as incidence of acute rejection, refractory rejection or use of OKT3 for steroid-resistant rejection, could not be reliably made.

Kidney Transplantation

Tacrolimus/azathioprine

Tacrolimus-based immunosuppression in conjunction with azathioprine and corticosteroids following kidney transplantation was assessed in a Phase 3 randomized, multicenter, non-blinded, prospective study. There were 412 kidney transplant patients enrolled at 19 clinical sites in the United States. Study therapy was initiated when renal function was stable as indicated by a serum creatinine ≤ 4 mg/dL (median of 4 days after transplantation, range 1 to 14 days). Patients less than 6 years of age were excluded.
There were 205 patients randomized to tacrolimus-based immunosuppression and 207 patients were randomized to cyclosporine-based immunosuppression. All patients received prophylactic induction therapy consisting of an antilymphocyte antibody preparation, corticosteroids and azathioprine. Overall 1 year patient and graft survival was 96.1% and 89.6%, respectively and was equivalent between treatment arms.
Because of the nature of the study design, comparisons of differences in secondary endpoints, such as incidence of acute rejection, refractory rejection or use of OKT3 for steroid-resistant rejection, could not be reliably made.

Tacrolimus/mycophenolate mofetil(MMF)

Tacrolimus-based immunosuppression in conjunction with MMF, corticosteroids, and induction has been studied. In a randomized, open-label, multi-center trial (Study 1), 1589 kidney transplant patients received tacrolimus (Group C, n=401), sirolimus (Group D, n=399), or one of two cyclosporine regimens (Group A, n=390 and Group B, n=399) in combination with MMF and corticosteroids; all patients, except those in one of the two cyclosporine groups, also received induction with daclizumab. The study was conducted outside the United States; the study population was 93% Caucasian. In this study, mortality at 12 months in patients receiving tacrolimus/MMF was similar (2.7%) compared to patients receiving cyclosporine/MMF (3.3% and 1.8%) or sirolimus/MMF (3 %). Patients in the tacrolimus group exhibited higher estimated creatinine clearance rates (eCL_{cr}) using the Cockcroft-Gault formula **(Table 1)** and experienced fewer efficacy failures, defined as biopsy proven acute rejection (BPAR), graft loss, death, and/or lost to follow-up **(Table 2)** in comparison to each of the other three groups. Patients randomized to tacrolimus/MMF were more likely to develop diarrhea and diabetes after the transplantation and experienced similar rates of infections compared to patients randomized to either cyclosporine/MMF regimen (see **ADVERSE REACTIONS**).

Table 1: Estimated Creatinine Clearance at 12 Months in Study 1

Group	eCLcr [mL/min] at Month 12[a]				
	N	MEAN	SD	MEDIAN	Treatment Difference with Group C (99.2%CI[b])
(A) CsA/MMF/CS	390	56.5	25.8	56.9	-8.6 (-13.7,-3.7)
(B) CsA/MMF/CS/Daclizumab	399	58.9	25.6	60.9	-6.2 (-11.2,-1.2)
(C) Tac/MMF/CS/Daclizumab	401	65.1	27.4	66.2	-
(D) Siro/MMF/CS/Daclizumab	399	56.2	27.4	57.3	-8.9 (-14.1, -3.9)
Total	1589	59.2	26.8	60.5	

Key: CsA=Cyclosporine, CS=Corticosteroids, Tac=Tacrolimus, Siro=Sirolimus
a) All death/graft loss (n=41,27, 23 and 42 in Groups A, B, C and D) and patients whose last recorded creatinine values were prior to month 3 visit (n=10, 9, 7 and 9 in Groups A, B, C and D) were inputed with GFR of 10 mL/min; a subject's last observed creatinine value from month 3 on was used for the remainder of subjects with missing creatinine at month 12 (n=11, 12, 15 and 19 for Groups A, B, C and D). Weight was also imputed in the calculation of estimated GFR, if missing
b) Adjusted for multiple (6) pairwise comparisons using Bonferroni corrections.

Table 2: Incidence of BPAR, Graft Loss, Death or Loss to Follow-up at 12 Months in Study 1

	A	B	C	D
	N=390	N=399	N=401	N=399
Overall Failure	141 (36.2%)	126(31.6%)	82 (20.4%)	185 (46.4%)
Components of efficacy failure				
BPAR	113(29%)	106 (26.6%)	60 (15%)	152(38.1%)
Graft loss excluding death	28 (7.2%)	20 (5%)	12 (3%)	30 (7.5%)
Mortality	13 (3.3%)	7(1.8%)	11(2.7%)	12 (3%)
Lost to follow-up	5(1.3%)	7(1.8%)	5 (1.3%)	6(1.5%)
Treatment Difference of efficacy failure compared to Group C (99.2% CI[a])	15.8% (7.1%, 24.3%)	11.2% (2.7%, 19.5%)	-	26% (17.2%, 34.7%)

Group A =CsA/MMF/CS, B =CsA/MMF/CS/Daclizumab, C=Tac/MMF/CS/Daclizumab, and D=Siro/MMF/CS/Daclizumab
a) Adjusted for multiple (6) pairwise comparisons using Bonferroni corrections.

The protocol-specified target tacrolimus trough concentrations (C_{trough},Tac) were 3-7 ng/mL; however, the observed median $C_{troughs}$,Tac approximated 7 ng/mL throughout the 12 month study **(Table 3)**.

Table 3: Tacrolimus Whole Blood Trough Concentrations (Study 1)

Time	Median (P10-P90 [a]) tacrolimus whole blood trough concentrations (ng/mL)
Day 30 (N=366)	6.9 (4.4-11.3)
Day90 (N=351)	6.8 (4.1-10.7)
Day 180 (N=355)	6.5 (4 - 9.6)
Day 365 (N=346)	6.5 (3.8 -10)

a) Range of C_{trough}, Tac that excludes lowest 10% and highest 10% of C_{trough}, Tac

The protocol-specified target cyclosporine trough concentrations (C_{trough},CsA) for Group B were 50-100 ng/mL; however, the observed median C_{trougs}, CsA approximated 100 ng/mL throughout the 12 month study. The protocol-specified target C_{trougs},CsA for Group A were 150-300 ng/mL for the first 3 months and 100-200 ng/mL from month 4 to month 12; the observed median C_{trougs}, CsA approximated 225 ng/mL for the first 3 months and 140 ng/mL from month 4 to month 12.
While patients in all groups started MMF at 1g BID, the MMF dose was reduced to <2 g/day in 63% of patients in the tacrolimus treatment arm by month 12 **(Table 4)**; approximately 50% of these MMF dose reductions were due to adverse events. By comparison, the MMF dose was reduced to <2 g/day in 49% and 45% of patients in the two cyclosporine arms (Group A and Group B, respectively), by month 12 and approximately 40% of MMF dose reductions were due to adverse events.

Table 4: MMF Dose Over Time in tacrolimus/MMF (Group C) (Study 1)

Time period (Days)	Time-averaged MMF dose (g/day)[a]		
	<2	2	>2
0-30 (N=364)	37%	60%	2%
0-90 (N=373)	47%	51%	2%
0-180 (N=377)	56%	42%	2%
0-365 (N=380)	63%	36%	1%

Time-averaged MMF dose = (total MMF dose)/(duration of treatment)
a) Percentage of patients for each time-averaged MMF dose range during various treatment periods. Two g/day of time-averaged MMF dose means that MMF dose was not reduced in those patients during the treatment periods.

In a second randomized, open-label, multi-center trial (Study 2), 424 kidney transplant patients received tacrolimus (n=212) or cyclosporine (n=212) in combination with MMF 1 gram BID, basiliximab induction, and corticosteroids. In this study, the rate for the combined endpoint of biopsy proven acute rejection, graft failure, death, and/or lost to follow-up at 12 months in the tacrolimus/MMF group was similar to the rate in the cyclosporine/MMF group. There was, however, an imbalance in mortality at 12 months in those patients receiving tacrolimus/MMF (4.2%) compared to those receiving cyclosporine/MMF (2.4%), including cases attributed to overimmunosuppression **(Table 5)**.

Table 5: Incidence of BPAR, Graft Loss, Death or Loss to Follow-up at 12 Months in Study 2

	Tacrolimus/MMF (n=212)	Cyclosporine/MMF (n=212)
Overall Failure	32(15.1%)	36 (17%)
Components of efficacy failure		
BPAR	16 (7.5%)	29 (13.7%)
Graft loss excluding death	6 (2.8%)	4(1.9%)
Mortality	9 (4.2%)	5 (2.4%)
Lost to follow-up	4(1.9%)	1 (0.5%)
Treatment Difference of efficacy failure compared to tacrolimus/MMF group (95% CI[a])	-	1.9% (-5.2%, 9%)

a) 95% confidence interval calculated using Fisher's Exact Test

The protocol-specified target tacrolimus whole blood trough concentrations (C_{trough},Tac) in Study 2 were 7-16 ng/mL for the first three months and 5-15 ng/mL thereafter. The observed median $C_{troughs}$,Tac approximated 10 ng/mL during the first three months and 8 ng/mL from month 4 to month 12 **(Table 6)**.

Table 6: Tacrolimus Whole Blood Trough Concentrations (Study 2)

Time	Median (P10-P90[a]) tacrolimus whole blood trough concentrations ng/mL
Day 30 (N=174)	10.5 (6.3 -16.8)
Day 60 (N=179)	9.2(5.9-15.3)
Day 120 (N=176)	8.3 (4.6 -13.3)
Day 180(N=171)	7.8 (5.5 -13.2)
Day 365 (N=178)	7.1(4.2-12.4)

a) Range of $C_{troughs}$, Tac that excludes lowest 10% and highest 10% of $C_{troughs}$ Tac

The protocol-specified target cyclosporine whole blood concentrations (C_{trough},CsA) were 125 to 400 ng/mL for the first three months, and 100 to 300 ng/mL thereafter. The observed median Ctroughs, CsA approximated 280 ng/mL during the first three months and 190 ng/mL from month 4 to month 12.
Patients in both groups started MMF at 1g BID. The MMF dose was reduced to <2 g/day by month 12 in 62% of patients in the tacrolimus/MMF group **(Table 7)** and in 47% of patients in the cyclosporine/MMF group. Approximately 63% and 55% of these MMF dose reductions were because of adverse events in the tacrolimus/MMF group and the cyclosporine/MMF group, respectively.

Table 7: MMF Dose Over Time in the tacrolimus/MMF group (Study 2)

Time period (Days)	Time-averaged MMF dose (g/day)[a]		
	<2	2	>2
0-30(N=212)	25%	69%	6%
0-90 (N=212)	41%	53%	6%
0-180 (N=212)	52%	41%	7%
0-365 (N=212)	62%	34%	4%

Time-averaged MMF dose=(total MMF dose)/(duration of treatment)
a) Percentage of patients for each time-averaged MMF dose range during various treatment periods. Two g/day of time-averaged MMF dose means that MMF dose was not reduced in those patients during the treatment periods.

INDICATIONS AND USAGE

Tacrolimus capsules are indicated for the prophylaxis of organ rejection in patients receiving allogeneic liver, or kidney transplants. It is recommended that tacrolimus be used concomitantly with adrenal corticosteroids. In kidney transplant recipients, it is recommended that tacrolimus be used in conjunction with azathioprine or mycophenolate mofetil (MMF). The safety and efficacy of the use of tacrolimus with sirolimus has not been established (see **CLINICAL STUDIES**).

CONTRAINDICATIONS

Tacrolimus capsules are contraindicated in patients with a hypersensitivity to tacrolimus.

WARNINGS

(See boxed **WARNING**.)

Post-Transplant Diabetes Mellitus

Insulin-dependent post-transplant diabetes mellitus (PTDM) was reported in 20% of tacrolimus-treated kidney transplant patients without pretransplant history of diabetes mellitus in the Phase III study (See Tables Below). The median time to onset of PTDM was 68 days. Insulin dependence was reversible in 15% of these PTDM patients at one year and in 50% at 2 years post transplant. Black and Hispanic kidney transplant patients were at an increased risk of development of PTDM.

Incidence of Post Transplant Diabetes Mellitus and Insulin Use at 2 Years in Kidney Transplant Recipients in the Phase III study

Status of PTDM*	Tacrolimus	CBIR
Patients without pretransplant history of diabetes mellitus.	151	151
New onset PTDM*, 1st Year	30/151 (20%)	6/151 (4%)
Still insulin dependent at one year in those without prior history of diabetes.	25/151 (17%)	5/151 (3%)
New onset PTDM* post 1 year	1	0
Patients with PTDM* at 2 years	16/151 (11%)	5/151 (3%)

* use of insulin for 30 or more consecutive days, with <5 day gap, without a prior history of insulin dependent diabetes mellitus or non insulin dependent diabetes mellitus.

Development of Post Transplant Diabetes Mellitus by Race and by Treatment Group during First Year Post Kidney Transplantation in the Phase III study

Patient Race	Tacrolimus		CBIR	
	No. of Patients at Risk	Patients Who Developed PTDM*	No. of Patients At Risk	Patients Who Developed PTDM*
Black	41	15 (37%)	36	3 (8%)
Hispanic	17	5 (29%)	18	1 (6%)
Caucasian	82	10 (12%)	87	1 (1%)
Other	11	0 (0%)	10	1 (10%)
Total	151	30 (20%)	151	6 (4%)

*use of insulin for 30 or more consecutive days, with <5 day gap, without a prior history of insulin dependent diabetes mellitus or non insulin dependent diabetes mellitus.

Insulin-dependent post-transplant diabetes mellitus was reported in 18% and 11% of tacrolimus-treated liver transplant patients and was reversible in 45% and 31% of these patients at 1 year post transplant, in the U.S. and European randomized studies, respectively (See Table below). Hyperglycemia was associated with the use of tacrolimus in 47% and 33% of liver transplant recipients in the U.S. and European randomized studies, respectively, and may require treatment (see **ADVERSE REACTIONS**)

Incidence of Post Transplant Diabetes Mellitus and Insulin Use at 1 Year in Liver Transplant Recipients

Status of PTDM*	U.S. Study		European Study	
	Tacrolimus	CBIR	Tacrolimus	CBIR
Patients at risk**	239	236	239	249
New Onset PTDM*	42(18%)	30(13%)	26(11%)	12(5%)
Patients still on insulin at 1 year	23(10%)	19(8%)	18(8%)	6 (2%)

* use of insulin for 30 or more consecutive days, with < 5 day gap, without a prior history of insulin dependent diabetes mellitus or non insulin dependent diabetes mellitus
** Patients without pretransplant history of diabetes mellitus

Nephrotoxicity

Tacrolimus can cause nephrotoxicity, particularly when used in high doses. Nephrotoxicity was reported in approximately 52% of kidney transplantation patients and in 40% and 36% of liver transplantation patients receiving tacrolimus in the U.S. and European randomized trials, respectively (see **ADVERSE REACTIONS**). More overt nephrotoxicity is seen early after transplantation, characterized by increasing serum creatinine and a decrease in urine output. Patients with impaired renal function should be monitored closely as the dosage of tacrolimus may need to be reduced. In patients with persistent elevations of serum creatinine who are unresponsive to dosage adjustments, consideration should be given to changing to another immunosuppressive therapy. Care should be taken in using tacrolimus with other nephrotoxic drugs. **In particular, to avoid excess nephrotoxicity, tacrolimus should not be used simultaneously with cyclosporine. tacrolimus or cyclosporine should be discontinued at least 24 hours prior to initiating the other. In the presence of elevated tacrolimus or cyclosporine concentrations, dosing with the other drug usually should be further delayed.**

Hyperkalemia

Mild to severe hyperkalemia was reported in 31% of kidney transplant recipients and in 45% and 13% of liver transplant recipients treated with tacrolimus capsules in the U.S. and European randomized trials, respectively, and may require treatment (see **ADVERSE REACTIONS**). **Serum potassium levels should be monitored and potassium-sparing diuretics should not be used during tacrolimus capsules therapy** (see **PRECAUTIONS**).

Neurotoxicity

Tacrolimus capsules can cause neurotoxicity, particularly when used in high doses. Neurotoxicity, including tremor, headache, and other changes in motor function, mental status, and sensory function were reported in approximately 55% of liver transplant recipients in the two randomized studies. Tremor occurred more often in tacrolimus capsules-treated kidney transplant patients (54%) compared to cyclosporine-treated patients. The incidence of other neurological events in kidney transplant patients was similar in the two treatment groups (see **ADVERSE REACTIONS**). Tremor and headache have been associated with high whole-blood concentrations of tacrolimus and may respond to dosage adjustment. Seizures have occurred in adult and pediatric patients receiving tacrolimus capsules (see **ADVERSE REACTIONS**). Coma and delirium also have been associated with high plasma concentrations of tacrolimus.
Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES). Symptoms indicating PRES include headache, altered mental status, seizures, visual disturbances and hypertension. Diagnosis may be confirmed by radiological procedure. If PRES is suspected or diagnosed, blood pressure control should be maintained and immediate reduction of immunosuppression is advised. This syndrome is characterized by reversal of symptoms upon reduction or discontinuation of immunosuppression.

Malignancy and Lymphoproliferative Disorders

As in patients receiving other immunosuppressants, patients receiving tacrolimus capsules are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. A lymphoproliferative disorder (LPD) related to Epstein-Barr Virus (EBV) infection has been reported in immunosuppressed organ transplant recipients. The risk of LPD appears greatest in young children who are at risk for primary EBV infection while immunosuppressed or who are switched to tacrolimus capsules following long-term immunosuppression therapy. Because of the danger of oversuppression of the immune system which can increase susceptibility to infection, combination immunosuppressant therapy should be used with caution.

Latent Viral Infections

Immunosuppressed patients are at increased risk for opportunistic infections, including latent viral infections. These include BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML) which have been observed in patients receiving tacrolimus. These infections may lead to serious, including fatal, outcomes.

PRECAUTIONS

General

Hypertension is a common adverse effect of tacrolimus therapy (see **ADVERSE REACTIONS**). Mild or moderate hypertension is more frequently reported than severe hypertension. Antihypertensive therapy may be required; the control of blood pressure can be accomplished with any of the common antihypertensive agents. Since tacrolimus may cause hyperkalemia, potassium-sparing diuretics should be avoided. While calcium-channel blocking agents can be effective in treating tacrolimus-associated hypertension, care should be taken since interference with tacrolimus metabolism may require a dosage reduction (see **Drug Interactions**).

Renally and Hepatically Impaired Patients

For patients with renal insufficiency some evidence suggests that lower doses should be used (see **CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION**).
The use of tacrolimus capsules in liver transplant recipients experiencing post-transplant hepatic impairment may be associated with increased risk of developing renal insufficiency related to high whole-blood levels of tacrolimus. These patients should be monitored closely and dosage adjustments should be considered. Some evidence suggests that lower doses should be used in these patients (see **DOSAGE AND ADMINISTRATION**).

Myocardial Hypertrophy

Myocardial hypertrophy has been reported in association with the administration of tacrolimus capsules, and is generally manifested by echocardiographically demonstrated concentric increases in left ventricular posterior wall and interventricular septum thickness. Hypertrophy has been observed in infants, children and adults. This condition appears reversible in most cases following dose reduction or discontinuance of therapy. In a group of 20 patients with pre- and post-treatment echocardiograms who showed evidence of myocardial hypertrophy, mean tacrolimus whole blood concentrations during the period prior to diagnosis of myocardial hypertrophy ranged from 11 to 53 ng/mL in infants (N=10, age 0.4 to 2 years), 4 to 46 ng/mL in children (N=7, age 2 to 15 years) and 11 to 24 ng/mL in adults (N=3, age 37 to 53 years).
In patients who develop renal failure or clinical manifestations of ventricular dysfunction while receiving tacrolimus therapy, echocardiographic evaluation should be considered. If myocardial hypertrophy is diagnosed, dosage reduction or discontinuation of tacrolimus should be considered.

Information for Patients

Patients should be informed of the need for repeated appropriate laboratory tests while they are receiving tacrolimus capsules. They should be given complete dosage instructions, advised of the potential risks during pregnancy, and informed of the increased risk of neoplasia. Patients should be informed that changes in dosage should not be undertaken without first consulting their physician.
Patients should be informed that tacrolimus capsules can cause diabetes mellitus and should be advised of the need to see their physician if they develop frequent urination, increased thirst or hunger.
As with other immunosuppressive agents, owing to the potential risk of malignant skin changes, exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Laboratory Tests

Serum creatinine, potassium, and fasting glucose should be assessed regularly. Routine monitoring of metabolic and hematologic systems should be performed as clinically warranted.

Drug Interactions

Due to the potential for additive or synergistic impairment of renal function, care should be taken when administering tacrolimus capsules with drugs that may be associated with renal dysfunction. These include, but are not limited to, aminoglycosides, amphotericin B, and cisplatin. Initial clinical experience with the co-administration of tacrolimus and cyclosporine resulted in additive/synergistic nephrotoxicity. Patients switched from cyclosporine to tacrolimus should receive the first tacrolimus capsules dose no sooner than 24 hours after the last cyclosporine dose. Dosing may be further delayed in the presence of elevated cyclosporine levels.

Drugs that May Alter Tacrolimus Concentrations

Since tacrolimus is metabolized mainly by the CYP3A enzyme systems, substances known to inhibit these enzymes may decrease the metabolism or increase bioavailability of tacrolimus as indicated by increased whole blood or plasma concentrations. Drugs known to induce these enzyme systems may result in an increased metabolism of tacrolimus or decreased bioavailability as indicated by decreased whole blood or plasma concentrations. Monitoring of blood concentrations and appropriate dosage adjustments are essential when such drugs are used concomitantly.

***Drugs That May Increase Tacrolimus Blood Concentrations**

Calcium Channel Blockers	Antifungal Agents	Macrolide Antibiotics
diltiazem	clotrimazole	clarithromycin
nicardipine	fluconazole	erythromycin
nifedipine	itraconazole	troleandomycin
verapamil	ketoconazole**	
	voriconazole	

Gastrointestinal Prokinetic Agents	Other Drugs
cisapride	bromocriptine
metoclopramide	chloramphenicol
	cimetidine
	cyclosporine
	danazol
	ethinyl estradiol
	methylprednisolone
	lansoprazole***
	omeprazole
	protease inhibitors
	nefazodone
	magnesium-aluminum-hydroxide

* This table is not all inclusive
**In a study of 6 normal volunteers, a significant increase in tacrolimus oral bioavailability (14±5% vs. 30±8%) was observed with concomitant ketoconazole administration (200 mg). The apparent oral clearance of tacrolimus during ketoconazole administration was significantly decreased compared to tacrolimus alone (0.430±0 129 L/hr/kg vs. 0 148±0.043 L/hr/kg). Overall, IV clearance of tacrolimus was not significantly changed by ketoconazole co-administration, although it was highly variable between patients.
*** Lansoprazole (CYP2C19, CYP3A4 substrate) may potentially inhibit CYP3A4-mediated metabolism of tacrolimus and thereby substantially increase tacrolimus whole blood concentrations, especially in transplant patients who are intermediate or poor CYP2C19 metabolizers, as compared to those patients who are efficient CYP2C19 metabolizers.

***Drugs That May Decrease Tacrolimus Blood Concentrations**

Anticonvulsants	Antimicrobials
carbamazepine	rifabutin
phenobarbital	caspofungin
phenytoin	rifampin
Herbal Preparations	**Other Drugs**
St. John's Wort	sirolimus

*This table is not all inclusive.

St. John's Wort *(Hypericum perforatum)* induces CYP3A4 and P-glycoprotein. Since tacrolimus is a substrate for CYP3A4, there is the potential that the use of St. John's Wort in patients receiving tacrolimus capsules could result in reduced tacrolimus levels.
In a single-dose crossover study in healthy volunteers, co-administration of tacrolimus and magnesium-aluminum-hydroxide resulted in a 21% increase in the mean tacrolimus AUC and a 10% decrease in the mean tacrolimus C_{max} relative to tacrolimus administration alone.
In a study of 6 normal volunteers, a significant decrease in tacrolimus oral bioavailability (14 ± 6% vs. 7 ± 3%) was observed with concomitant rifampin administration (600 mg). In addition, there was a significant increase in tacrolimus clearance (0.036 ± 0.008 L/hr/kg vs. 0.053 ± 0.01 L/hr/kg) with concomitant rifampin administration.
Interaction studies with drugs used in HIV therapy have not been conducted. However, care should be exercised when drugs that are nephrotoxic (e.g., ganciclovir) or that are metabolized by CYP3A (e.g., nelfinavir, ritonavir) are administered concomitantly with tacrolimus. Based on a clinical study of 5 liver transplant recipients, co-administration of tacrolimus with nelfinavir increased blood concentrations of tacrolimus significantly and, as a result, a reduction in the tacrolimus dose by an average of 16-fold was needed to maintain mean trough tacrolimus blood concentrations of 9.7 ng/mL. Thus, frequent monitoring of tacrolimus blood concentrations and appropriate dosage adjustments are essential when nelfinavir is used concomitantly. Tacrolimus may affect the pharmacokinetics of other drugs (e.g., phenytoin) and increase their concentration. Grapefruit juice affects CYP3A-mediated metabolism and should be avoided (see **DOSAGE AND ADMINISTRATION**).
Following co-administration of tacrolimus and sirolimus (2 or 5 mg/day) in stable renal transplant patients, mean tacrolimus AUC_{0-12} and C_{min} decreased approximately by 30% relative to tacrolimus alone. Mean tacrolimus AUC_{0-12} and C_{min} following co-administration of 1 mg/day of sirolimus decreased approximately 3% and 11%, respectively. The safety and efficacy of tacrolimus used in combination with sirolimus for the prevention of graft rejection has not been established and is not recommended.

Other Drug Interactions

Immunosuppressants may affect vaccination. Therefore, during treatment with tacrolimus capsules, vaccination may be less effective. The use of live vaccines should be avoided; live vaccines may include, but are not limited to measles, mumps, rubella, oral polio, BCG, yellow fever, and TY 21a typhoid.[1]
At a given MMF dose, mycophenolic acid (MPA) exposure is higher with tacrolimus co-administration than with cyclosporine co-administration due to the differences in the interruption of the enterohepatic recirculation of MPA. Clinicians should be aware that there is also a potential for increased MPA exposure after crossover from cyclosporine to tacrolimus in patients concomitantly receiving MMF or MPA.

Carcinogenesis, Mutagenesis, Impairment of Fertility

An increased incidence of malignancy is a recognized complication of immunosuppression in recipients of organ transplants. The most common forms of neoplasms are non-Hodgkin's lymphomas and carcinomas of the skin. As with other immunosuppressive therapies, the risk of malignancies in tacrolimus recipients may be higher than in the normal, healthy population. Lymphoproliferative disorders associated with Epstein-Barr Virus infection have been seen. It has been reported that reduction or discontinuation of immunosuppression may cause the lesions to regress.
No evidence of genotoxicity was seen in bacterial *(Salmonella* and *E. coli)* or mammalian (Chinese hamster lung-derived cells) *in vitro* assays of mutagenicity, the *in vitro* CHO/HGPRT assay of mutagenicity, or *in vivo* clastogenicity assays performed in mice; tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes.
Carcinogenicity studies were carried out in male and female rats and mice. In the 80-week mouse study and in the 104-week rat study no relationship of tumor incidence to tacrolimus dosage was found. The highest doses used in the mouse and rat studies were 0.8 - 2.5 times (mice) and 3.5 - 7.1 times (rats) the recommended clinical dose range of 0.1 - 0.2 mg/kg/day when corrected for body surface area.
No impairment of fertility was demonstrated in studies of male and female rats. Tacrolimus, given orally at 1 mg/kg (0.7 - 1.4X the recommended clinical dose range of 0.1 - 0.2 mg/kg/day based on body surface area corrections) to male and female rats, prior to and during mating, as well as to dams during gestation and lactation, was associated with embryolethality and with adverse effects on female reproduction. Effects on female reproductive function (parturition) and embryolethal effects were indicated by a higher rate of pre-implantation loss and increased numbers of undelivered and nonviable pups. When given at 3.2 mg/kg (2.3 - 4.6X the recommended clinical dose range based on body surface area correction), tacrolimus was associated with maternal and paternal toxicity as well as reproductive toxicity including marked adverse effects on estrus cycles, parturition, pup viability, and pup malformations.

Pregnancy
Category C
In rep oduction studies in rats and rabbits, adverse effects on the fetus were observed mainly at dose levels hat were toxic to dams. Tac olimus at oral doses of 0.32 and 1 mg/kg during organogenesis in rabbits was associated wi h mate nal toxicity as well as an increase in incidence of abortions; these doses are equivalent to 0.5 - 1X and 1.6 - 3.3X he recommended clinical dose range (0.1 - 0.2 mg/kg) based on body surface area corrections. At the higher dose only, an increased incidence of malformations and developmental variations was also seen. Tac olimus, at oral doses of 3.2 mg/kg during organogenesis in rats, was associated wi h mate nal toxicity and caused an increase in late resorptions, decreased numbers of live births, and decreased pup weight and viability. Tac olimus, given orally at 1 and 3.2 mg/kg (equivalent to 0.7 - 1.4X and 2.3 - 4.6X the recommended clinical dose range based on body surface area corrections) to pregnant rats after organogenesis and during lactation, was associated wi h reduced pup weights.
No reduction in male or female fertility was evident.
There are no adequate and well-cont olled studies in pregnant women. Tac olimus is transferred ac oss the placenta. The use of tac olimus during pregnancy has been associated wi h neonata hyperkalemia and renal dysfunction. Tac olimus capsules should be used during pregnancy only if he potential benefit to he mo her justifies potential risk to he fetus.

Nursing Mothers
Since tac olimus is excreted in human milk, nursing should be avoided.

Pediatric Patients
Experience wi h tac olimus in pediatric kidney patients is limited. Successful liver transplants have been performed in pediatric patients (ages up to 16 years) using tac olimus capsules. Two randomized active-cont olled trials of tac olimus capsules in primary liver transplantation included 56 pediatric patients. Thirty-one patients were randomized to tac olimus-based and 25 to cyclosporine-based herapies. Additionally, a minimum of 122 pediatric patients were studied in an uncont olled trial of tac olimus in living related donor liver transplantation. Pediatric patients generally required higher doses of tac olimus capsules to maintain blood t ough concentrations of tac olimus similar to adult patients (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Liver Transplantation
The principal adverse reactions of tac olimus are tremor, headache, diar hea, hypertension, nausea, and abnormal renal function. These occur with oral and IV administration of tac olimus and may respond to a reduction in dosing. Diar hea was sometimes associated wi h other gast ointestinal complaints such as nausea and vomiting.
Hyperkalemia and hypomagnesemia have occurred in patients receiving tac olimus herapy. Hyperglycemia has been noted in many patients; some may require insulin therapy (see **WARNINGS**).
The incidence of adverse events was determined in two randomized comparative liver transplant trials among 514 patients receiving tac olimus and ste oids and 515 patients receiving a cyclosporine-based regimen (CBIR). The p oportion of patients reporting more han one adverse event was 99.8% in he tac olimus g oup and 99.6% in he CBIR g oup. Precautions must be taken when comparing the incidence of adverse events in the U.S. study to hat in he European study. The 12-month posttransplant information f om he U.S. study and f om he Eu opean study is presented below. The two studies also included different patient populations and patients were treated wi h immunosuppressive regimens of differing intensities. Adverse events reported in ≥ 15% in tac olimus patients (combined study results) are presented below for he two cont olled trials in liver transplantation:

LIVER TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN ≥ 15% OF TACROLIMUS-TREATED PATIENTS

	U.S. STUDY		EUROPEAN STUDY	
	Tacrolimus (N=250)	CBIR (N=250)	Tac olimus (N=264)	CBIR (N=265)
Nervous System				
Headache (see **WARNINGS**)	64%	60%	37%	26%
Tremor (see **WARNINGS**)	56%	46%	48%	32%
Insomnia	64%	68%	32%	23%
Pares hesia	40%	30%	17%	17%
Gastrointestinal				
Diar hea	72%	47%	37%	27%
Nausea	46%	37%	32%	27%
Constipation	24%	27%	23%	21%
LFT Abnormal	36%	30%	6%	5%
Anorexia	34%	24%	7%	5%
Vomiting	27%	15%	14%	11%
Cardiovascular				
Hypertension (see **PRECAUTIONS**)	47%	56%	38%	43%
Urogenital				
Kidney Function Abnormal (see **WARNINGS**)	40%	27%	36%	23%
Creatinine Increased (see **WARNINGS**)	39%	25%	24%	19%
BUN Increased (see **WARNINGS**)	30%	22%	12%	9%
Urinary Tract Infection	16%	18%	21%	19%
Oliguria	18%	15%	19%	12%
Metabolic and Nutritional				
Hyperkalemia (see **WARNINGS**)	45%	26%	13%	9%
Hypokalemia	29%	34%	13%	16%
Hyperglycemia (see **WARNINGS**)	47%	38%	33%	22%
Hypomagnesemia	48%	45%	16%	9%
Hemic and Lymphatic				
Anemia	47%	38%	5%	1%
Leukocytosis	32%	26%	8%	8%
Th ombocytopenia	24%	20%	14%	19%
Miscellaneous				
Abdominal Pain	59%	54%	29%	22%
Pain	63%	57%	24%	22%
Fever	48%	56%	19%	22%
Asthenia	52%	48%	11%	7%
Back Pain	30%	29%	17%	17%
Ascites	27%	22%	7%	8%
Peripheral Edema	26%	26%	12%	14%
Respiratory System				
Pleural Effusion	30%	32%	36%	35%
Atelectasis	28%	30%	5%	4%
Dyspnea	29%	23%	5%	4%
Skin and Appendages				
Pruritus	36%	20%	15%	7%
Rash	24%	19%	10%	4%

Less frequently observed adverse reactions in bo h liver transplantation and kidney transplantation patients are described under he subsection **Less Frequently Reported Adverse Reactions** below.

Kidney Transplantation
The most common adverse reactions reported were infection, tremor, hypertension, abnormal renal function, constipation, diar hea, headache, abdominal pain and insomnia.
Adverse events hat occurred in ≥ 15% of kidney transplant patients treated with tac olimus in conjunction wi h azathioprine are presented below:

KIDNEY TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN ≥ 15% OF PATIENTS WITH TACROLIMUS IN CONJUCTION WITH AZATHIOPRINE

	Tac olimus (N=205)	CBIR (N=207)
Nervous System		
Tremor (see **WARNINGS**)	54%	34%
Headache (see **WARNINGS**)	44%	38%
Insomnia	32%	30%
Pares hesia	23%	16%
Dizziness	19%	16%
Gastrointestinal		
Diar hea	44%	41%
Nausea	38%	36%
Constipation	35%	43%
Vomiting	29%	23%
Dyspepsia	28%	20%
Cardiovascular		
Hypertension (see **PRECAUTIONS**)	50%	52%
Chest pain	19%	13%
Urogenital		
Creatinine Increased (see **WARNINGS**)	45%	42%
Urinary Tract Infection	34%	35%
Metabolic and Nutritional		
Hypophosphatemia	49%	53%
Hypomagnesemia	34%	17%
Hyperlipemia	31%	38%
Hyperkalemia (see **WARNINGS**)	31%	32%
Diabetes Mellitus (see **WARNINGS**)	24%	9%
Hypokalemia	22%	25%
Hyperglycemia (see **WARNINGS**)	22%	16%
Edema	18%	19%
Hemic and Lymphatic		
Anemia	30%	24%
Leukopenia	15%	17%
Miscellaneous		
Infection	45%	49%
Peripheral Edema	36%	48%
Asthenia	34%	30%
Abdominal Pain	33%	31%
Pain	32%	30%
Fever	29%	29%
Back Pain	24%	20%
Respiratory System		
Dyspnea	22%	18%
Cough Increased	18%	15%
Musculoskeletal		
Ar hralgia	25%	24%
Skin		
Rash	17%	12%
Pruritus	15%	7%

Adverse events hat occurred in ≥ 10% of kidney transplant patients treated with tac olimus in conjunction wi h MMF in Study 1* are presented below:

KIDNEY TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN ≥ 10% OF TACROLIMUS-TREATED PATIENTS

	Tacrolimus (Group C) (N=403)	Cyclosporine (Group A) (N=384)	Cyclosporine (Group B) (N=408)
Anemia	17%	19%	17%
Leucopenia	13%	10%	10%
Diar hea	25%	16%	13%
Edema peripheral	11%	12%	13%
Urinary tract infection	24%	28%	24%
Hyperlipidemia	10%	15%	13%
Hypertension (see **PRECAUTIONS**)	13%	14%	12%

* Study 1 was conducted entirely outside of he United States. Such studies often report a lower incidence of adverse events in comparison to U S. studies.

Adverse events hat occurred in ≥15% of kidney transplant patients treated wi h tac olimus in conjunction wi h MMF in Study 2 are presented below:

KIDNEY TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN ≥15% OF TACROLIMUS-TREATED PATIENTS

	Tacrolimus (N=212)	Cyclosporine (N=212)
Gastrointestinal Disorders		
Diar hea	44%	26%
Nausea	39%	47%
Constipation	36%	41%
Vomiting	26%	25%
Dyspepsia	18%	15%
Injury, Poisoning, and Procedural Complications		
Post P ocedural Pain	29%	27%
Incision Site Complication	28%	23%
Graft Dysfunction	24%	18%

(continued)

Metabolism and Nutrition Disorders		
Hypomagnesemia	28%	22%
Hypophosphatemia	28%	21%
Hyperkalemia (see **WARNINGS**)	26%	19%
Hyperglycemia (see **WARNINGS**)	21%	15%
Hyperlipidemia	18%	25%
Hypokalemia	16%	18%
Nervous System Disorders		
Tremor	34%	20%
Headache	24%	25%
Blood and Lymphatic System Disorders		
Anemia	30%	28%
Leukopenia	16%	12%
Miscellaneous		
Edema Peripheral	35%	46%
Hypertension (see **PRECAUTIONS**)	32%	35%
Insomnia	30%	21%
Urinary Tract Infection	26%	22%
Blood creatinine increased	23%	23%

Less frequently observed adverse reactions in bo h liver transplantation and kidney transplantation patients are described under he subsection **Less Frequently Reported Adverse Reactions** shown below.

Less Frequently Reported Adverse Reactions
The following adverse events were reported in ei her liver and/or kidney transplant recipients who were treated with tac olimus in clinical trials.

Nervous System
(see **WARNINGS**)
Abnormal dreams, agitation, amnesia, anxiety, confusion, convulsion, crying, depression, dizziness, elevated mood, emotional lability, encephalopa hy, haemor hagic st oke, hallucinations, headache, hypertonia, incoordination, insomnia, monoparesis, myoclonus, nerve compression, nervousness, neuralgia, neuropa hy, pares hesia, paralysis flaccid, psychomotor skills impaired, psychosis, quadriparesis, somnolence, hinking abnormal, vertigo, writing impaired

Special Senses
Abnormal vision, amblyopia, ear pain, otitis media, tinnitus

Gastrointestinal
Anorexia, cholangitis, cholestatic jaundice, diar hea, duodenitis, dyspepsia, dysphagia, esophagitis, flatulence, gastritis, gast oesophagitis, gast ointestinal hemorrhage, GGT increase, GI disorder, GI perforation, hepatitis, hepatitis granulomatous, ileus, increased appetite, jaundice, liver damage, liver function test abnormal, nausea, nausea and vomiting, oesophagitis ulcerative, oral moniliasis, pancreatic pseudocyst, rectal disorder, stomatitis, vomiting

Cardiovascular
Abnormal ECG, angina pectoris, ar hy hmia, atrial fibrillation, atrial flutter, bradycardia, cardiac fibrillation, cardiopulmonary failure, cardiovascular disorder, chest pain, congestive heart failure, deep th ombophlebitis, echocardiogram abnormal, elect ocardiogram QRS complex abnormal, elect ocardiogram ST segment abnormal, heart failure, heart rate decreased, hemor hage, hypotension, peripheral vascular disorder, phlebitis, postural hypotension, syncope, tachycardia, h ombosis, vasodilatation

Urogenital
(see **WARNINGS**)
Acute kidney failure, albuminuria, BK neph opa hy, bladder spasm, cystitis, dysuria, hematuria, hyd oneph osis, kidney failure, kidney tubular nec osis, nocturia, oliguria, pyuria, toxic neph opathy, urge incontinence, urinary frequency, urinary incontinence, urinary retention, vaginitis

Metabolic/Nutritional
Acidosis, alkaline phosphatase increased, alkalosis, ALT (SGPT) increased, AST (SGOT) increased, bicarbonate decreased, bilirubinemia, BUN increased, dehydration, edema, GGT increased, gout, healing abnormal, hypercalcemia, hypercholesterolemia, hyperkalemia, hyperlipemia, hyperphosphatemia, hyperuricemia, hypervolemia, hypocalcemia, hypoglycemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, hypop oteinemia, lactic dehyd ogenase increase, peripheral edema, weight gain

Endocrine
(see **PRECAUTIONS**)
Cushing's synd ome, diabetes mellitus

Hemic/Lymphatic
Coagulation disorder, ecchymosis, haematocrit increased, haemoglobin abnormal, hypoch omic anemia, leukocytosis, leukopenia, polycy hemia, p oth ombin decreased, serum i on decreased, h ombocytopenia

Miscellaneous
Abdomen enlarged, abdominal pain, abscess, accidental injury, allergic reaction, as henia, back pain, cellulitis, chills, fall, feeling abnormal, fever, flu synd ome, generalized edema, he nia, mobility decreased, pain, peritonitis, photosensitivity reaction, sepsis, temperature intolerance, ulcer

Musculoskeletal
Arthralgia, cramps, generalized spasm, joint disorder, leg cramps, myalgia, myas henia, osteopo osis

Respiratory
As hma, b onchitis, cough increased, dyspnea, emphysema, hiccups, lung disorder, lung function decreased, pharyngitis, pleural effusion, pneumonia, pneumothorax, pulmonary edema, respiratory disorder, rhinitis, sinusitis, voice alteration

Skin
Acne, alopecia, exfoliative dermatitis, fungal dermatitis, herpes simplex, herpes zoster, hirsutism, neoplasm skin benign, skin discoloration, skin disorder, skin ulcer, sweating.

Post Marketing

Post Marketing Adverse Events
The following adverse events have been reported f om worldwide marketing experience with tac olimus. Because hese events are reported voluntarily f om a population of uncertain size, are associated wi h concomitant diseases and multiple drug therapies and surgical p ocedures, it is not always possible to reliably estimate heir frequency or establish a causal relationship to drug exposure. Decisions to include hese events in labeling are typically based on one or more of he following factors: (1) seriousness of the event, (2) frequency of the reporting, or (3) strength of causal connection to he drug.
There have been rare spontaneous reports of myocardia hypert ophy associated wi h clinically manifested ventricular dysfunction in patients receiving tac olimus herapy (see **PRECAUTIONS-Myocardial Hypertrophy**).
O her events include:

Cardiovascular
Atrial fibrillation, atrial flutter, cardiac ar hythmia, cardiac arrest, elect ocardiogram T wave abnormal, flushing, myocardial infarction, myocardial ischaemia, pericardial effusion, QT p olongation, Torsade de Pointes, venous th ombosis deep limb, ventricular extrasystoles, ventricular fibrillation

Gastrointestinal
Bile duct stenosis, colitis, ente ocolitis, gast oenteritis, gast ooesophageal reflux disease, hepatic cytolysis, hepatic nec osis, hepatotoxicity, impaired gastric emptying, liver fatty, mou h ulceration, pancreatitis haemor hagic, pancreatitis nec otizing, stomach ulcer, venoocclusive liver disease

Hemic/Lymphatic
Disseminated intravascular coagulation, neut openia, pancytopenia, h ombocytopenic purpura, th ombotic h ombocytopenic purpura

Metabolic/Nutritional
Glycosuria, increased amylase including pancreatitis, weight decreased

Miscellaneous
Feeling hot and cold, feeling jittery, hot flushes, multi-organ failure, primary graft dysfunction

Nervous System
Carpal tunnel synd ome, cerebral infarction, hemiparesis, leukoencephalopathy, mental disorder, mutism, posterior reversible encephalopa hy synd ome (PRES), p ogressive multifocal leukoencephalopathy (PML), quadriplegia, speech disorder, syncope

Respiratory
Acute respiratory distress synd ome, interstitial lung disease, lung infiltration, respiratory distress, respiratory failure

Skin
Stevens-Johnson synd ome, toxic epidermal nec olysis

Special Senses
Blindness, blindness cortical, hearing loss including deafness, photophobia

Urogenital
Acute renal failure, cystitis haemorrhagic, hemolytic-uremic synd ome, micturition disorder.

OVERDOSAGE

Limited overdosage experience is available. Acute overdosages of up to 30 times the intended dose have been reported. Almost all cases have been asymptomatic and all patients recovered wi h no sequelae. Occasionally, acute overdosage has been followed by adverse reactions consistent wi h hose listed in he **ADVERSE REACTIONS** section except in one case where transient urticaria and le hargy were observed. Based on the poor aqueous solubility and extensive ery h ocyte and plasma p otein binding, it is anticipated hat tac olimus is not dialyzable to any significant extent; here is no experience with charcoal hemoperfusion. The oral use of activated charcoal has been reported in treating acute overdoses, but experience has not been sufficient to warrant recommending its use. General supportive measures and treatment of specific symptoms should be followed in all cases of overdosage.
In acute oral and IV toxicity studies, mortalities were seen at or above he following doses: in adult rats, 52X he recommended human oral dose; in immature rats, 16X he recommended oral dose; and in adult rats, 16X he recommended human IV dose (all based on body surface area corrections).

DOSAGE AND ADMINISTRATION

In patients unable to take oral tac olimus capsules, herapy may be initiated with tac olimus injection. The initial dose of tac olimus should be administered no sooner han 6 hours after transplantation.

Summary of Initial Oral Dosage Recommendations and Typical Whole Blood Trough Concentrations

Patient Population	Recommended Initial Oral Dose*	Typical Whole Blood Trough Concentrations
Adult kidney transplant patients		
In combination with azathioprine	0.2 mg/kg/day	mon h 1-3: 7-20 ng/mL mon h 4-12: 5-15 ng/mL
In combination with MMF/IL-2 receptor antagonist**	0.1 mg/kg/day	mon h 1-12: 4-11 ng/mL
Adult liver transplant patients	0.10-0.15 mg/kg/day	mon h 1-12: 5-20 ng/mL
Pediatric liver transplant patients	0.15-0.20 mg/kg/day	month 1-12: 5-20 ng/mL

*Note: two divided doses, q12h
In a second smaller study, he initial dose of tacrolimus was 0.15-0 2 mg/kg/day and observed tacrolimus concent ations were 6-16 ng/mL du ing mon h 1-3 and 5-12 ng/mL du ing mon h 4-12 (see **CLINICAL STUDIES).

Liver Transplantation
It is recommended hat patients initiate oral herapy wi h tac olimus capsules if possible. If IV herapy is necessary, conversion f om IV to oral tac olimus is recommended as soon as oral herapy can be tolerated. This usually occurs wi hin 2-3 days. The initial dose of tac olimus should be administered no sooner han 6 hours after transplantation. In a patient receiving an IV infusion, he first dose of oral herapy should be given 8-12 hours after discontinuing he IV infusion. The recommended starting oral dose of tac olimus capsules is 0.1 to 0.15 mg/kg/day administered in two divided daily doses every 12 hours. Co-administered grapefruit juice has been reported to increase tac olimus blood t ough concentrations in liver transplant patients. (See **Drugs that May Alter Tacrolimus Concentrations**).
Dosing should be titrated based on clinical assessments of rejection and tolerability. Lower tac olimus dosages may be sufficient as maintenance herapy. Adjunct therapy wi h adrenal corticosteroids is recommended early post-transplant.
Dosage and typical tac olimus whole blood t ough concentrations are shown in he table above; blood concentration details are described in **Blood Concentration Monitoring: Liver Transplantation** below.

Kidney Transplantation
The recommended starting oral dose of tac olimus (administered every 12 hours in two divided doses) is 0.2 mg/kg/day when used in combination wi h aza hioprine or 0.1 mg/kg/day when used in combination with MMF and IL-2 receptor antagonist (see **CLINICAL STUDIES**). The initial dose of tac olimus may be administered within 24 hours of transplantation, but should be delayed until renal function has recovered (as indicated for example by a serum creatinine ≤ 4 mg/dL). Black patients may require higher doses to achieve comparable blood concentrations. Dosage and typical tac olimus whole blood t ough concentrations are shown in he table above; blood concentration details are described in **Blood Concentration Monitoring Kidney Transplantation** below.
The data in kidney transplant patients indicate that the Black patients required a higher dose to attain comparable t ough concentrations compared to Caucasian patients.

Time After Transplant	Caucasian n=114		Black n=56	
	Dose (mg/kg)	Trough Concentrations (ng/mL)	Dose (mg/kg)	Trough Concentrations (ng/mL)
Day 7	0.18	12	0.23	10.9
Mon h 1	0.17	12.8	0.26	12.9
Mon h 6	0.14	11.8	0.24	11.5
Mon h 12	0.13	10.1	0.19	11

Pediatric Patients
Pediatric liver transplantation patients wi hout pre-existing renal or hepatic dysfunction have required and tolerated higher doses han adults to achieve similar blood concentrations. Therefore, it is recommended hat herapy be initiated in pediatric patients at a starting oral dose of 0.15-0.2 mg/kg/day. Dose adjustments may be required. Experience in pediatric kidney transplantation patients is limited.

Patients with Hepatic or Renal Dysfunction
Due to he reduced clearance and p olonged half-life, patients with severe hepatic impairment (Pugh ≥ 10) may require lower doses of tac olimus. Close monitoring of blood concentrations is warranted.
Due to the potential for neph otoxicity, patients wi h renal or hepatic impairment should receive doses at he lowest value of he recommended oral dosing ranges. Further reductions in dose below hese ranges may be required. Tac olimus herapy usually should be delayed up to 48 hours or longer in patients with post-operative oliguria.

Conversion from One Immunosuppressive Regimen to Another
Tac olimus should not be used simultaneously w th cyclosporine. Tac olimus or cyclosporine should be discontinued at least 24 hours before initiating he o her. In he presence of elevated tac olimus or cyclosporine concentrations, dosing wi h the o her drug usually should be fur her delayed.

Blood Concentration Monitoring
Monitoring of tac olimus blood concentrations in conjunction with o her laboratory and clinical parameters is considered an essential aid to patient management for he evaluation of rejection, toxicity, dose adjustments and compliance. Factors influencing frequency of monitoring include but are not limited to hepatic or renal dysfunction, he addition or discontinuation of potentially interacting drugs and he posttransplant time. Blood concentration monitoring is not a replacement for renal and liver function monitoring and tissue biopsies.
Two me hods have been used for the assay of tac olimus, a mic oparticle enzyme immunoassay (MEIA) and ELISA. Bo h methods have he same monoclonal antibody for tac olimus. Comparison of the concentrations in published literature to patient concentrations using he current assays must be made with detailed knowledge of he assay methods and biological matrices employed. Whole blood is the matrix of choice and specimens should be collected into tubes containing e hylene diamine tetraacetic acid (EDTA) anticoagulant. Heparin anticoagulation is not recommended because of he tendency to form clots on storage. Samples which are not analyzed immediately should be stored at oom temperature or in a refrigerator and assayed within 7 days; if samples are to be kept longer they should be deep f ozen at -20°C for up to 12 months.

Liver Transplantation
Al hough here is a lack of direct correlation between tac olimus concentrations and drug efficacy, data f om Phase II and III studies of liver transplant patients have shown an increasing incidence of adverse events with increasing t ough blood concentrations. Most patients are stable when t ough whole blood concentrations are maintained between 5 to 20 ng/mL. Long-term post-transplant patients often are maintained at the low end of this target range.
Data f om he U.S. clinical trial show hat tac olimus whole blood concentrations, as measured by ELISA, were most variable during he first week post-transplantation. After his early period, he median t ough blood concentrations, measured at intervals f om the second week to one year post-transplantation, ranged f om 9.8 ng/mL to 19.4 ng/mL.
Therapeutic Drug Monitoring, 1995, Volume 17, Number 6 contains a consensus document and several position papers regarding he therapeutic monitoring of tac olimus f om he 1995 Inte national Consensus Conference on Immunosuppressive Drugs. Refer to hese manuscripts for fur her discussions of tac olimus monitoring.

Kidney Transplantation
Data f om a Phase 3 study of tac olimus in conjunction wi h aza hioprine indicate hat t ough concentrations of tac olimus in whole blood, as measured by IMx® were most variable during he first week of dosing. During the first hree mon hs of hat trial, 80% of he patients maintained t ough concentrations between 7-20 ng/mL, and hen between 5-15 ng/mL, h ough 1 year.
In a separate clinical trial of tac olimus in conjunction wi h MMF and daclizumab, app oximately 80% of patients maintained tacrolimus whole blood concentrations between 4-11 ng/mL h ough 1 year post-transplant.
In another clinical trial of tac olimus in conjunction wi h MMF and basiliximab, app oximately 80% of patients maintained tac olimus whole t ough blood concentrations between 6-16 ng/mL during mon h 1-3 and, then, between 5-12 ng/mL f om month 4 th ough 1 year.
The relative risks of toxicity and efficacy failure are related to tac olimus whole blood t ough concentrations. Therefore, monitoring of whole blood t ough concentrations is recommended to assist in he clinical evaluation of toxicity and efficacy failure.

HOW SUPPLIED

Tac olimus capsules, containing white to off white powder equivalent to 0.5 mg of anhyd ous tac olimus, are hard gelatin capsules with white opaque body and ivory cap. The body is imprinted '643' and cap is imprinted S in black ink.
They are supplied as follows:
NDC 0781-2102-01, bottle of 100 capsules with child-resistant closure

Tac olimus capsules, containing white to off white powder equivalent to 1 mg of anhyd ous tac olimus, are hard gelatin capsules with white opaque body and b own cap. The body is imprinted '644' and cap is imprinted S in black ink.
They are supplied as follows:
NDC 0781-2103-01, bottle of 100 capsules with child-resistant closure

Tac olimus capsules, containing white to off white powder equivalent to 5 mg of anhyd ous tac olimus, are hard gelatin capsules wi h white opaque body and orange cap. The body is imprinted '645' and cap is imprinted S in black ink.
They are supplied as follows:
NDC 0781-2104-01, bottle of 100 capsules with child-resistant closure.

Tac olimus capsules should be stored at 20°- 25°C (68°- 77° F) [see USP Cont olled Room Temperature].

REFERENCE

1. CDC: Recommendations of he Advisory Committee on Immunization Practices: Use of vaccines and immune globulins in persons w th altered immunocompetence. MMWR 1993;42(RR-4):1-18.

Patient Information

Tacrolimus Capsules

Read this important information before you start using tacrolimus capsules and each time you refill your prescription. This summary does not take the place of talking with your transplant team.

Talk with your transplant team if you have any questions or want more information about tacrolimus capsules. You can also find more about tacrolimus capsules by calling at 1-800-525-8747.

What Is Tacrolimus Capsule?
Tac olimus capsule is a medicine hat slows down the body's immune system. For his reason, it works as an anti-rejection medicine. Tac olimus capsule helps patients who have had a liver or kidney transplant p otect heir new organ and prevent it f om being rejected by he body.

How Does Tacrolimus Capsule Protect My New Organ?
The body's immune system protects the body against anything that it does not recognize as part of the body. For example, when the immune system detects a virus or bacteria it tries to get rid of it to prevent infection. When a person has a liver or kidney transplant, the immune system does not recognize the new organ as a part of the body and tries to get rid of it, too. This is called "rejection." Tacrolimus capsule protects your new organ by slowing down the body's immune system.

Who Should Not Take Tacrolimus Capsules?
Do not take tac olimus capsules if you are allergic to any of he ingredients in tac olimus. The active ingredient is tac olimus. Ask your doctor or pharmacist about he inactive ingredients.
Tell your transplant team about all your heal h conditions, including kidney and /or liver p oblems.Discuss with your transplant team the use of any o her prescription and non-prescription medications, including any herbal or over- he-counter remedies hat you make take while on tac olimus capsule. In very rare cases, you may not be able to take tac olimus capsule.
Tell your transplant team if you are pregnant, planning to have a baby, or are breastfeeding. Talk wi h your transplant doctor about possible effects tac olimus capsule could have on your child. Do not nurse a baby while taking tac olimus capsule since the medicine will be in he breast milk.

How Should I take Tacrolimus Capsule?
Tac olimus capsules can p otect your new kidney or liver only if you take he medicine correctly. Your new organ needs a ound-the-clock p otection so your body does not reject it. The success of your transplant depends a great deal upon how well you help tac olimus capsules do its job. Here is what you can do to help.

- **Take tacrolimus capsules exactly as prescribed**
  It is important to take tac olimus capsules exactly as your transplant team tells you to.
  Tac olimus capsules comes in several different streng h capsules-0.5 mg, 1 mg and 5 mg. Your transplant team will tell you what dose to take and how often to take it. Your transplant team may adjust your dose until they find what works best for you.
  Never change your dose on your own. Never stop taking tac olimus capsules even if you are feeling well. However, if you feel poorly on tac olimus capsules, discuss his w th your transplant team.
- **Take Tacrolimus capsules two time a day, 12 hours apart**
  Try to pick times hat will be easy for you. For example, if you take your first dose at 7:00 AM you should take your second dose at 7:00 PM. Do not vary he times. You must take tac olimus capsules at the same times every day. If you decide to take tac olimus capsules at 7:00 AM and 7:00 PM, take it at these same times every day. This will make sure you always have enough medicine in your body to give your new organ he a ound-the-clock p otection it needs.
- **Take Tacrolimus capsules the same way each day**
  Some people prefer to take tac olimus capsules wi h food to help reduce possible stomach upset. Whe her you take tac olimus capsules wi h or without food, it is important to take tac olimus capsules the same way every day. For example, if you take tac olimus capsules wi h food, you should always take it with food. Do not eat grapefruit or drink grapefruit juice in combination with your medicine unless your transplant team app oves. Do not change the way you take his medicine wi hout telling your transplant team, since his could change he amount of p otection you get f om tac olimus capsules.
- **Take all your doses**
  It is important to take your doses twice a day exactly as prescribed by your doctor. If you miss even two doses, your new liver or kidney could lose the p otection it needs to defend itself against rejection by your body. If you miss one dose, do not try to catch up on your own. Call your transplant team right away for instructions on what to do. If you travel and change time zones, be sure to ask your transplant team how to adjust your dosage schedule so your new organ does not lose its p otection.
- **Plan ahead so that you do not run out of tacrolimus capsules**
  Make sure you have your prescription for tac olimus capsules refilled and at home before you need it. Circle the date on a calendar when you need to order your refill. Allow extra time if you receive your medicines h ough he mail.

Your transplant team will follow your p ogress and watch for early signs of side effects. This is why you will have blood tests done often after your transplant. On he days you are going to have a blood test to measure he amount of tac olimus capsules in your body, your transplant team may ask you not to take your mo ning dose until after he blood sample is taken. Check w th your transplant team before skipping his dose.

Can Other Medicines Affect How Tacrolimus Capsules Works?
Some medicines and alcohol can affec how well tac olimus capsules works. After you start taking tac olimus capsules:

- Be sure to tell your transplant team, family doctor, dentist, pharmacist and any o her heal h care p ofessional treating you the names of **all** he medicines you are taking. This includes tac olimus capsules as well as all other prescription medicines and non-prescription medicines, natural or herbal remedies, nutritional supplements, and vitamins. This is the only way hat your health care team can help prevent drug interactions hat could be serious.
- Always check wi h your transplant team before you start taking any new medicine.
- While you are taking tac olimus capsules, **do not get any vaccinations without your transplant team's approval**. The vaccination may not work as well as it should.
- Liver transplant patients, including those taking tac olimus capsules should not drink alcohol.

What Are the Possible Side Effects of Tacrolimus Capsules?
Tell your transplant team right away if you think you might be having a side effect. Your transplant team will decide if it is a medicine side effect or a sign that has nothing to do wi h the medicine but needs to be treated. Infection or reduced urine can be signs of serious p oblems hat you should discuss wi h your transplant team.
Your transplant team will also follow your p ogress and watch for he early signs of any side effects. This is why you wil have blood tests done often during he first few mon hs after your transplant. On he days you are going to have a blood test to measure the amount of tac olimus capsules in your body, your transplant team may ask you not to take your mo ning dose until after he blood sample is taken. Check with your transplant team before skipping his dose.

For Kidney Transplant Patients
The most common side effects of tac olimus capsules for kidney transplant patients are infection, headache, tremors (shaking of he body), diar hea, constipation, nausea, high blood pressure, changes in the amount of urine, and t ouble sleeping.
Less common side effects are abdominal pain (stomach pain), numbness or tingling in your hands or feet; loss of appetite; indigestion or "upset stomach"; vomiting; urinary tract infections; fever; pain; swelling of he hands, ankles or legs; shortness of brea h or t ouble brea hing; cough; leg cramps; heart "fluttering," palpitations or chest pain; unusual weakness or tiredness; dizziness; confusion; changes in mood or emotions; itchy skin, skin rash, and diabetes.

For Liver Transplant Patients
The most common side effects of tac olimus capsules for liver transplant patients are headache, tremors (shaking of he body), diar hea, high blood pressure, nausea and changes in the amount of urine.
Less common side effects are numbness or tingling in your hands or feet; t ouble sleeping; constipation; loss of appetite; vomiting; urinary tract infections; fever, pain (especially in the back or abdomen [stomach area]); swelling of the hands, ankles, legs or abdomen; shortness of brea h or t ouble brea hing; cough; unusual bruising; leg cramps; heart 'fluttering' or palpitations; unusual weakness or tiredness; confusion; changes in mood or emotions; itchy skin, skin rash, and diabetes.
Be sure to tell your transplant team right away if you notice that you are thirstier than usual, have to urinate more often, have blurred vision or seem to get confused. These may be the early signs of high blood sugar or diabetes.
All anti-rejection medicines, including tac olimus capsules, suppress your body's immune system. As a result, hey may increase your chances of getting infections and some kinds of cancer, including skin and lymph gland cancer (lymphoma). As usual for patients wi h increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clo hing and using a sunscreen wi h a high sun p otection factor (SPF>15). However, getting cancer f om taking an anti-rejection medicine is not common. Talk wi h your transplant team about any concerns or questions you have.

How Should I Store Tacrolimus Capsules?
Tac olimus capsules should be stored at 20° - 25°C (68° - 77°F) [see USP Cont olled Room Temperature]. For instance, do not leave tac olimus capsules in he glove compartment of your car in he summer or winter. Do not keep tac olimus capsules in a hot or moist place such as he medicine cabinet in the ba h oom.

General Advice about Prescription Medicines
Medicines are sometimes prescribed for conditions hat are not mentioned in patient information leaflets. Do not use tac olimus capsules for a condition for which it was not prescribed. Do not give tac olimus capsules to other people.
This leaflet summarizes he most important information about tac olimus capsules. If you would like more information, talk wi h your doctor. You can ask your pharmacist or doctor for information about tac olimus capsules hat is written for heal h p ofessionals.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Manufactured in India by Sandoz Private Limited for
Sandoz Inc; Princeton NJ 08540

Iss. May 2009

Patient Information

Tacrolimus Capsules

Read this important information before you start using tacrolimus capsules and each time you refill your prescription. This summary does not take the place of talking with your transplant team.

Talk with your transplant team if you have any questions or want more information about tacrolimus capsules. You can also find more about tacrolimus capsules by calling at 1-800-525-8747.

What Is Tacrolimus Capsule?

Tacrolimus capsule is a medicine that slows down the body's immune system. For this reason, it works as an anti-rejection medicine. Tacrolimus capsule helps patients who have had a liver or kidney transplant protect their new organ and prevent it from being rejected by the body.

How Does Tacrolimus Capsule Protect My New Organ?

The body's immune system protects the body against anything that it does not recognize as part of the body. For example, when the immune system detects a virus or bacteria it tries to get rid of it to prevent infection. When a person has a liver or kidney transplant, the immune system does not recognize the new organ as a part of the body and tries to get rid of it, too. This is called "rejection." Tacrolimus capsule protects your new organ by slowing down the body's immune system.

Who Should Not Take Tacrolimus Capsules?

Do not take tacrolimus capsules if you are allergic to any of the ingredients in tacrolimus. The active ingredient is tacrolimus. Ask your doctor or pharmacist about the inactive ingredients.

Tell your transplant team about all your health conditions, including kidney and /or liver problems.Discuss with your transplant team the use of any other prescription and non-prescription medications, including any herbal or over-the-counter remedies that you make take while on tacrolimus capsule. In very rare cases, you may not be able to take tacrolimus capsule. Tell your transplant team if you are pregnant, planning to have a baby, or are breastfeeding. Talk with your transplant doctor about possible effects tacrolimus capsule could have on your child. Do not nurse a baby while taking tacrolimus capsule since the medicine will be in the breast milk.

How Should I take Tacrolimus Capsule?

Tacrolimus capsules can protect your new kidney or liver only if you take the medicine correctly. Your new organ needs around-the-clock protection so your body does not reject it. The success of your transplant depends a great deal upon how well you help tacrolimus capsules do its job. Here is what you can do to help.

- **Take tacrolimus capsules exactly as prescribed**
  It is important to take tacrolimus capsules exactly as your transplant team tells you to.

  Tacrolimus capsules comes in several different strength capsules-0.5 mg, 1 mg and 5 mg. Your transplant team will tell you what dose to take and how often to take it. Your transplant team may adjust your dose until they find what works best for you.

  Never change your dose on your own. Never stop taking tacrolimus capsules even if you are feeling well. However, if you feel poorly on tacrolimus capsules, discuss this with your transplant team.

- **Take Tacrolimus capsules two time a day, 12 hours apart**
  Try to pick times that will be easy for you. For example, if you take your first dose at 7:00 AM you should take your second dose at 7:00 PM. Do not vary the times. You must take tacrolimus capsules at the same times every day. If you decide to take tacrolimus capsules at 7:00 AM and 7:00 PM, take it at these same times every day. This will make sure you always have enough medicine in your body to give your new organ the around-the-clock protection it needs.

- **Take Tacrolimus capsules the same way each day**
  Some people prefer to take tacrolimus capsules with food to help reduce possible stomach upset. Whether you take tacrolimus capsules with or without food, it is important to take tacrolimus capsules the same way every day. For example, if you take tacrolimus capsules with food, you should always take it with food. Do not eat grapefruit or drink grapefruit juice in combination with your medicine unless your transplant team approves. Do not change the way you take this medicine without telling your transplant team, since this could change the amount of protection you get from tacrolimus capsules.

- **Take all your doses**
  It is important to take your doses twice a day exactly as prescribed by your doctor. If you miss even two doses, your new liver or kidney could lose the protection it needs to defend itself against rejection by your body. If you miss one dose, do not try to catch up on your own. Call your transplant team right away for instructions on what to do. If you travel and change time zones, be sure to ask your transplant team how to adjust your dosage schedule so your new organ does not lose its protection.

- **Plan ahead so that you do not run out of tacrolimus capsules**
  Make sure you have your prescription for tacrolimus capsules refilled and at home before you need it. Circle the date on a calendar when you need to order your refill. Allow extra time if you receive your medicines through the mail.

Your transplant team will follow your progress and watch for early signs of side effects. This is why you will have blood tests done often after your transplant. On the days you are going to have a blood test to measure the amount of tacrolimus capsules in your body, your transplant team may ask you not to take your morning dose until after the blood sample is taken. Check with your transplant team before skipping this dose.

Can Other Medicines Affect How Tacrolimus Capsules Works?
Some medicines and alcohol can affect how well tacrolimus capsules works. After you start taking tacrolimus capsules:

- Be sure to tell your transplant team, family doctor, dentist, pharmacist and any other health care professional treating you the names of **all** the medicines you are taking. This includes tacrolimus capsules as well as all other prescription medicines and non-prescription medicines, natural or herbal remedies, nutritional supplements, and vitamins. This is the only way that your health care team can help prevent drug interactions that could be serious.
- Always check with your transplant team before you start taking any new medicine.
- While you are taking tacrolimus capsules, **do not get any vaccinations without your transplant team's approval**. The vaccination may not work as well as it should.
- Liver transplant patients, including those taking tacrolimus capsules should not drink alcohol.

What Are the Possible Side Effects of Tacrolimus Capsules?
Tell your transplant team right away if you think you might be having a side effect. Your transplant team will decide if it is a medicine side effect or a sign that has nothing to do with the medicine but needs to be treated. Infection or reduced urine can be signs of serious problems that you should discuss with your transplant team.
Your transplant team will also follow your progress and watch for the early signs of any side effects. This is why you will have blood tests done often during the first few months after your transplant. On the days you are going to have a blood test to measure the amount of tacrolimus capsules in your body, your transplant team may ask you not to take your morning dose until after the blood sample is taken. Check with your transplant team before skipping this dose.

For Kidney Transplant Patients
The most common side effects of tacrolimus capsules for kidney transplant patients are infection, headache, tremors (shaking of the body), diarrhea, constipation, nausea, high blood pressure, changes in the amount of urine, and trouble sleeping.
Less common side effects are abdominal pain (stomach pain), numbness or tingling in your hands or feet; loss of appetite; indigestion or "upset stomach"; vomiting; urinary tract infections; fever; pain; swelling of the hands, ankles or legs; shortness of breath or trouble breathing; cough; leg cramps; heart "fluttering," palpitations or chest pain; unusual weakness or tiredness; dizziness; confusion; changes in mood or emotions; itchy skin, skin rash, and diabetes.

For Liver Transplant Patients
The most common side effects of tacrolimus capsules for liver transplant patients are headache, tremors (shaking of the body), diarrhea, high blood pressure, nausea and changes in the amount of urine.
Less common side effects are numbness or tingling in your hands or feet; trouble sleeping; constipation; loss of appetite; vomiting; urinary tract infections; fever, pain (especially in the back or abdomen [stomach area]); swelling of the hands, ankles, legs or abdomen; shortness of breath or trouble breathing; cough; unusual bruising; leg cramps; heart 'fluttering' or palpitations; unusual weakness or tiredness; confusion; changes in mood or emotions; itchy skin, and skin rash.
Be sure to tell your transplant team right away if you notice that you are thirstier than usual, have to urinate more often, have blurred vision or seem to get confused. These may be the early signs of high blood sugar or diabetes.
All anti-rejection medicines, including tacrolimus capsules, suppress your body's immune system. As a result, they may increase your chances of getting infections and some kinds of cancer, including skin and lymph gland cancer (lymphoma). As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high sun protection factor (SPF$\geq$15). However, getting cancer from taking an anti-rejection medicine is not common. Talk with your transplant team about any concerns or questions you have.

How Should I Store Tacrolimus Capsules?
Tacrolimus capsules should be stored at 20° - 25°C (68° - 77°F) [see USP Controlled Room Temperature]. For instance, do not leave tacrolimus capsules in the glove compartment of your car in the summer or winter. Do not keep tacrolimus capsules in a hot or moist place such as the medicine cabinet in the bathroom.

General Advice about Prescription Medicines
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use tacrolimus capsules for a condition for which it was not prescribed. Do not give tacrolimus capsules to other people.
This leaflet summarizes the most important information about tacrolimus capsules. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about tacrolimus capsules that is written for health professionals.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Manufactured in India by Sandoz Private Limited for
Sandoz Inc; Princeton NJ 08540

Iss. May 2009

NDC 0781-2102-01

Tacrolimus Capsules

0.5 mg*

℞ only

100 Capsules

SANDOZ

Note: Tacrolimus capsules are not filled to maximum capsule capacity.
*Each capsule contains: Tacrolimus 0.5 mg
Usual Dosage: See package insert.
Store at 20°–25°C (68°–77°F) [see USP Controlled Room Temperature]. Protect from moisture.
Dispense in a tight, light-resistant container.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
Code No.: MH/DRUGS/KD-548
Manufactured in India by Sandoz Private Ltd.
for Sandoz Inc., Princeton, NJ 08540

Rev. 10/2007
2XXXXX

N 3 0 7 8 1 – 2 1 0 2 – 0 1 5

NDC 0781-2103-01

Tacrolimus Capsules

1 mg*

℞ only

100 Capsules

SANDOZ

Note: Tacrolimus capsules are not filled to maximum capsule capacity.
*Each capsule contains: Tacrolimus 1 mg
Usual Dosage: See package insert.
Store at 20°–25°C (68°–77°F) [see USP Controlled Room Temperature]. Protect from moisture.
Dispense in a tight, light-resistant container.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
Code No.: MH/DRUGS/KD-548
Manufactured in India by Sandoz Private Ltd.
for Sandoz Inc., Princeton, NJ 08540

Rev. 10/2007
2XXXXX

N 3 | 0 7 8 1 – 2 1 0 3 – 0 1 | 2

NDC 0781-2104-01

Tacrolimus Capsules

5 mg*

℞ only

100 Capsules

SANDOZ

*Each capsule contains: Tacrolimus 5 mg
Usual Dosage: See package insert.
Store at 20°–25°C (68°–77°F) [see USP Controlled Room Temperature]. Protect from moisture.
Dispense in a tight, light-resistant container.
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
Code No.: MH/DRUGS/KD-548
Manufactured in India by Sandoz Private Ltd.
for Sandoz Inc., Princeton, NJ 08540

Rev. 10/2007 2XXXXX

N 3 0 7 8 1 – 2 1 0 4 – 0 1 9

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

/s/

Angela Payne
6/9/2009 02:20:16 PM
LABELING REVIEWER

John Grace
6/9/2009 02:29:11 PM
LABELING REVIEWER

APPROVAL SUMMARY #1
LABELING REVIEW BRANCH

1. APPLICANT INFORMATION:

ANDA Number	65-461
Date of Submission	25 FEB 2009
Applicant	Sandoz
Drug Name	Tacrolimus Capsules
Strength(s)	0.5 mg,1 mg, and 5 mg

LABELS AND LABELING SUMMARY-

Containers- 100s
Satisfactory in Jan. 4, 2008
\\Fdswa150\nonectd\N65461\N_000\2008-01-04\ Revised Tacrolimus 0.5 mg.pdf
\\Fdswa150\nonectd\N65461\N_000\2008-01-04\Revised Tacrolimus1 mg.pdf
Satisfactory in Oct. 23, 2007
\\Fdswa150\nonectd\N65461\N_000\2007-10-23\Container labels\Tacrolimus 5 mg 100s for FDA.pdf

Satisfactory in Feb. 25, 2009
Insert \\Fdswa150\nonectd\N65461\N_000\2009-02-25\TO FDA\Proposed PI (FPL).pdf
Patient Leaflet- Attached to insert.

2. NOTE TO CHEMIST: None

3. MODEL LABELING-This review was based on the labeling NDA- See below.

Reference Listed Drug

RLD on the 356(h) form	Prograf®
NDA Number	50-708
RLD established name	Tacrolimus Capsules 0.5 mg, 1 mg and 5 mg (equivalent to anhydrous)
Firm	Astellas
Currently approved PI	S-034
AP Date	2.13.09

Note: This insert is a combined IV and PO insert. The generic will have only limited information regarding the IV dosage form in the labeling.

4. PATENTS/EXCLUSIVITIES: [Vol. A1.1 pg.] REFERENCE LISTED DRUG:

Patent Data For NDA 50-708

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None				PII	

Exclusivity Data - 50-708

Code/sup	Expiration	Use Code	Description		Labeling Impact
ODE	3-29-13		Prophylaxis of Organ Rejection in Patients Receiving Heart Transplants		Firm carved out information.

5. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM - Sandoz Private Limited – INDIA

6. INACTIVE INGREDIENTS

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition.

7. CONTAINER/CLOSURE

The containers are made of HDPE – the 100s have CRC caps.

8. PACKAGING CONFIGURATIONS
   NDA: 100s (all three strengths) and Blister Packs of 100s 1 mg and 5 mg only]
   ANDA: 100s

9. STORAGE AND DISPENSING STATEMENT
   USP: not USP
   NDA: Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).
   ANDA: Store at 20° - 25°C (68° - 77°F) [see USP Controlled Room Temperature]. (b) (4) .

10. The inactive ingredients in the DESCRIPTION section are the same as those listed in the Components and Composition statement.

11. FOR THE RECORD:

Review based on the labeling of Prograf® Capsules (Astellas- NDA 50-708/S-0), approved. The RLD has a shared insert with Prograf® Injection. Some of the information relating to the IV has been retained – see REVIEW NOTES below:

Some of the information relating to the IV has been retained as follows:

a. CLINICAL PHARMACOLOGY, (1) Pharmacokinetics table – leave in IV – (2) Excretion – leave in IV (65-461 was excluded- will need to revisit) (3) Special Populations – (a) Pediatric – leave in IV (change 65-461) – (b) Renal and Hepatic Insufficiency table – include IV

b. INDICATIONS AND USAGE- Delete sentence (relating to IV)

c. CONTRAINDICATIONS – Retain second sentence IV (need to revisit 65-461).

d. WARNINGS (1) Include the last two paragraph regarding the injection. It is important information.

f. DOSAGE AND ADMINISTRATION (1) Leave out IV dosing text (2) Retain "NOTE: Anaphylactic reactions….(See WARNINGS)" (3) Pediatric Patients – (a) Do include the

---

Date of Review: 3-03-09 Date of Submission: 25 FEB 2009
Primary Reviewer: Angela Payne Date:
Team Leader: John Grace Date:

---

cc: ANDA 65-461
DUP/DIVISION FILE
HFD-613/APayne/JGrace
V:\FIRMSNZ\SANDOZ\LTRS&REV\65461AP1labdfsreview.doc
Review

5 Pages of Draft Labeling have been Withheld as b4 (CCI/TS) immediately following this page

---

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

/s/

Angela Payne
3/5/2009 10:25:58 AM
LABELING REVIEWER

John Grace
3/5/2009 01:56:32 PM
LABELING REVIEWER

(this approval summary supersedes the approval summary done on the 10-23-07 submission)
APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW

ANDA Number: **65-461** **Date** of Submission: **January 4, 2008**

Applicant's Name: **Sandoz Inc**

Established Name: **Tacrolimus Capsules, 0.5 mg, 1 mg and 5 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? NO – ELECTRONIC
Container Labels: 100s
Professional Package Insert Labeling:
Patient Package Insert Labeling:

	SUBMIT	ACTION
Label – 0.5 mg	1-4-08	APPROVE
Label – 1 mg	1-4-08	APPROVE
Label – 5 mg	10-23-07	APPROVE
Insert	10-23-07	APPROVE
PPI	10-23-07	APPROVE

Revisions needed post-approval: PPI – (1) Include a website with the company phone number in the second paragraph and also in the last paragraph (2) For Liver Transplant Patients – Bold the following two sentences "Be sure to tell your … to get confused. These may be … early signs of high blood sugar or diabetes"

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Prograf®
NDA Number: 50-708
NDA Drug Name: Prograf® (tacrolimus) Capsules
NDA Firm: Astellas
Date of Approval of NDA Insert and supplement #: 4-27-06 (S-026)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling of Prograf® Capsules (Astellas- NDA 50-708/S-026), approved 4-27-06. The RLD has a shared insert with Prograf® Injection. Some of the information relating to the IV has been retained – see REVIEW NOTES below (the **bolded** notes below are a result of the ODE exclusivity – see FTR #2 table):
   a. CLINICAL PHARMACOLOGY, (1) Mechanism of Action, first paragraph **– Delete** (b) (4) (2) Pharmacokinetics (a) First paragraph – **Leave out** (b) (4) (b) table – leave in IV – **take out** (b) (4) (c) Absorption (i) First

paragraph, second sentence – **Delete** [redacted] (ii) Third paragraph – **Delete the last sentence**. (d) Excretion – leave out IV (e) Special Populations – (i) Pediatric – leave out IV – (ii) Renal and Hepatic Insufficiency table – include IV

b. CLINICAL STUDIES - **Leave out Heart Transplantation**

c. INDICATIONS AND USAGE (1) First sentence – **Delete** [redacted] (2) Delete third sentence (relating to IV)

d. CONTRAINDICATIONS – Leave out second sentence.

e. WARNINGS (1) [redacted] (2) **Delete** [redacted] (3) Paragraph Tacrolimus capsules can …(a) Second sentence – **Delete** [redacted] (b) **Delete third sentence** [redacted] (4) Paragraph "Mild to severe …" First sentence – **Delete** [redacted] (5) Paragraph "Neurotoxicity, including …" (a) Second sentence – **Delete** [redacted] (b) Third sentence – **Delete the third sentence** (6) Delete the last two paragraphs.

f. PRECAUTIONS – Pediatric Patients, first sentence – **Delete** [redacted]

g. ADVERSE REACTIONS (1) **Delete** [redacted] **subsection** (2) Less Frequently Reported Adverse Reactions – retain [redacted]

h. DOSAGE AND ADMINISTRATION (1) Leave out IV dosing text (2) Retain first sentence as is "In patients unable to take oral tacrolimus capsules, therapy may be initiated with tacrolimus injection." (3) **Delete both** [redacted] **subsection**s (4) Pediatric Patients – (a) Do not include the IV dosing information (b) Last sentence – **Delete** [redacted] (5) Patients with Hepatic or Renal Dysfunction, second paragraph, first sentence – "… of the recommended IV and oral dosing ranges."

The RLD container label has the following text on the principal display panel: "Note: Prograf capsules are not filled to maximum capsule capacity. Capsule contains labeled amount." I spoke to Carmelle Lucas of the firm on 12-5-07 and she believes that the ANDA's capsules are full and stated that she would call me if she was in error. With this submission (1-4-08) the firm submitted the 0.5 mg and 1 mg container labels with the new statement [redacted] I spoke to Carmelle Lucas of the firm on 1-22-08 and asked her about the 5 mg capsules – she let me know that those capsules are full to capacity and did not require the new statement.

2. PATENTS/EXCLUSIVITIES

Patent/ Exclusivities

Patent Data – 50-708

No	Expiration	Use Code	Use	File
None				

Exclusivity Data – 50-708

Code/sup	Expiration	Use Code	Description		Labeling Impact
ODE	3-29-13		Prophylaxis of Organ Rejection in Patients Receiving Heart Transplants		Info left out**

** See FTR # 1 above.

3. INACTIVE INGREDIENTS

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition.

4. CONTAINER/CLOSURE

The containers are made of HDPE – the 100s have CRC caps.

5. PACKAGING CONFIGURATIONS
NDA: 100s (all three strengths) and Blister Packs of 100s 1 mg and 5 mg only]
ANDA: 100s

6. STORAGE AND DISPENSING STATEMENT
USP: not USP
NDA: Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).
ANDA: Store at 20° - 25°C (68° - 77°F) [see USP Controlled Room Temperature]. (b) (4)

7. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM
Sandoz Private Limited – INDIA

8. The inactive ingredients in the DESCRIPTION section are the same as those listed in the Components and Composition statement.

9. The maximum total daily elemental iron intake is less than 0.5 mg.

Date of Review: 1-22-08 Date of Submission: 1-4-08

Primary Reviewer: Adolph Vezza Date:

Team Leader: Captain Lillie Golson Date:

---

cc: ANDA 65-461
DUP/DIVISION FILE
HFD-613/AVezza
HFD-613/LGolson
aev/1/22/08|C:\FIRMSNZ\SANDOZ\LTRS&REV\65461AP2.LABELING.doc
Review


(b) (4)


(b) (4)

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

/s/

Adolph Vezza
1/25/2008 10:23:19 AM
LABELING REVIEWER

Chan Park
1/25/2008 10:42:59 AM
LABELING REVIEWER
Chan Park for Lillie Golson

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW

ANDA Number: **65-461** **Date** of Submission: **October 23, 2007**

Applicant's Name: **Sandoz Inc**

Established Name: **Tacrolimus Capsules, 0.5 mg, 1 mg and 5 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? NO – ELECTRONIC
Container Labels: 100s
Professional Package Insert Labeling:
Patient Package Insert Labeling:

	SUBMIT	ACTION
Label – 0.5 mg	10-23-07	APPROVE
Label – 1 mg	10-23-07	APPROVE
Label – 5 mg	10-23-07	APPROVE
Insert	10-23-07	APPROVE
PPI	10-23-07	APPROVE

Revisions needed post-approval: PPI – (1) Include a website with the company phone number in the second paragraph and also in the last paragraph (2) For Liver Transplant Patients – Bold the following two sentences "Be sure to tell your … to get confused. These may be … early signs of high blood sugar or diabetes"

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Prograf®
NDA Number: 50-708
NDA Drug Name: Prograf® (tacrolimus) Capsules
NDA Firm: Astellas
Date of Approval of NDA Insert and supplement #: 4-27-06 (S-026)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in he PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? NO.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a		X	

CRC.			
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must he package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)	X		
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of he statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list dyes in imprinting inks? (Coloring agents e g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommenda ions fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		**X**	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling of Prograf® Capsules (Astellas- NDA 50-708/S-026), approved 4-27-06. The RLD has a shared insert with Prograf® Injection. Some of the information relating to the IV has been retained – see REVIEW NOTES below (the **bolded** notes below are a result of the ODE exclusivity – see FTR #2 table):
   a. CLINICAL PHARMACOLOGY, (1) Mechanism of Action, first paragraph **– Delete** (b) (4) (2) Pharmacokinetics (a) First paragraph – **Leave out** (b) (4) (b) table – leave in IV – **take out** (b) (4) (c) Absorption (i) First paragraph, second sentence – **Delete** (b) (4) (ii) Third paragraph – **Delete the last sentence**. (d) Excretion – leave out IV (e) Special

Populations – (i) Pediatric – leave out IV – (ii) Renal and Hepatic Insufficiency table – include IV

b. CLINICAL STUDIES - **Leave out** (b) (4)

c. INDICATIONS AND USAGE (1) First sentence – **Delete** (b) (4) (2) Delete third sentence (relating to IV)

d. CONTRAINDICATIONS – Leave out second sentence.

e. WARNINGS (1) **Delete paragraph "** (b) (4) (2) **Delete** (b) (4) **table** (3) Paragraph Tacrolimus capsules can …(a) Second sentence – **Delete** (b) (4) (b) **Delete third sentence** (b) (4) (4) Paragraph "Mild to severe …" First sentence – **Delete** (b) (4) (5) Paragraph "Neurotoxicity, including …" (a) Second sentence – **Delete** (b) (4) (b) Third sentence – **Delete the third sentence** (6) Delete the last two paragraphs.

f. PRECAUTIONS – Pediatric Patients, first sentence – **Delete** (b) (4)

g. ADVERSE REACTIONS (1) **Delete** **" subsection** (2) Less Frequently Reported Adverse Reactions – retain "and/or heart"

h. DOSAGE AND ADMINISTRATION (1) Leave out IV dosing text (2) Retain first sentence as is "In patients unable to take oral tacrolimus capsules, therapy may be initiated with tacrolimus injection." (3) **Delete both** (b) (4) **subsectio**ns (4) Pediatric Patients – (a) Do not include the IV dosing information (b) Last sentence – **Delete** (b) (4) (5) Patients with Hepatic or Renal Dysfunction, second paragraph, first sentence – … of the recommended IV and oral dosing ranges."

The RLD container label has the following text on the principal display panel: "Note: Prograf capsules are not filled to maximum capsule capacity. Capsule contains labeled amount." I spoke to Carmelle Lucas of the firm on 12-5-07 and she believes that the ANDA's capsules are full and stated that she would call me if she was in error.

2. PATENTS/EXCLUSIVITIES

Patent/ Exclusivities

Patent Data – 50-708

No	Expiration	Use Code	Use	File
None				

Exclusivity Data – 50-708

Code/sup	Expiration	Use Code	Description		Labeling Impact
ODE	3-29-13		Prophylaxis of Organ Rejection in Patients Receiving Heart Transplants		Info left out**

** See FTR # 1 above.

3. INACTIVE INGREDIENTS

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition.

4. CONTAINER/CLOSURE

The containers are made of HDPE – the 100s have CRC caps.

5. PACKAGING CONFIGURATIONS

NDA: 100s (all three strengths) and Blister Packs of 100s 1 mg and 5 mg only]
ANDA: 100s

6. STORAGE AND DISPENSING STATEMENT
   USP: not USP
   NDA: Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).
   ANDA: Store at 20° - 25°C (68° - 77°F) [see USP Controlled Room Temperature]. (b) (4)

7. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM
   Sandoz Private Limited – INDIA

8. The inactive ingredients in the DESCRIPTION section are the same as those listed in the Components and Composition statement.

9. The maximum total daily elemental iron intake is less than 0.5 mg.

Date of Review: 12-5-07 Date of Submission: 10-23-07

Primary Reviewer: Adolph Vezza Date:

Team Leader: Captain Lillie Golson Date:

---

cc: ANDA 65-461
DUP/DIVISION FILE
HFD-613/AVezza
HFD-613/LGolson
aev/12/5/07|
Review


(b) (4)


(b) (4)

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

/s/

Adolph Vezza
12/13/2007 09:22:02 AM
LABELING REVIEWER

Lillie Golson
12/13/2007 03:45:04 PM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW

ANDA Number: **65-461** **Date** of Submission: **December 28, 2006**

Applicant's Name: **Sandoz Inc**

Established Name: **Tacrolimus Capsules, 0.5 mg, 1 mg and 5 mg**

Labeling Deficiencies:

1. CONTAINER 100s

   Increase the prominence of the established name.

2. INSERT

   a. GENERAL COMMENTS

      i. "U.S." rather than "US"

      ii. Replace "Prograf" with "tacrolimus" wherever it appears in the insert labeling.

      iii. "*in vitro*" and "*in vivo*" [*italics*]

      iv. Delete terminal zeroes throughout your insert.

      v. Delete the extra space between hyphenated words, e.g., "tacrolimus-based" rather than "tacrolimus -based".

      vi. There is an Orphan Drug Exclusivity for "prophylaxis of Organ Rejection in Patients Receiving Heart Transplants" which expires on March 29, 2013 for the reference listed drug. As a result thereof you must delete all information relating to this indication from your insert labeling including that found in tables.

   b. DESCRIPTION

      i. Inactive ingredients – There is no need to list the inactive ingredients which are not present in the finished drug product, e.g., (b) (4).

      ii. First paragraph, second sentence – Place "1" and "mg" on the same line of text.

      iii. Third paragraph – "… black iron oxide, gelatin …" [add comma]

      iv. Last paragraph – "molecular" rather than (b) (4)

   c. CLINICAL PHARMACOLOGY

      Pharmacokinetics

      i. First table

A). Replace the hyphens and "…" with "---"

B). Footnotes – Make sure the hyphens are placed properly in the subscripts.

ii. Special Populations – Renal and Hepatic Insufficiency

A). Table

1). Include the IV information in the table.

2). Second column – "8 mg", "5 mg" and "4 mg" rather than "8mg", "5mg" and "4mg"

3). Third column

a). Place "120" and "hr)" on the same line of text.

b). Place "144" and "hr)" on the same line of text.

B). Include the "Renal Insufficiency" paragraphs.

C). Hepatic Insufficiency, first sentence – "… following single IV and oral administrations. The mean …"

d. WARNINGS

Third paragraph, second sentence – "… tacrolimus …" [lower case "t"]

e. PRECAUTIONS

Carcinogenesis, Mutagenesis, Impairment of Fertility - Delete the word "and" in the subsection title.

f. ADVERSE REACTIONS

i. Liver Transplantation, Table

A). Nervous System, third column of data – Place "17%" in the "Paresthesia" row.

B). Gastrointestinal

1). "Nausea" [spelling}

2). Third column of data – Relocate "37%" and "32%" to be in the correct rows.

ii. Kidney Transplantation

A). Second paragraph – "tacrolimus" [lower case "t"]

B). Table

1). Urogenital – Delete the excess spacing between "Creatinine",

"Increased" and "(see".

2). Delete the underline from "Hypophosphatemia"

3). Respiratory System – Relocate the data to be in the correct rows.

4). Musculoskeletal - Relocate the data to be in the correct rows.

g. DOSAGE AND ADMINISTRATION

i. First sentence – "tacrolimus" [lower case "t" – two instances]

ii. Liver Transplantation, first paragraph, last line – "Tacrolimus" [upper case "T"]

ii. Blood Concentration Monitoring, second paragraph

A). Fourth sentence – "anticoagulant" [delete hyphen]

B). Fifth sentence – "anticoagulation" [delete hyphen]

h. HOW SUPPLIED

Delete (b) (4)

3. PPI

The labeling of the reference listed drug includes a patient package insert (PPI). Please include this in your next labeling submission.

Please revise your labeling as described above and submit in final print. Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format - ANDA". The immediate container labels may be submitted either electronically or in hard copy. However, for ease of review, we ask that you submit electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

{See appended electronic signature page}

_____

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? NO – ELECTRONIC
Container Labels: 100s
Professional Package Insert Labeling:
Patient Package Insert labeling: NOT SUBMITTED

	SUBMIT	ACTION
Label – 0.5 mg	12-28-06	REVISE
Label – 1 mg	12-28-06	REVISE
Label – 5 mg	12-28-06	REVISE
Insert	12-28-06	REVISE
PPI	N/A	

Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Prograf®
NDA Number: 50-708
NDA Drug Name: Prograf® (tacrolimus) Capsules
NDA Firm: Astellas
Date of Approval of NDA Insert and supplement #: 4-27-06 (S-026)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: side-by-sides
Other Comments

FOR THE RECORD:

1. Review based on the labeling of Prograf® Capsules (Astellas- NDA 50-708/S-026), approved 4-27-06. The RLD has a shared insert with Prograf® Injection. Some of the information relating to the IV has been retained – see REVIEW NOTES below:
    a. CLINICAL PHARMACOLOGY, (1) Mechanism of Action, first paragraph – Delete (b) (4) (2) Pharmacokinetics (a) First paragraph – Leave out (b) (4) (b) table – leave in IV – take out (b) (4) (c) Absorption (i) First paragraph, second sentence – Delete (b) (4) (ii) Third paragraph – Delete the last sentence. (d) Excretion – leave out IV (e) Special Populations – (i) Pediatric – leave out IV – (ii) Renal and Hepatic Insufficiency table – include IV
    b. CLINICAL STUDIES - Leave out Heart Transplantation
    c. INDICATIONS AND USAGE (1) First sentence – Delete (b) (4) (2) Delete third sentence (relating to IV)
    d. CONTRAINDICATIONS – Leave out second sentence.
    e. WARNINGS (1) Delete paragraph (b) (4) (2) Delete heart transplant table (3) Paragraph "Tacrolimus capsules can … (a) Second sentence – Delete (b) (4) (b) Delete third sentence (b) (4) (4) Paragraph "Mild to severe …" First sentence – Delete (b) (4) (5) Paragraph "Neurotoxicity, including …" (a) Second sentence – Delete (b) (4) (b) Third sentence – Delete the third sentence (6) Delete the last two paragraphs.
    f. PRECAUTIONS – Pediatric Patients, first sentence – Delete (b) (4)
    g. ADVERSE REACTIONS (1) Delete (b) (4) subsection

(2) Less Frequently Reported Adverse Reactions – retain [redacted]

h. DOSAGE AND ADMINISTRATION (1) Leave out IV dosing text (2) Retain first sentence as is "In patients unable to take oral tacrolimus capsules, therapy may be initiated with tacrolimus injection." (3) Delete both [redacted] subsections (4) Pediatric Patients – (a) Do not include the IV dosing information (b) Last sentence – Delete [redacted] (5) Patients with Hepatic or Renal Dysfunction, second paragraph, first sentence – "… of the recommended IV and oral dosing ranges."

2. PATENTS/EXCLUSIVITIES

Patent/ Exclusivities

Patent Data – 50-708

No	Expiration	Use Code	Use	File
None				

Exclusivity Data - 19-834

Code/sup	Expiration	Use Code	Description		Labeling Impact
ODE	3-29-13		Prophylaxis of Organ Rejection in Patients Receiving Heart Transplants		Info left out**

** See FTR # 1 above.

3. INACTIVE INGREDIENTS
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition.

4. CONTAINER/CLOSURE

The containers are made of HDPE – the 100s have CRC caps.

5. PACKAGING CONFIGURATIONS
NDA: 100s (all three strengths) and Blister Packs of 100s 1 mg and 5 mg only]
ANDA: 100s

6. STORAGE AND DISPENSING STATEMENT
USP: not USP
NDA: Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).
ANDA: Store at 20° - 25°C (68° - 77°F) [see USP Controlled Room Temperature]. [redacted]

7. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM
Sandoz Private Limited – INDIA

8. The inactive ingredients in the DESCRIPTION section are the same as those listed in the Components and Composition statement.

9. The firm neglected to submit a PPI – see comment in review.

Date of Review: 9-25-07 Date of Submission: 12-28-07

Primary Reviewer: Adolph Vezza Date:

Team Leader: Captain Lillie Golson Date:

---

cc: ANDA 65-461
DUP/DIVISION FILE
HFD-613/AVezza
HFD-613/LGolson
aev/9/25/07|V:\DIVISION\LABEL\VEZZA\LTRS&REV\TACROLIMUS\65461na1.LABELING.doc
Review

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

/s/

Adolph Vezza
9/28/2007 03:58:41 PM
LABELING REVIEWER

Lillie Golson
9/28/2007 04:30:00 PM
LABELING REVIEWER

Telephone Fax

ANDA 65-461

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8987

TO: SANDOZ INC

TEL: 609-627-8854

ATTN: CARMELLE LUCAS

FAX: 609-627-2792

FROM: ADOLPH VEZZA

:

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for _Tacrolimus Capsules, 0.5 mg, 1 mg and 5 mg.

Pages (including cover): __6__

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW

ANDA Number: **65-461** **Dat**e of Submission: **December 28, 2006**

Applicant's Name: **Sandoz Inc**

Established Name: **Tacrolimus Capsules, 0.5 mg, 1 mg and 5 mg**

Labeling Deficiencies:

1. CONTAINER 100s

   Increase the prominence of the established name.

2. INSERT

   a. GENERAL COMMENTS

      i. "U.S." rather than "US"

      ii. Replace "Prograf" with "tacrolimus" wherever it appears in the insert labeling.

      iii. "*in vitro*" and "*in vivo*" [*italics*]

      iv. Delete terminal zeroes throughout your insert.

      v. Delete the extra space between hyphenated words, e.g., "tacrolimus-based" rather than "tacrolimus -based".

      vi. There is an Orphan Drug Exclusivity for "prophylaxis of Organ Rejection in Patients Receiving Heart Transplants" which expires on March 29, 2013 for the reference listed drug. As a result thereof you must delete all information relating to this indication from your insert labeling including that found in tables.

   b. DESCRIPTION

      i. Inactive ingredients – There is no need to list the inactive ingredients which are not present in the finished drug product, e.g., (b) (4).

      ii. First paragraph, second sentence – Place "1" and "mg" on the same line of text.

      iii. Third paragraph – "… black iron oxide, gelatin …" [add comma]

      iv. Last paragraph – "molecular" rather than (b) (4)

   c. CLINICAL PHARMACOLOGY

      Pharmacokinetics

i. First table

A). Replace the hyphens and "…" with "---"

B). Footnotes – Make sure the hyphens are placed properly in the subscripts.

ii. Special Populations – Renal and Hepatic Insufficiency

A). Table

1). Include the IV information in the table.

2). Second column – "8 mg", "5 mg" and "4 mg" rather than "8mg", "5mg" and "4mg"

3). Third column

a). Place "120" and "hr)" on the same line of text.

b). Place "144" and "hr)" on the same line of text.

B). Include the "Renal Insufficiency" paragraphs.

C). Hepatic Insufficiency, first sentence – "… following single IV and oral administrations. The mean …"

d. WARNINGS

Third paragraph, second sentence – "… tacrolimus …" [lower case "t"]

e. PRECAUTIONS

Carcinogenesis, Mutagenesis, Impairment of Fertility - Delete the word "and" in the subsection title.

f. ADVERSE REACTIONS

i. Liver Transplantation, Table

A). Nervous System, third column of data – Place "17%" in the "Paresthesia" row.

B). Gastrointestinal

1). "Nausea" [spelling}

2). Third column of data – Relocate "37%" and "32%" to be in the correct rows.

ii. Kidney Transplantation

A). Second paragraph – "tacrolimus" [lower case "t"]

B). Table

1). Urogenital – Delete the excess spacing between “Creatinine”, “Increased” and “(see”.

2). Delete the underline from “Hypophosphatemia”

3). Respiratory System – Relocate the data to be in the correct rows.

4). Musculoskeletal - Relocate the data to be in the correct rows.

g. DOSAGE AND ADMINISTRATION

i. First sentence – “tacrolimus” [lower case “t” – two instances]

ii. Liver Transplantation, first paragraph, last line – “Tacrolimus” [upper case “T”]

ii. Blood Concentration Monitoring, second paragraph

A). Fourth sentence – “anticoagulant” [delete hyphen]

B). Fifth sentence – “anticoagulation” [delete hyphen]

h. HOW SUPPLIED

Delete (b) (4)

3. PPI

The labeling of the reference listed drug includes a patient package insert (PPI). Please include this in your next labeling submission.

Please revise your labeling as described above and submit in final print. Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format - ANDA". The immediate container labels may be submitted either electronically or in hard copy. However, for ease of review, we ask that you submit electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

{See appended electronic signature page}

_____

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Lillie Golson
9/28/2007 04:29:05 PM
Lillie Golson for Wm. Peter Rickman

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-461

CHEMISTRY REVIEWS

ANDA 65-461

Tacrolimus Capsules
0.5 mg, 1 mg and 5 mg

Sandoz, Inc.

Marco Bennett, Ph.D.

Division of Chemistry III, Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 65-461

2. REVIEW #: 4

3. REVIEW DATE: 10-JUL-2008; 28-JUL-2008; 8/8/08 *added by SZ;* 28-AUG-2008; 23-OCT-2008; 12/1/2008; 12/11/2008; 30-JAN-2009

4. REVIEWER: Marco Bennett, PhD

5. PREVIOUS DOCUMENTS:

Original Submission	28-DEC-2006
Acceptable for Filing	29-DEC-2006 (letter dated 4/6/07)
Amendment Submission	08-AUG-2007
Amendment Submission	07-MAR-2008
Correspondence (Attachment for 356h)	12-MAR-2008
Gratuitous Amendment	20-MAR-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Telephone Amendment	20-JUN-2008
Telephone Amendment	27-JUN-2008
Telephone Amendment	21-JUL-2008
Telephone Amendment	08-AUG-2008
Telephone Amendment	25-AUG-2008
Telephone Amendment	21-OCT-2008
Gratuitous Amendment (Correspondence)	26-NOV-2008
Telephone Amendment (Correspondence)	08-DEC-2008
Telephone Amendment	30-JAN-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Sandoz Inc.
Address:	506 Carnegie Center, Suite 400 Princeton, NJ 08540
Representative:	Srinivasa Rao, Pharm.D.
Telephone:	(609) 627-8885
Fax:	(609) 395-2792

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): Tacrolimus Capsules, 0.5 mg, 1 mg, 5 mg

9. LEGAL BASIS FOR SUBMISSION:

The reference listed drug for this application is Prograf® Capsules, 0.5 mg, 1 mg, 5 mg manufactured by Astellas Pharma US, Inc. under NDA #50-708.

Firm claims that there are no unexpired patents or exclusivity for the RLD (Section 1.3.5.2).

10. PHARMACOL. CATEGORY: Immunomodulator

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 0.5 mg, 1 mg, 5 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: x Rx ___OTC

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

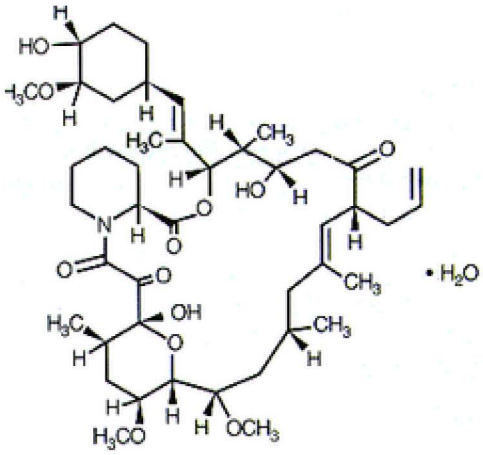
SPOTS product – Form Completed

x Not a SPOTS product

16. 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**,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-methoxycyclohexyl)-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.

Molecular Formula: $C_{44}H_{69}NO_{12} \cdot H_2O$
Molecular Weight: 822.05



17. RELATED/SUPPORTING DOCUMENTS: N/A

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
19979	II	Lek Pharmaceuticals	Tacrolimus	1	Adequate	3/19/09	
[redacted]				(b) (4)	-	-	-
					-	-	-
					-	-	-
					-	-	-
					-	-	-
					-	-	-
					-	-	-
					-	-	-
					-	-	-

[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: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	18-APR-2007	S. Adams (HFD-325)
Methods Validation	N/A		
Labeling	Acceptable	5-MAR-2009	A.Payne
Bioequivalence	Acceptable	15-APR-2008	N. Chun

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___x_ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 65-461

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Recommended for Approval

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

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)
The reference listed drug for this application is Prograf® Capsules, 0.5 mg, 1 mg, 5 mg manufactured by Astellas Pharma US, Inc. under NDA #50-708. Tacrolimus is an immunosuppresant. Tacrolimus prolongs the survival of the host and transplanted graft in animal transplant models of liver, kidney, heart, bone marrow, small bowel and pancreas, lung and trachea, skin, cornea, and limb. Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. The net result is the inhibition of T-lymphocyte activation (i.e., immunosuppression). Tacrolimus is produced by fermentation from the micro-organism *Streptomyces tsukubaensis*.

Drug substance
Tacrolimus Monohydrate is a non-hygroscopic white to almost crystalline powder. It is practically insoluble in water but soluble in absolute alcohol. Its molecular weight is 822.05 g/mol as the monohydrate. Tacrolimus is manufactured by Lek Pharmaceuticals d.d. in DMF 19979.

Drug product
The drug product is Tacrolimus Capsules of strengths 0.5mg, 1 mg and 5 mg. The inactive ingredients present in the drug product are Hyperomellose USP ((b) (4)), Lactose Monohydrate NF ((b) (4)), Croscarmellose Sodium NF ((b) (4)), (b) (4), Magnesium Stearate NF and the active ingredient is Tacrolimus Monohydrate. The drug product will be marketed in (b) (4) cc HDPE Bottles, (b) (4) cc HDPE Bottles and (b) (4)

Process
(b) (4)

[redacted] (b) (4)

Sandoz submitted three months of accelerated and 24 months controlled room temperature stability in the original ANDA to support a 24 month expiration period for the 1 mg and 5 mg strengths packaged in HDPE bottles and Bulk Packages. Owing to out-of-specification results of the Tacrolimus [redacted] (b) (4) impurity in the 0.5 mg strength, all three strengths will have an 18 month expiration period.

[redacted]

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

Tacrolimus is recommended for use in organ transplant patients to prevent organ rejection. The maximum daily dose is 0.2 mg/kg/day.

C. Basis for Approvability or Not-Approval Recommendation

The application is approvable.

[redacted]

72 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Administrative

A. Reviewer's Signature

B. Endorsement Bloc

HFD-630/MBennett/7/10/2008; 7/28/2008; 8/08/08; 8/28/08; 10/23/2008; 12/1/2008; 12/11/2008; 01/30/2009

HFD-630/SZuk/7/14/08; 8/08/08; 8/28/08; 10/23/08; 12/11/08; 1/30/09

HFD-617/RSzydlo/9/3/08; 10/24/08; 12/11/08; 1/30/09; 5/26/09

V:\Chemistry Division III\Team 6\Final Version For DFS Folder\65461.R04.AP.doc

F/T by:

TYPE OF LETTER: APPROVABLE

C. CC Block

ANDA 65-461
ANDA DUP
DIV FILE
Field Copy

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

/s/

Marco Bennett
5/26/2009 10:52:47 AM
CHEMIST

Susan Zuk
5/26/2009 01:43:49 PM
CHEMIST

Roberta Szydlo
5/26/2009 04:01:21 PM
CSO

MINOR AMENDMENT

ANDA 65-461

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Sandoz Inc. TEL: 609-627-8854

ATTN: Carmelle Lucas, Ph.D. FAX: 609-395-2792

FROM: Roberta Szydlo FDA CONTACT PHONE: (240) 276-8476

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 28, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Tacrolimus Capsules, 0.5 mg, 1 mg, and 5 mg.

Reference is also made to your amendments dated March 7, March 12, and March 20, 2008.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__**3**__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-461 APPLICANT: Sandoz Inc.

DRUG PRODUCT: Tacrolimus Capsules, 0.5 mg, 1 mg, and 5 mg

The deficiencies presented below represent MINOR deficiencies:

A. Deficiencies:

1. In your response to deficiency #2, (b) (4) amendment dated March 7, 2008, you state (b) (4)

2. Since you have tightened your drug product assay values to acceptable limits ((b) (4) %) we also recommend that you tighten your (b) (4) limits accordingly.

3. During the manufacturing process, the drug substance is (b) (4)

4. Your drug substance supplier lists (b) (4)

5. (b) (4)

6.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. If available, please provide updated long-term stability data for the drug product in your amendment.

2. (b) (4)

Sincerely yours,

{See appended electronic signature page}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Susan Zuk

6/9/2008 10:00:15 AM

ANDA 65-461

Tacrolimus Capsules
0.5 mg, 1 mg and 5 mg

Sandoz, Inc.

Marco Bennett, Ph.D.

Division of Chemistry III, Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 65-461

2. REVIEW #: 3

3. REVIEW DATE: 30-MAY-2008

4. REVIEWER: Marco Bennett, PhD

5. PREVIOUS DOCUMENTS:

Original Submission	28-DEC-2006
Acceptable for Filing	29-DEC-2006 (letter dated 4/6/07)
Amendment Submission	08-AUG-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment Submission	07-MAR-2008
Correspondence (Attachment for 356h)	12-MAR-2008
Gratuitous Amendment	20-MAR-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Sandoz Inc.
Address:	506 Carnegie Center, Suite 400 Princeton, NJ 08540
Representative:	Carmelle Lucas, Ph.D.
Telephone:	(609) 627-8854
Fax:	(609) 395-2792

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): Tacrolimus Capsules, 0.5 mg, 1 mg, 5 mg

9. LEGAL BASIS FOR SUBMISSION:

The reference listed drug for this application is Prograf® Capsules, 0.5 mg, 1 mg, 5 mg manufactured by Astellas Pharma US, Inc. under NDA #50-708.

Firm claims that there are no unexpired patents or exclusivity for the RLD (Section 1.3.5.2).

10. PHARMACOL. CATEGORY: Immunomodulator

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 0.5 mg, 1 mg, 5 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: x Rx ___OTC

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

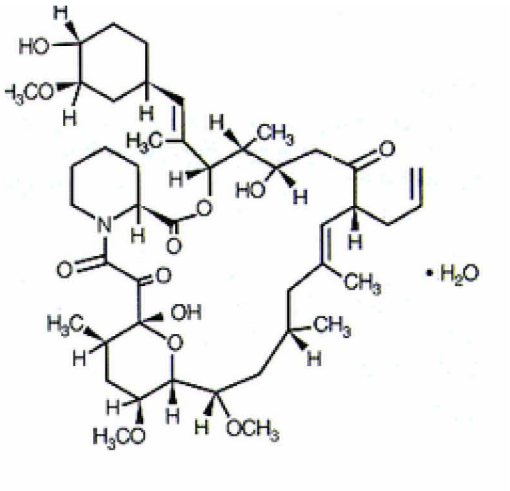
SPOTS product – Form Completed

x Not a SPOTS product

16. 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**,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-methoxycyclohexyl)-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.

Molecular Formula: $C_{44}H_{69}NO_{12} \cdot H_2O$
Molecular Weight: 822.05



17. RELATED/SUPPORTING DOCUMENTS: N/A

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
19979	II	Lek Pharmaceuticals	Tacrolimus	1	Adequate	6/05/2008	tecon
		(b) (4)		4	-	-	-
				4	-	-	-
				4	-	-	-
				4	-	-	-
				4	-	-	-
				4	-	-	-
				4	-	-	-
				4	-	-	-
				4	-	-	-

[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: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	18-APR-2007	S. Adams (HFD-322)
Methods Validation	N/A		
Labeling	Acceptable	25-JAN-2008	A.Vezza
Bioequivalence	Acceptable	15-APR-2008	N. Chun

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___x_ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 65-461

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Not Recommended for Approval

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

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)
The reference listed drug for this application is Prograf® Capsules, 0.5 mg, 1 mg, 5 mg manufactured by Astellas Pharma US, Inc. under NDA #50-708. Tacrolimus is an immunosuppresant. Tacrolimus prolongs the survival of the host and transplanted graft in animal transplant models of liver, kidney, heart, bone marrow, small bowel and pancreas, lung and trachea, skin, cornea, and limb. Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. The net result is the inhibition of T-lymphocyte activation (i.e., immunosuppression). Tacrolimus is produced by fermentation from the micro-organism *Streptomyces tsukubaensis*.

Drug substance
Tacrolimus Monohydrate is a non-hygroscopic white to almost crystalline powder. It is practically insoluble in water but soluble in absolute alcohol. Its molecular weight is 822.05 g/mol as the monohydrate. Tacrolimus is manufactured by Lek Pharmaceuticals d.d. in DMF 19979.

Drug product
The drug product is Tacrolimus Capsules of strengths 0.5mg, 1 mg and 5 mg. The inactive ingredients present in the drug product are Hyperomellose USP ((b) (4)), Lactose Monohydrate NF ((b) (4)), Croscarmellose Sodium NF ((b) (4)), (b) (4) , Magnesium Stearate NF and the active ingredient is Tacrolimus Monohydrate. The drug product will be marketed in (b) (4) cc HDPE Bottles, (b) (4) cc HDPE Bottles and (b) (4)

Process
(b) (4)

(b) (4)

Sandoz submitted three months of accelerated and nine months controlled room temperature stability in the original ANDA to support a 24 month expiration period for product packaged in HDPE bottles and Bulk Packages.

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

Tacrolimus is recommended for use in organ transplant patients to prevent organ rejection. The maximum daily dose is 0.2 mg/kg/day.

C. Basis for Approvability or Not-Approval Recommendation

The application is not approvable for MINOR CMC issues.

61 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Administrative

A. Reviewer's Signature

B. Endorsement Bloc

HFD-630/MBennett/5/30/2008; revised 6/5/2008

HFD-630/SZuk/6/5/08

HFD-617/RSzydlo/6/6/08

V:\Chemistry Division III\Team 6\Final Version For DFS Folder\65461.R03.NA.doc

F/T by:

TYPE OF LETTER: NOT APPROVABLE

C. CC Block

ANDA 65-461
ANDA DUP
DIV FILE
Field Copy

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-461 APPLICANT: Sandoz Inc.

DRUG PRODUCT: Tacrolimus Capsules, 0.5 mg, 1 mg, and 5 mg

The deficiencies presented below represent MINOR deficiencies:

A. Deficiencies:

1. In your response to deficiency #2, (b) (4) amendment dated March 7, 2008, (b) (4)

2. Since you have tightened your drug product assay values to acceptable limits (b) (4)%) we also recommend that you tighten your (b) (4) limits accordingly.

3. (b) (4)

4. (b) (4)

(b) (4)

5. (b) (4)

6. (b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. If available, please provide updated long-term stability data for the drug product in your amendment.

2. (b) (4)

Sincerely yours,

{See appended electronic signature page}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA
ANDA Duplicate
DIV FILE
Field Copy

Endorsement Block:

B. Endorsement Block

HFD-630/Reviewer /MBennett/5/30/2008; revised 6/5/2008
HFD-630/Team Leader/SZuk/6/5/08
HFD-617/Project Manager/RSzydlo/6/6/08

F/T by/

V:\Chemistry Division III\Team 6\Final Version For DFS Folder\65461.R03.NA.doc

TYPE OF LETTER: Not Approvable

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

/s/

Marco Bennett
6/6/2008 10:03:51 AM
CHEMIST

Roberta Szydlo
6/9/2008 09:21:12 AM
CSO

Susan Zuk
6/9/2008 09:58:03 AM
CHEMIST

ANDA 65-461

Tacrolimus Capsules
0.5 mg, 1 mg and 5 mg

Sandoz, Inc.

Marco Bennett, Ph.D.

Division of Chemistry III, Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 65-461

2. REVIEW #: 2

3. REVIEW DATE: 19-FEB-2008; revised 27-FEB-2008

4. REVIEWER: Marco Bennett, PhD

5. PREVIOUS DOCUMENTS:

Original Submission	28-DEC-2006
Acceptable for Filing	05-APR-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment Submission	08-AUG-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Sandoz Inc.
Address:	506 Carnegie Center, Suite 400 Princeton, NJ 08540
Representative:	Carmelle Lucas, Ph.D.
Telephone:	(609) 627-8854
Fax:	(609) 395-2792

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): Tacrolimus Capsules, 0.5 mg, 1 mg, 5 mg

9. LEGAL BASIS FOR SUBMISSION:

The reference listed drug for this application is Prograf® Capsules, 0.5 mg, 1 mg, 5 mg manufactured by Astellas Pharma US, Inc. under NDA #50-708.

Firm claims that there are no unexpired patents or exclusivity for the RLD (Section 1.3.5.2).

10. PHARMACOL. CATEGORY: Immunomodulator

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 0.5 mg, 1 mg, 5 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: x Rx ___OTC

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

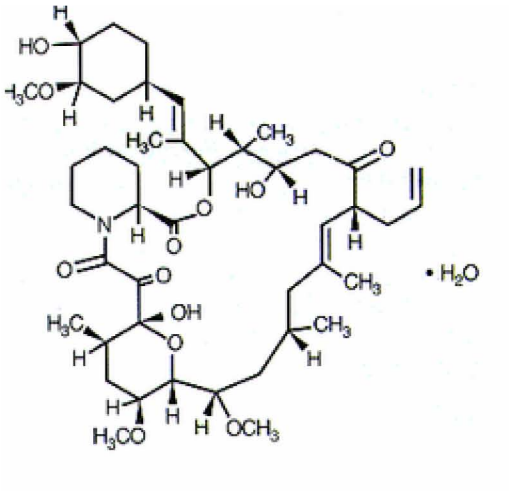
SPOTS product – Form Completed

x Not a SPOTS product

16. 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**,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-methoxycyclohexyl)-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.

Molecular Formula: $C_{44}H_{69}NO_{12} \cdot H_2O$
Molecular Weight: 822.05



17. RELATED/SUPPORTING DOCUMENTS: N/A

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS [2]	DATE REVIEW COMPLETED	COMMENTS
19979	II	Lek Pharmaceuticals	Tacrolimus	1	Inadequate	2/19/2008	-
[redacted] (b) (4)				4	-	-	-
				4	-	-	-
				4	-	-	-
				4	-	-	-
				4	-	-	-
				4	-	-	-
				4	-	-	-
				4	-	-	-
				4	-	-	-
				4	-	-	-

[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: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	18-APR-2007	S. Adams (HFD-322)
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Pending		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___x_ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 65-461

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Not Recommended for Approval

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

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)
The reference listed drug for this application is Prograf® Capsules, 0.5 mg, 1 mg, 5 mg manufactured by Astellas Pharma US, Inc. under NDA #50-708. Tacrolimus is an immunosuppresant. Tacrolimus prolongs the survival of the host and transplanted graft in animal transplant models of liver, kidney, heart, bone marrow, small bowel and pancreas, lung and trachea, skin, cornea, and limb. Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. The net result is the inhibition of T-lymphocyte activation (i.e., immunosuppression). Tacrolimus is produced by fermentation from the micro-organism *Streptomyces tsukubaensis*.

Drug substance
Tacrolimus Monohydrate is a non-hygroscopic white to almost crystalline powder. It is practically insoluble in water but soluble in absolute alcohol. Its molecular weight is 822.05 g/mol as the monohydrate. Tacrolimus is manufactured by Lek Pharmaceuticals d.d. in DMF 19979.

Drug product
The drug product is Tacrolimus Capsules of strengths 0.5mg, 1 mg and 5 mg. The inactive ingredients present in the drug product are Hyperomellose USP ((b) (4)), Lactose Monohydrate NF ((b) (4)), Croscarmellose Sodium NF ((b) (4)), (b) (4) , Magnesium Stearate NF and the active ingredient is Tacrolimus Monohydrate. The drug product will be marketed in (b) (4) cc HDPE Bottles, (b) (4) cc HDPE Bottles and (b) (4)

Process
(b) (4)

(b) (4)

Sandoz submitted three months of accelerated and nine months controlled room temperature stability in the original ANDA to support a 24 month expiration period for product packaged in HDPE bottles and Bulk Packages.

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

Tacrolimus is recommended for use in organ transplant patients to prevent organ rejection. The maximum daily dose is 0.2 mg/kg/day.

C. Basis for Approvability or Not-Approval Recommendation

The application is not approvable for MINOR CMC issues.

54 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

3. In your drug product stability specifications, we recommend that you report the limit for "Any other unknown" to two significant figures to read "Not more than (b) (4)%."

Sincerely yours,

{See appended electronic signature page}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA
ANDA Duplicate
DIV FILE
Field Copy

Endorsement Block:

B. Endorsement Block

Reviewer /MBennett/2/19/2008; 2/27/2008
Team Leader/SZuk/2/24/08; 2/28/08
Project Manager/RSzydlo/2/28/08

F/T by/

V:\Chemistry Division III\Team 6\Final Version For DFS Folder\65461.R02.NA.doc

TYPE OF LETTER: Not Approvable

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

/s/

Marco Bennett
2/28/2008 02:06:45 PM
CHEMIST

Roberta Szydlo
2/28/2008 03:04:11 PM
CSO

Susan Zuk
2/28/2008 03:14:50 PM
CHEMIST

ANDA 65-461

Tacrolimus Capsules
0.5 mg, 1 mg and 5 mg

Sandoz, Inc.

Marco Bennett, Ph.D.

Division of Chemistry III, Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 65-461

2. REVIEW #: 1

3. REVIEW DATE: 26-JUN-2007; 2-JUL-2007

4. REVIEWER: Marco Bennett, PhD

5. PREVIOUS DOCUMENTS:

NA -

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	28-DEC-2006
Acceptable for Filing	05-APR-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Sandoz Inc.
Address:	506 Carnegie Center, Suite 400 Princeton, NJ 08540
Representative:	Carmelle Lucas, Ph.D.
Telephone:	(609) 627-8854

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): Tacrolimus Capsules, 0.5 mg, 1 mg, 5 mg

9. LEGAL BASIS FOR SUBMISSION:

The reference listed drug for this application is Prograf® Capsules, 0.5 mg, 1 mg, 5 mg manufactured by Astellas Pharma US, Inc. under NDA #50-708.

Firm claims that there are no unexpired patents or exclusivity for the RLD (Section 1.3.5.2).

10. PHARMACOL. CATEGORY: Immunomodulator

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 0.5 mg, 1 mg, 5 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: x Rx ___OTC

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

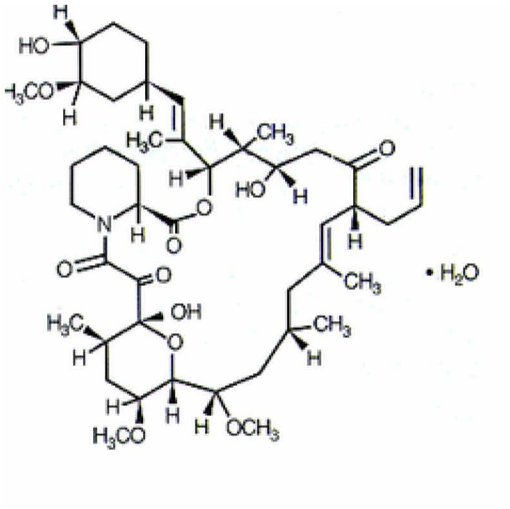
SPOTS product – Form Completed

x Not a SPOTS product

16. 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**,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-methoxycyclohexyl)-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.

Molecular Formula: $C_{44}H_{69}NO_{12} \cdot H_2O$
Molecular Weight: 822.05



17. RELATED/SUPPORTING DOCUMENTS: N/A

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS [2]	DATE REVIEW COMPLETED	COMMENTS
19979	II	Lek Pharmaceuticals	Tacrolimus	1	Inadequate	Under review	-
[redacted]				(b) (4)	-	-	-
					-	-	-
					-	-	-
					-	-	-
					-	-	-
					-	-	-
					-	-	-
					-	-	-
					-	-	-
					-	-	-

[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: N/A

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	18-APR-2007	S. Adams (HFD-322)
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Pending		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___x_ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 65-461

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Not Recommended for Approval

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

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)
The reference listed drug for this application is Prograf® Capsules, 0.5 mg, 1 mg, 5 mg manufactured by Astellas Pharma US, Inc. under NDA #50-708. Tacrolimus is an immunosuppresant. Tacrolimus prolongs the survival of the host and transplanted graft in animal transplant models of liver, kidney, heart, bone marrow, small bowel and pancreas, lung and trachea, skin, cornea, and limb. Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. The net result is the inhibition of T-lymphocyte activation (i.e., immunosuppression). Tacrolimus is produced by fermentation from the micro-organism *Streptomyces tsukubaensis*.

Drug substance
Tacrolimus Monohydrate is a non-hygroscopic white to almost crystalline powder. It is practically insoluble in water but soluble in absolute alcohol. Its molecular weight is 822.05 g/mol as the monohydrate. Tacrolimus is manufactured by Lek Pharmaceuticals d.d. in DMF 19979.

Drug product
The drug product is Tacrolimus Capsules of strengths 0.5mg, 1 mg and 5 mg. The inactive ingredients present in the drug product are Hyperomellose USP ((b) (4)), Lactose Monohydrate NF ((b) (4)), Croscarmellose Sodium NF ((b) (4)), (b) (4) , Magnesium Stearate NF and the active ingredient is Tacrolimus Monohydrate. The drug product will be marketed in (b) (4) cc HDPE Bottles, (b) (4) cc HDPE Bottles and (b) (4)

Sandoz submitted three months of accelerated and three months controlled room temperature stability in the original ANDA to support a 24 month expiration period for product packaged in HDPE bottles and Bulk Packages.

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

Tacrolimus is recommended for use in organ transplant patients to prevent organ rejection. The maximum daily dose is 0.2 mg/kg/day.

C. Basis for Approvability or Not-Approval Recommendation

The application is not approvable for MINOR CMC issues.

57 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Sincerely yours,

{See appended electronic signature page}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA
ANDA Duplicate
DIV FILE
Field Copy

Endorsement Block:

B. Endorsement Block

Reviewer /MBennett/6/26/2007; 7/2/2007
Team Leader/SZuk/6/29/07
Project Manager/RSzydlo/7/3/07

F/T by/

V:\Chemistry Division III\Team 6\Final Version For DFS Folder\65461.R01.NA.doc

TYPE OF LETTER: Not Approvable

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

/s/

Marco Bennett
7/3/2007 09:52:03 AM
CHEMIST

Roberta Szydlo
7/3/2007 10:40:54 AM
CSO

Susan Zuk
7/3/2007 11:07:21 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-461

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE DISSOLUTION ACKNOWLEDGEMENT REVIEW

ANDA No.	65-461
Drug Product Name	Tacrolimus Capsules
Strength	0.5 mg, 1 mg and 5 mg
Applicant Name	Sandoz, Inc.
Submission Date	March 7, 2008
Reviewer	Nam Chun, Pharm.D.

EXECUTIVE SUMMARY

This is a review of the dissolution specification acknowledgement from the firm.

The firm has accepted the FDA-recommended dissolution method and specification.

The application is complete.

COMMENTS:

None

DEFICIENCY COMMENTS:

None

RECOMMENDATIONS:

From a bioequivalence point of view, the firm has met the requirements for *in-vivo* bioequivalence and *in-vitro* dissolution testing and the application is approvable.

I. Completed Assignment for 65461 ID: 5265

Reviewer: Chun, Nam **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
5265	3/7/2008	Dissolution Data	Dissolution Acknowledgement	1	0
				Bean Total:	0

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

/s/

Nam J Chun
4/15/2008 02:55:02 PM
BIOPHARMACEUTICS

Lizzie Sanchez
4/15/2008 03:05:59 PM
BIOPHARMACEUTICS

BIOEQUIVALENCY AMENDMENT

ANDA 65-461

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Sandoz Inc. TEL: 609-627-8854

ATTN: Carmelle Lucas, Ph.D. FAX: 609-395-2792

FROM: Keri Suh PROJECT MANAGER: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on December 31, 2007, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Tacrolimus Capsules, 0.5 mg, 1 mg and 5 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __**one**__ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCY

ANDA: 065461 (Amendment dated December 31, 2007)

APPLICANT: Sandoz, Inc.

DRUG PRODUCT: Tacrolimus Capsules; 5 mg, 1 mg, 0.5 mg

The Division of Bioequivalence has completed its review and has identified the following deficiency:

Please acknowledge the following dissolution method and specification:

Apparatus: USP Apparatus II (Paddle) with sinker
Speed: 50 rpm
Medium: Phosphate Buffer, pH 7.0
Volume: 900ml at 37°C

Specification: NLT (b)(4) *% (Q) of the labeled drug is dissolved in 60 minutes.*

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Barbara Davit
3/6/2008 05:20:09 PM
Signing for Dale P Conner

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	065461
Drug Product Name	Tacrolimus Capsules
Strength(s)	0.5mg, 1mg and 5mg
Applicant Name	Sandoz Inc.
Address	506 Carnegie Center, Suite 400 Princeton NJ 08540
Applicant's Point of Contact	Carmelle Lucas Ph.D., Director, Regulatory Affairs
Contact's Telephone Number	609-627-8854
Contact's Fax Number	609-395-2792
Original Submission Date(s)	12/28/2006
Submission Date(s) of Amendment(s) Under Review	December 31, 2007
Reviewer	Utpal M. Munshi, Ph.D.
Study Number (s)	Study #TCU-P6-130
Study Type (s)	Fasting
Strength (s)	5mg
Clinical Site	Algorithme Pharma Inc.
Clinical Site Address	1200 Beaumont Ave Mount-Royal, Quebec, Canada H3P 3P1
Analytical Site	(b) (4)
Analytical Site Address	
Study Number (s)	Study #TCU-P6-131
Study Type (s)	Fed
Strength (s)	5mg
Clinical Site	Algorithme Pharma Inc.
Clinical Site Address	1200 Beaumont Ave Mount-Royal, Quebec, Canada H3P 3P1
Analytical Site	(b) (4)
Analytical Site Address	
OUTCOME DECISION	**INCOMPLETE**

Review of a Study Amendment

1 EXECUTIVE SUMMARY

Sandoz, Inc's original ANDA 065641 for Tacrolimus Capsules, 0.5mg, 1mg, and 5mg contained comparative dissolution data employing an in-house method. The DBE issued a deficiency to the firm in the dissolution-only review of this submission in June 2007 asking the firm to submit new dissolution data on test and reference products using the FDA-recommended method. The firm replied in July 2007 by submitting the requested data.

The DBE conducted the full review of the original submission and the July 2007 dissolution amendment in November 2007. The only deficiency identified by the DBE was with respect to the dissolution testing. Specifically, the DBE asked the firm to: 1) repeat the comparative dissolution testing using the firm's in-house method with an agitation speed of 50rpm instead of (b) (4) rpm and 2) repeat the comparative dissolution testing with the FDA-recommended method using 50rpm and a sinker (if no sinker was used in the original testing) or 75rpm and a sinker (if a sinker was used in the original dissolution testing). The DBE issued these deficiencies to the firm because 1) the original dissolution testing using the firm's method gave non-discriminatory results (dissolution was too fast) and 2) in the original dissolution testing using the FDA-recommended method, the test and reference products did not meet the specification given to the innovator [NLT (b) (4) %(Q) in 90 minutes]. The firm has responded to these deficiencies by providing new dissolution studies using the recommended approaches.

Two of the three strengths of the RLD and none of the three strengths of the test product passed at the (b) (4) level using the FDA-recommended method at 75rpm with a sinker. Furthermore, none of the products gave (b) (4) % dissolution by the final time point. As a result, this dissolution approach is unacceptable.

Using the firm's dissolution method at an agitation speed of 50rpm with a sinker, the lowest percent dissolution for a given product at 10 minutes was generally (b) (4) %. While this dissolution approach isn't ideal, it is acceptable given that the 90% confidence intervals for lnAUCt, lnAUCi, and lnCmax are well above the lower limit to demonstrate bioequivalence. (Please see "Reviewer's Comments" for PK parameters). As a result, the firm will be asked to acknowledge this method and the appropriate specification [NLT (b) (4) % (Q) in 60 minutes].

The waiver request under 21 CFR 320.22 (d)(2) is incomplete pending the firm's acceptance of the dissolution method and specification.

No DSI inspections are pending or necessary for the clinical or analytical sites given above.

2 REVIEW OF THE SUBMISSION

Deficiency #1 (the only deficiency)

1. The DBE has reviewed all dissolution data submitted thus far. The DBE recommends two additional dissolution tests be conducted. These are summarized below.

- Please repeat dissolution testing using your in house method with sinkers and reduce your stirrer speed from (b) (4) rpm to 50 rpm.

  Apparatus: USP Apparatus II (Paddle) sinker
  Speed: 50 RPM
  Medium: Buffer at pH 7.0
  Volume: 900ml at 37°C

- Please repeat dissolution testing using the FDA-recommended method with sinkers. We assume sinkers were not used as it was not documented in your dissolution amendment dated 7/25/2007. Alternatively, if a sinker was used, but omitted from the method write up, please repeat this testing with sinkers and increase the stirrer speed to 75 rpm versus the 50 rpm currently recommended.

  Apparatus: USP Apparatus II (Paddle) sinker
  Speed: 50 or 75 RPM based on sinker use
  Medium: HPC(1:20,000) pH 4.5 H_3PO_4
  Volume: 900ml at 37°C

Firm's Response (taken from firm's submission):

Batch No. 031621 (0.5 mg)					
	% Released in Phosphate buffer pH 7.0				
Time	10 minutes	15 minutes	30 minutes	45 minutes	60 minutes
Mean	82	88	92	95	97
Minimum	(b) (4)				
Maximum					
%RSD	11.2	7.4	5.7	3.9	4.8

Range of means from 10min to 60 min in original dissolution testing using original method: (b) (4) (used lot 027591)

Range of means from 10min to 60 min in new dissolution testing using original method: (b) (4) (used lot 031621)

Batch No. KW06G38NA (0.5 mg)					
	% Released in Phosphate buffer pH 7.0				
Time	10 minutes	15 minutes	30 minutes	45 minutes	60 minutes
Mean	82	89	96	100	101
Minimum	(b) (4)				
Maximum					
%RSD	16.4	13.8	10	8.1	6.9

Range of means from 10min to 60 min in original dissolution testing using original method: (b) (4) (used same lot)

Batch No. 027191 (1mg)					
	% Released in Phosphate buffer pH 7.0				
Time	10 minutes	15 minutes	30 minutes	45 minutes	60 minutes
Mean	85	93	97	103	105
Minimum	(b) (4)				
Maximum					
%RSD	8.7	6.0	4.4	3.6	3.6

Range of means from 10min to 60 min in original dissolution testing using original method: (b) (4) (used same lot)

Batch No.KW06G37NA (1mg)					
	% Released in Phosphate buffer pH 7.0				
Time	10 minutes	15 minutes	30 minutes	45 minutes	60 minutes
Mean	70	84	90	96	98
Minimum	(b) (4)				
Maximum					
%RSD	14.4	9.3	7.2	4.7	4.5

Range of means from 10min to 60 min in original dissolution testing using original method: (b) (4) (used same lot)

Batch No. 030852 (5mg)					
	% Released in Phosphate buffer pH 7.0				
Time	10 minutes	15 minutes	30 minutes	45 minutes	60 minutes
Mean	79	90	99	100	99
Minimum	(b) (4)				
Maximum					
%RSD	9.4	6.0	2.8	2.1	2.7

Range of means from 10min to 60 min in original dissolution testing using original method: (b) (4) (used lot 025581)

Range of means from 10min to 60 min in new dissolution testing using original method: (b) (4) (used lot 030852)

Batch No.KW06G36NA(5mg)					
	% Released in Phosphate buffer pH 7.0				
Time	10 minutes	15 minutes	30 minutes	45 minutes	60 minutes
Mean	64	79	93	102	104
Minimum	(b) (4)				
Maximum					
%RSD	10.3	8.6	6.2	5.1	3.7

Range of means from 10min to 60 min in original dissolution testing using original method: (b) (4) (used same lot)

Batch No. 031621(0.5mg)					
	% Released in Hydroxypropyl cellulose solution pH 4.5				
Time	15 minutes	30 minutes	60 minutes	90 minutes	120 minutes
Mean	39	62	82	87	89
Minimum	(b) (4)				
Maximum					
%RSD	15.2	8.2	4.5	2.8	3.4

Range of means from 15min to 120min in original dissolution testing using original method: (b) (4) (used lot 027591)

Range of means from 15min to 120min in new dissolution testing using original method: (b) (4) (used 031621)

Batch No. KW06G38NA(0.5mg)					
	% Released in Hydroxypropyl cellulose solution pH 4.5				
Time	15 minutes	30minutes	60 minutes	90 minutes	120 minutes
Mean	31	55	70	78	80
Minimum	(b) (4)				
Maximum					
%RSD	15.5	8.1	7.3	6.2	5.9

Range of means from 15min to 120min in original dissolution testing using original method (b) (4) used the same lot)

Batch No. 027191 (1 mg)	
	% Released in Hydroxypropyl cellulose solution pH 4.5

Time	15 minutes	30 minutes	60 minutes	90 minutes	120 minutes
Mean	31	58	78	85	88
Minimum					
Maximum					
%RSD	9.3	6.0	6.2	6.0	5.7

(b) (4)

Range of means from 15min to 120min in original dissolution testing using original method: (b) (4) (used the same lot)

Batch No. KW06G37NA (1 mg)					
	% Released in Hydroxypropyl cellulose solution pH 4.5				
Time	15 minutes	30minutes	60 minutes	PO minutes	120 minuter
Mean	34	54	66	76	81
Minimum					
Maximum					
%RSD	8.6	5.9	10.3	7.4	5.9

(b) (4)

Range of means from 15min to 120min in original dissolution testing using original method: (b) (4) (used the same lot)

Batch No. 030852 (5 mg)					
	% Released in Hydroxypropyl cellulose solution pH 4.5				
Time	15 minutes	30minutes	60 minutes	90 minutes	120 minutes
Mean	29	58	81	88	89
Minimum					
Maximum					
%RSD	8.3	7.3	2.8	2.5	2.3

(b) (4)

Range of means from 15min to 120min in original dissolution testing using original method: (b) (4) (used lot#025581).

Range of means from 15min to 120min in new dissolution testing using original method: (b) (4) (used lot# 030582).

Batch No. KW06G36NA (5 mg)					
	% Released in Hydroxypropyl cellulose solution pH 4.5				
Time	15 minutes	30minutes	60 minutes	90 minutes	120 minutes
Mean	33	57	73	80	85
Minimum	(b) (4)				
Maximum					
%RSD	11.6	7.9	5.7	4.0	4.0

Range of means from 15min to 120min in original dissolution testing using original method: (b) (4) (used same lot)

OGD METHOD 50 RPM

Batch No. 030852 (5 mg)					
	% Released in Hydroxypropyl cellulose solution pH 4.5				
Time	15 minutes	30 minutes	60 minutes	90 minutes	120 minutes
Mean	22	49	74	86	90
Minimum	(b) (4)				
Maximum					
%RSD	13.8	8.8	4.6	3.3	2.2

OGD METHOD 50 RPM

Batch No. 031621 (0.5 mg)					
	% Released in Hydroxypropyl cellulose solution pH 4.5				
Time	**15 minutes**	**30 minutes**	**60 minutes**	**90 minutes**	**120 minutes**
Mean	36	54	72	87	91
Minimum	(b) (4)				
Maximum					
%RSD	22.2	10.7	20.3	5.9	6.7

RELEASE METHOD, (b) (4) RPM

Batch No. 030852 (5 mg)					
	% Released in Phosphate buffer pH 7.0				
Time	**10 minutes**	**15 minutes**	**30 minutes**	**45 minutes**	**60 minutes**
Mean	83	94	98	98	99
Minimum	(b) (4)				
Maximum					
%RSD	8.7	5.4	1.7	1.9	2.1

RELEASE METHOD, (b) (4) RPM

Batch No. 031621 (0.5 mg)					
	% Released in Phosphate buffer pH 7.0				
Time	**10 minutes**	**15 minutes**	**30 minutes**	**45 minutes**	**60 minutes**
Mean	93	100	101	102	101
Minimum	(b) (4)				
Maximum					
%RSD	2.5	3.5	4.1	4.3	4.6

Reviewer's Comments:

1. All batches of reference products used are unexpired lots. It is noted that the 5mg reference product lot# is different than that used in the biostudies. This is because the lot used in the biostudies (025581) expired in September 2007. It is not clear why the firm chose to use a different lot for the 0.5mg product, as the lot used in the original dissolution testing has an expiry date of August 2008. The new dissolution testing of the test products occurred prior to the proposed expiration date of June 2008. The test product batch used in the biostudies is the same as that used in the new dissolution testing.

2. An agitation speed of (b)(4)rpm in the hydroxypropyl cellulose solution, pH 4.5, does not result in (b)(4)% dissolution for any product examined.

3. With respect to the hydroxypropyl cellulose solution ((b)(4)rpm), the RLD does not meet the specification given to the innovator (NLT (b)(4)% (Q) in 90 minutes) at the (b)(4) level for the 0.5mg and 1mg formulations (these strengths meet the specification at the (b)(4) level).

4. With respect to the hydroxypropyl cellulose solution (b)(4)rpm), no strength of the test products meets the specification given to the innovator (NLT (b)(4)% (Q) in 90 minutes) at the (b)(4) level. Only the 5mg strength meets the specification at the (b)(4) level.

5. Given points 2 through 4, the dissolution method utilizing hydroxypropyl cellulose solution is unacceptable for the test product.

6. With an agitation speed of 50 rpm in phosphate buffer, pH 7.0, the lowest % dissolution was (b)(4)% at 10 minutes for batch # KW06G36NA (5mg). In general, the lowest % dissolution for a given formulation was approximately (b)(4)% at 10 minutes.

7. The 90% confidence intervals lnAUCt, lnAUCi, and lnCmax are well above the lower acceptable limit of (b)(4) for both the fasted and fed biostudies. Below are tables taken from the original full review of this application.

Tacrolimus Capsule, 5mg Fasting Bioequivalence Study No. (TCU-P6-130), N=37 (Male=37 and Female=0) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t} (ng·hr/mL)	331.18	299.19	110.69	(100.47-121.96)
AUC_{∞} (ng·hr/mL)	355.17	322.02	110.29	(100.30-121.28)
C_{max} (ng/mL)	36.18	32.93	109.87	(101.81-118.56)

Tacrolimus Capsule, 5mg Fed Bioequivalence Study No. (TCU-P6-131), N=39 (Male=39 and Female=0) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t} (ng·hr/mL)	143.72	149.59	96.08	(92.36-99.94)
AUC_{∞} (ng·hr/mL)	157.13	164.39	95.58	(92.03-99.27)
C_{max} (ng/mL)	7.33	7.63	96.07	(90.11-102.26)

8. Given point 7, the DBE proposes the following method and specification:

   Apparatus: USP Apparatus II (Paddle) with sinker
   Speed: 50 rpm
   Medium: Phosphate buffer, pH 7.0
   Volume: 900ml at 37°C

Specification: NLT (b) (4) *(Q) of the labeled drug is dissolved in 60 minutes.*

9. Once the firm has accepted the DBE proposed method and specification, the DBE will grant a waiver of *in vivo* BE studies for the 1mg and 0.5mg test formulations based on the provisions set forth under 21 CFR 320.22 (d)(2). The waiver is justified based on proportional formulation of lower strengths as documented in the original full BE review of the application and based on the f2 values being greater than or equal to 50 as seen in the tables below.

time	5mg	1.0mg	
10	64	70	36
15	79	84	25
30	93	90	9
45	102	96	36
60	104	98	36
			5
			142
	f2		**63.29132**

time	5mg	0.5mg	
10	64	82	324
15	79	89	100
30	93	96	9
45	102	100	4
60	104	101	9
			5
			446
		f2	**51.11984**

2.1 Deficiency Comments

1. The following deficiency will be communicated to the firm:

Please acknowledge the following dissolution method and specification:

Apparatus: USP Apparatus II (Paddle) with sinker
Speed: 50 RPM
Medium: Phosphate Buffer, pH 7.0
Volume: 900ml at 37°C

Specification: NLT (b)(4) *% (Q) of the labeled drug is dissolved in 60 minutes.*

2.2 Recommendations

1. The firm's *in vitro* dissolution testing is **incomplete** pending its acceptance of the DBE-recommended method and specification.

2. The request for a waiver of *in vivo* bioequivalence study requirements for the 1mg and 0.5mg capsule of the test product under 21 CFR § 320.22 (d) (2) is **incomplete** due to the incomplete dissolution studies.

2.3 Additional Attachments

None.

BIOEQUIVALENCE DEFICIENCY

ANDA: 065461 (Amendment dated December 31, 2007)

APPLICANT: Sandoz, Inc.

DRUG PRODUCT: Tacrolimus Capsules; 5mg, 1mg, 0.5mg

The Division of Bioequivalence has completed its review and has identified the following deficiency:

Please acknowledge the following dissolution method and specification:

Apparatus: USP Apparatus II (Paddle) with sinker
Speed: 50 rpm
Medium: Phosphate Buffer, pH 7.0
Volume: 900ml at 37°C

Specification: NLT (b) (4) *% (Q) of the labeled drug is dissolved in 60 minutes.*

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

2.4 Outcome Page

ANDA: 065461

Reviewer: Munshi, Utpal **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Amendment to 065461

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
4724	12/31/2007	Other	Study Amendment	1	1
				Bean Total:	1

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

/s/

Utpal Munshi
2/27/2008 10:31:40 AM
BIOPHARMACEUTICS

Shriniwas G. Nerurkar
2/27/2008 03:02:06 PM
BIOPHARMACEUTICS

Barbara Davit
2/28/2008 04:17:13 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	65-461
Drug Product Name	Tacrolimus Capsules
Strength(s)	0.5mg, 1mg and 5mg
Applicant Name	Sandoz Inc.
Address	506 Carnegie Center, Suite 400 Princeton NJ 08540
Applicant's Point of Contact	Carmelle Lucas Ph.D., Director, Regulatory Affairs
Contact's Telephone Number	609-627-8854
Contact's Fax Number	609-395-2792
Original Submission Date(s)	12/28/2006
Submission Date(s) of Amendment(s) Under Review	7/25/2007 (Study Amendment)
Reviewer	S. Christopher Jones PharmD, MS
Study Number (s)	Study #TCU-P6-130
Study Type (s)	Fasting
Strength (s)	5mg
Clinical Site & Address	Algorithme Pharma Inc. 1200 Beaumont Ave Mount-Royal, Quebec, Canada H3P 3P1
Analytical Site & Address	(b) (4)
Study Number (s)	Study #TCU-P6-131
Study Type (s)	Fed
Strength (s)	5mg
Clinical Site & Address	Algorithme Pharma Inc. 1200 Beaumont Ave Mount-Royal, Quebec, Canada H3P 3P1
Analytical Site & Address	(b) (4)

1 EXECUTIVE SUMMARY

This is a first generic application. This application contains the results of fasting and fed bioequivalence (BE) studies comparing a test product, Tacrolimus Capsules, 5mg to the corresponding reference listed drug (RLD), Prograf® (Tacrolimus) Capsules, 5mg (Astellas Pharma). Each of the BE studies was designed as a single-dose, randomized, two-treatment, two-sequence, crossover study in healthy adult male subjects. The firm's fasting and fed BE studies are acceptable. The results are summarized in the tables below.

Tacrolimus Capsule, 5mg Fasting Bioequivalence Study No. (TCU-P6-130), N=37 (Male=37 and Female=0) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t} (ng·hr/mL)	331.18	299.19	110.69	(100.47-121.96)
AUC_{∞} (ng·hr/mL)	355.17	322.02	110.29	(100.30-121.28)
C_{max} (ng/mL)	36.18	32.93	109.87	(101.81-118.56)

Tacrolimus Capsule, 5mg Fed Bioequivalence Study No. (TCU-P6-131), N=39 (Male=39 and Female=0) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t} (ng·hr/mL)	143.72	149.59	96.08	(92.36-99.94)
AUC_{∞} (ng·hr/mL)	157.13	164.39	95.58	(92.03-99.27)
C_{max} (ng/mL)	7.33	7.63	96.07	(90.11-102.26)

The firm has conducted comparative dissolution testing on all strengths using both an in house and FDA-recommended dissolution methods. The firm's method is non-discriminatory and the FDA method results in incomplete dissolution through 120 minutes of testing. The firm is asked to conduct additional testing and submit it to the DBE. The dissolution testing is incomplete.

The waiver request for in vivo BE study requirements for the 0.5mg and 1mg strengths is not granted at this time, pending acceptable dissolution testing.

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

The application is incomplete.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Prograf® (Tacrolimus) Capsules (5mg = Biostudy Strength) (1mg & 0.5mg will also be marketed)
Reference Product	Prograf® (Tacrolimus) Capsules (5mg = Biostudy Strength) (1mg & 0.5mg are also marketed)
RLD Manufacturer	Astellas Pharma
NDA No.	050708
RLD Approval Date	07/08/1994
Indication	Prograf is indicated for the prophylaxis of organ rejection in patients receiving allogeneic liver, kidney, or heart transplants.

3.2 PK/PD Information[1]

Bioavailability	Absorption of tacrolimus from the gastrointestinal tract after oral administration is incomplete and variable. The absolute bioavailability of tacrolimus was 17±10% in adult kidney transplant patients (N=26), 22±6% in adult liver transplant patients (N=17), 23±9% in adult heart transplant patients (N=11) and 18±5% in healthy volunteers (N=16).
Food Effect	The rate and extent of tacrolimus absorption were greatest under fasted conditions. The presence and composition of food decreased both the rate and extent of tacrolimus absorption when administered to 15 healthy volunteers. The effect was most pronounced with a high-fat meal (848 kcal, 46% fat): mean AUC and C_{max} were decreased 37% and 77%, respectively; T_{max} was lengthened 5-fold. A high-carbohydrate meal (668 kcal, 85% carbohydrate) decreased mean AUC and mean C_{max} by 28% and 65%, respectively. In healthy volunteers (N=16), the time of the meal also affected tacrolimus bioavailability. When given immediately following the meal, mean C_{max} was reduced 71%, and mean AUC was reduced 39%, relative to the fasted condition. When administered 1.5 hours following the meal, mean C_{max} was reduced 63%, and mean AUC was reduced 39%, relative to the fasted condition.
Tmax	After capsule ingestion in normal healthy volunteers (n=16), the peak serum concentration (C_{max}) was reached in 1.6±0.7 hours.
Metabolism	Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily the cytochrome P-450 system (CYP3A). A metabolic pathway leading to the formation of 8 possible metabolites has been proposed. Demethylation and hydroxylation were identified as the primary mechanisms of biotransformation in vitro. The major metabolite identified in incubations with human liver microsomes is 13-demethyl tacrolimus. In in vitro studies, a 31-demethyl metabolite has been

[1] All data are taken from the PDR Online unless otherwise referenced.

	reported to have the same activity as tacrolimus.
Excretion	In man, less than 1% of the tacrolimus dose administered is excreted unchanged in urine. When radiolabeled tacrolimus was administered by mouth, the mean recovery of the radiolabel was 94.9±30.7%. Fecal elimination accounted for 92.6±30.7%, urinary elimination accounted for 2.3±1.1%.
Half-life	After an oral dose, the elimination half-life based on radioactivity was 31.9±10.5 hours whereas it was 48.4±12.3 hours based on tacrolimus concentrations.
Drug Specific Issues (if any)	Tacrolimus maximum blood concentrations (C_{max}) and area under the curve (AUC) appeared to increase in a dose-proportional fashion in 18 fasted healthy volunteers receiving a single oral dose of 3, 7, and 10 mg.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	Two, fasting and fed

1.	**Type of study:**	Fasting
	Design:	A single-dose, two-treatment, two-period, crossover, fasting *in-vivo* bioquivalence study in healthy subjects comparing Tacrolimus Capsules, 5mg, to the reference listed drug (RLD), Prograf® (Tacrolimus) Capsules, 5mg.
	Strength:	5 mg
	Subjects:	Normal healthy adults, general population.
	Additional Comments:	Females must have a negative baseline pregnanacy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study.

2.	**Type of study:**	Fed
	Design:	A single-dose, two-treatment, two-period, crossover, fed *in-vivo* bioquivalence study in healthy subjects comparing Tacrolimus Capsules, 5mg, to the reference listed drug (RLD), Prograf® (Tacrolimus) Capsules, 5mg.
	Strength:	5 mg
	Subjects:	Normal healthy adults, general population.
	Additional Comments:	Females must have a negative baseline pregnanacy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study.

Analytes to measure (in appropriate biological fluid):	Tacrolimus in whole blood
Bioequivalence based on (90% CI):	Yes

Waiver request of in-vivo testing (appropriate strengths):	Tacrolimus capsules 0.5mg and 1mg may be considered for a waiver of *in vivo* bioequivalence testing based on (1) acceptable bioequivalence studies on the 5mg strength, (2) acceptable dissolution testing of all strengths, and (3) proportional similarity in the formulations of all strengths.
Source of most recent recommendations:	Control Document #04-123 (Sandoz) BE Recommendations: Tacrolimus Capsules (http://www.fda.gov/cder/guidance/bioequivalence/default.htm)
Summary of OGD or DBE History:	for details, see Appendix 4.4

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	0
In vitro dissolution	Yes	3
Waiver requests	Yes	2
BCS Waivers	No	0
Clinical Endpoints	No	0
Failed Studies	No	0
Amendments	Yes	1

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Analyte		
Bioanalytical method validation report location	Pages 034-098 in Volume 7 of 18		
Study Report Number	N° TCU-V6-083(R2) Validation of a HPLC Method Using MS/MS Detection for the Determination of Tacrolimus in Human Whole Blood		
Analyte	Tacrolimus		
Internal standard (IS)	(b) (4)		
Method description	LC-MS/MS with liquid-liquid extraction		
Limit of quantitation	0.100 ng/ml		
% Recovery (%CV) at each concentration tested‡	1.000 ng/ml	33.333 ng/ml	133.500 ng/ml
	55.87% (14.94%) n=6	62.62% (8.40%) n=6	59.9% (5.3%) n=6
Average % recovery of IS (%CV)‡	78.19% (11.69%)		
Standard curve concentrations (ng/mL)	0.100, 0.200, 0.600, 2.500, 7.500, 12.500, 20.000, 35.000, 45.000, 50.000 ng/mL		
QC concentrations (ng/mL)	0.100, 0.300, 10.000, 40.000 (ng/ml)		
QC Intraday precision range (%CV)	2.4% - 11.5%		
QC Intraday accuracy range (%Nominal)	93.4% - 109.1%		
QC Interday precision range (%CV)	4.5% - 8.1%		
QC Interday accuracy range (%Nominal)	91.2% - 103.1%		
Bench-top stability (hrs, unextracted)	58.8 hours at a temperature of 22°C		
Stock stability (ACN:H O 70:30%) Analyte ((b) (4) **Internal Standard**	146 days at a temperature of 4°C for Tacrolimus 113 days at a temperature of 4°C for Clarithromycin		
Processed stability (hrs, extracted)	71.9 hours at 4°C		
Freeze-thaw stability (cycles)	4 cycles at -20°C		
Long-term storage stability (days)	94 days at -20°C		
Dilution integrity	100.0 ng/mL diluted 5-fold		
Selectivity	No interfering peaks were noted in blank matrix samples		
SOPs submitted	Yes, analytical method SOP was submitted		
Bioanalytical method is acceptable	Yes		

‡ Recoveries and %CV were calculated by the reviewer
**Biological Matrix was purchased from (b) (4).

Comments on the Pre-Study Method Validation: Acceptable.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (% CV)					
					Cmax (ng/mL)	Tmax* (hr)	AUC0-t (ng·h/mL)	AUC∞ (ng·h/mL)	T½ (hr)	Kel (hr^{-1})
Study # TCU-P6-130	Bioequivalence Study of Tacrolimus 5 mg Capsules of Sandoz Private Limited, India and Prograf® (Tacrolimus) 5mg Capsules of Fujisawa Healthcare Inc., USA in Healthy Male Volunteers / Fasting State	Randomized single-dose crossover	Tacrolimus 5 mg Capsule p.o. [Batch KW06G36NA] Prograf® 5 mg Capsule p.o. [Batch 025581]	37 completing (37M) Healthy subjects 40 (19-62)	37.626 (27.0) 34.332 (29.3)	1.50 (0.50-4.10) 1.75 (0.75-3.50)	354.055 (37.4) 316.779 (36.1)	380.062 (37.7) 342.152 (37.2)	35.30 (21.6) 37.19 (15.2)	0.0204 (18.6) 0.0191 (15.3)
Study # TCU-P6-131	Bioequivalence Study of Tacrolimus 5 mg Capsules of Sandoz Private Limited, India and Prograf® (Tacrolimus) 5 mg Capsules of Fujisawa Healthcare Inc., USA in Healthy Male Volunteers / Fed State	Randomized single-dose crossover	Tacrolimus 5 mg Capsule p.o. [Batch KW06G36NA] Prograf® 5 mg Capsule p.o. [Batch 025581]	39 completing (39M) Healthy subjects 37 (20-61)	7.763 (32.4) 8.181 (35.7)	6.00 (2.00-12.00) 5.50 (2.00-12.00)	154.674 (35.5) 161.631 (38.5)	169.440 (36.0) 178.093 (38.9)	36.44 (14.8) 38.01 (16.5)	0.0194 (15.6) 0.0187 (16.1)

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Tacrolimus Capsules 5mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No.TCU-P6-130				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t} (hr*ng/ml)	331.18	299.19	110.69	(100.47-121.96)
$AUC_{0-\infty}$ (hr*ng/ml)	355.17	322.02	110.29	(100.30-121.28)
C_{max} (ng/ml)	36.18	32.93	109.87	(101.81-118.56)

Tacrolimus Capsules 5mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study #TCU-P6-131				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t} (hr*ng/ml)	143.72	149.59	96.08	(92.36-99.94)
$AUC_{0-\infty}$ (hr*ng/ml)	157.13	164.39	95.58	(92.03-99.27)
C_{max} (ng/ml)	7.33	7.63	96.07	(90.11-102.26)

Table 3. Reanalysis of Study Samples

Study Number TCU-P6-130 Additional information on pages 28-29 Volume 7 of 18								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic fit	0	0	0.00%	0.00%	0	0	0.00%	0.00%
Above the Upper Limit of Quantitation	9	4	0.6%	0.2%	9	4	0.6%	0.2%
Sample Lost in Processing	6	7	0.4%	0.4%	6	7	0.4%	0.4%
Unacceptable Internal Standard	0	1	0.0%	0.1	0	1	0.0%	0.1
Total	15	12	1.0%	0.7%	15	12	1.0%	0.7%

The samples (n=1624) were analyzed in 29 runs.

Study Number TCU-P6-131 Additional information on pages 27-28 Volume 9 of 18								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used in reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	3	0	0.2%	0.0%	3	0	0.2%	0.0%
Sample Lost in Processing	2	0	0.1%	0.0%	2	0	0.1%	0.0%
Total	5	0	0.3%	0.0%	5	0	0.3%	0.0%

The samples (n=1869) were analyzed in 28 runs.

Did use of recalculated plasma concentration data change study outcome? No. Assays were conducted because of technical analytical difficulties experienced during the sample assays. The three reported PK repeats in the study #TCU-P6-131 were reviewed to assess any potential effect on the outcome of the study. These data are summarized in Table 3a below. The point estimates are near one and the confidence intervals are well within the 80-125% limit. Moreover, the assays were repeated twice and similar values were estimated on both occasions. The PK repeats did not alter the outcome of the study.

Table 3a. Detailed PK Repeat Information

Sample Number	Original Assay Conc	Repeat Assay Conc #1	Repeat Assay Conc #2	Final Reported Conc
Subject #29 (P1-11)	10.342 ng/ml	2.463 ng/ml	2.566 ng/ml	2.515 ng/ml
Subject #39 (P1-15)	3.530 ng/ml	1.604 ng/ml	1.683 ng/ml	1.644 ng/ml
Subject #30 (P2-10)	0.134 ng/ml	4.896 ng/ml	5.051 ng/ml	4.973 ng/ml

3.7 Formulation

Location in appendix	Section 4.2 , Page 36
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	Formulation Acceptable
If not acceptable, why?	N/A

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DFS
Source of Method (USP, FDA or Firm)	FDA
Medium	Hydroxypropyl cellulose (HPC) solution (1:20,000) pH 4.5 with H_3PO_4
Volume (mL)	900ml
USP Apparatus type	USP Apparatus II (Paddle)
Rotation (rpm)	50 rpm
FDA-recommended specification	Not yet determined for this test product
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Unacceptable Data
Is method acceptable?	No
If not then why?	Additional testing has been requested

F2 metric, biostudy strengths compared to other strength(s)			
Biostudy Strength	**Other Strength**	**F2 metric for test**	**F2 metric for RLD**
--	--	--	--

3.9 Waiver Request(s)

Strengths for which waivers are requested	0.5mg & 1mg
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	No
Waivers granted?	No
If not then why?	Pending acceptable dissolution testing

3.10 Deficiency Comment

1. The firm should repeat dissolution testing using their in house method with sinkers and reduce the stirrer speed from (b) (4) rpm to 50 rpm.

   Apparatus: USP Apparatus II (Paddle) sinker
   Speed: 50 RPM
   Medium: Buffer at pH 7.0
   Volume: 900ml at 37°C

   The firm should also repeat dissolution testing using the FDA recommended method with sinkers. Alternatively, if a sinker was used in previous testing using the FDA method, but omitted from the method write up, the firm should repeat this testing with sinkers and increase the stirrer speed to 75 rpm versus 50 rpm currently recommended.

   Apparatus: USP Apparatus II (Paddle) sinker
   Speed: 50 or 75 RPM based on sinker use
   Medium: HPC (1:20,000) pH 4.5 H_3PO_4
   Volume: 900ml at 37°C

3.11 Recommendations

1. The Division of Bioequivalence (DBE) accepts the fasting BE study (#TCU-P6-130) conducted by Sandoz Inc. on its Tacrolimus Capsule, 5mg, Lot #KW06G36NA, comparing it to Astellas Pharma's Prograf® Capsule (Tacrolimus), 5mg, Lot #025581.

2. The Division of Bioequivalence (DBE) accepts the fed BE study (#TCU-P6-131) conducted by Sandoz Inc. on its Tacrolimus Capsule, 5mg, Lot #KW06G36NA, comparing it to Astellas Pharma's Prograf® Capsule (Tacrolimus), 5mg, Lot #025581.

3. The *in vitro* dissolution testing conducted by the firm on its Tacrolimus Capsule, 5mg, lot#KW06G36NA, Tacrolimus Capsule, 1mg, lot#KW06G37NA, Tacrolimus Capsule, 0.5mg, lot#KW06G38NA comparing it to Prograf® Capsule (Tacrolimus), 5mg, Lot #025581, Prograf® Capsule (Tacrolimus), 1mg, Lot #027191, Prograf® Capsule (Tacrolimus), 0.5mg, Lot #027591 is incomplete.

4. The dissolution testing should be conducted by using two methods to aid the DBE in selecting a good method and specification for this test product.

   The firm should repeat dissolution testing using their in house method with sinkers and reduce the stirrer speed from (b) (4) rpm to 50 rpm.

   Apparatus: USP Apparatus II (Paddle) sinker
   Speed: 50 RPM

Medium: Buffer at pH 7.0
Volume: 900ml at 37°C

The firm should also repeat dissolution testing using the FDA recommended method with sinkers. Alternatively, if a sinker was used in previous testing, but omitted from the method write up, the firm should repeat this testing with sinkers and increase the stirrer speed to 75 rpm versus 50 rpm currently recommended.

Apparatus: USP Apparatus II (Paddle) sinker
Speed: 50 or 75 RPM based on sinker use
Medium: HPC(1:20,000) pH 4.5 H_3PO_4
Volume: 900ml at 37°C

5. The dissolution testing conducted by (Sandoz Inc.) on its Tacrolimus, 5 mg Capsule Lot #KW06G36NA is incomplete. The firm has conducted acceptable in vivo bioequivalence testing (Submission Date: 12/28/2006) comparing Tacrolimus Capsule, 5mg, Lot # KW06G36NA, the test product manufactured by Sandoz Inc with Prograf® Capsule (Tacrolimus), 5mg, Lot #025581, the reference product manufactured by Astellas Pharma. The formulation(s) for the lower strengths (1mg and 0.5mg) are proportionally similar to the 5mg of the test product which underwent bioequivalence testing. However, waivers of in vivo bioequivalence study requirements for 0.5mg and 1mg capsules of the test product are not granted at this time pending acceptable dissolution testing.

The firm should be informed of the recommendations.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
	None

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	Study#TCU-P6-130
Study Title	Bioequivalence Study of Tacrolimus 5mg Capsules of Sandoz Private Limited, India and Prograf® (Tacrolimus) 5mg Capsules of Fujisawa Healthcare Inc., USA in Healthy Male Volunteers in the Fasting State
Clinical Site (Name & Address)	Algorithme Pharma Inc. 1200 Beaumont Ave Mount-Royal, Quebec, Canada H3P 3P1
Principal Investigator	Eric Sicard M.D.
Dosing Dates	Period I: 9/29/2006 Period II: 10/20/2006
Analytical Site (Name & Address)	(b) (4)
Analytical Director	
Analysis Dates	November 6th – 15th 2006
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	48 days (Long Term Storage Stability = 94 days at -20°C)

Table 5. Product information

Product	Test	Reference
Treatment ID	(A)	(B)
Product Name	Tacrolimus Capsules	Prograf® Capsule (Tacrolimus)
Manufacturer	Sandoz Private Limited (Navi Mumbai India)	Astellas Pharma (Made in Japan for Fujisawa Healthcare)
Batch/Lot No.	KW06G36NA	025581
Manufacture Date	07/2006	
Expiration Date		9/2007
Strength	5mg	5mg

Dosage Form	Capsule	Capsule
Bio-Batch Size	(b) (4) capsules	
Production Batch Size	(b) (4) capsules	
Potency (Assay)	(b) (4)	(b) (4)
Content Uniformity (mean, %RSD)	104.2% (2.4%)	
Dose Administered	5mg	5mg
Route of Administration	Oral	Oral

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	40 normal, healthy male subjects (37 subjects completed)
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	21 days
Randomization Scheme	AB: 2, 4, 5, 8, 9, 11, 14, 15, 17, 19, 21, 23, 26, 28, 29, 32, 33, 36, 38, 39. BA: 1, 3, 6, 7, 10, 12, 13, 16, 18, 20, 22, 24, 25, 27, 30, 31, 34, 35, 37, 40.
Blood Sampling Times	0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 6, 8, 12, 24, 48, 72, 96 and 120 hours.
Blood Volume Collected/Sample	Blood was collected (7ml/sample) in K_3 EDTA vacutainers. There were 22 samples per treatment arm and blood was drawn for screening lab assessments. A total of approximately 359 ml of blood was taken from each subject during the course of the study.
Blood Sample Processing/Storage	Blood was collected in pre-cooled K_3 EDTA vacutainers. The blood was separated into duplicate polypropylene culture tubes and frozen in an upright position at -20°C until sent for analysis at the analytical lab.
IRB Approval	Approval, July 13^h 2006
Informed Consent	Approval, July 13^h 2006
Length of Fasting	Following an overnight fast of at least 10 hours, the study drug was administered with 240ml of water. The fast was maintained until approximately 5 hours after dosing.
Length of Confinement	≈ 58 hours. Subjects checked in about 10 hours before dosing and were not allowed to leave the facility until 48 hour post-dose blood draw had been taken.
Safety Monitoring	Blood pressure, heart rate and body temperature were monitored predose. BP and PR were recorded in a seated position at 1.5, 2.5, 4.5 and 8.5 hours post dose.

Comments on Study Design:
The study design is acceptable.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. TCU-P6-130			
		Treatment Groups	
		Test Product N =37	Reference Product N =37
Age (years)	Mean ± SD	40 ± 12	40 ± 12
	Range	19 - 62	19 – 62
Age Groups	< 18	0(0%)	0(0%)
	18 – 39	18(49%)	18(49%)
	40 – 64	19(51%)	19(51%)
	65 – 75	0(0%)	0(0%)
	> 75	0(0%)	0(0%)
Sex	Male	37(100%)	37(100%)
	Female	0(0%)	0(0%)
Race	White	36(97%)	36(97%)
	Black	0(0%)	0(0%)
	Asian	0(0%)	0(0%)
	American Native or Alaska Native	0(0%)	0(0%)
	Native Hawaiian or Pacific Islander	0(0%)	0(0%)
	Other	1(3%)	1(3%)
BMI	Mean ± SD	24 ± 3	24 ± 3
	Range	19 - 29	19 – 29
Other Factors		N/A	N/A

** The reviewer notes the lack of heterogeneity in the subject population as nearly all participants in the final analysis were white males. The firm should seek to diversify its test subjects to be consistent with FDA BA/BE guidance.

Table 8. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
025	Withdrew his consent on 10/17/2006 (before dosing in period II) for personal reasons and received only a single dose of the reference product	washout	No

026	Investigator withdrew subject on 10/4/2006 (after dosing in period I) for pharmacokinetic reasons (subject did not show up for the 96-hour and 120-hour post-dose blood samples for period 1) and receivd only a single dose of the test product	washout	No
036	Investigator withdrew subject on 10/20/2006 (before dosing in period II) due to abnormal laboratory results (platelet count decreased) and received only one single dose of the test product.	washout	No

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Study No.TCU-P6-130	
	Test	Reference
Gastrointestinal disorders		
Lip dry	1 (3%)	0 (0%)
General disorders and administration site conditions		
Catheter site bruise	0 (0%)	1 (3%)
Catheter site erythema	1 (3%)	0 (0%)
Fatigue	0 (0%)	2 (5%)
Feeling hot and cold	1 (3%)	0 (0%)
Investigations		
Platelet count decreased	1 (3%)	0 (0%)
Nervous system disorders		
Headache	1 (3%)	3 (8%)
Somnolence	3 (8%)	3 (8%)
Renal and urinary disorders		
Polyuria	1 (3%)	0 (0%)
Respiratory, thoracic and mediastinal disorders		
Nasal congestion	1 (3%)	1 (3%)
Pharyngolaryngeal pain	0 (0%)	1 (3%)
Rhinorrhoea	0 (0%)	1 (3%)
Skin and subcutaneous tissue disorders		
Pallor	1 (3%)	1 (3%)
Total	9 (23%)	11 (29%)

* A total of 14 of the 40 subjects experienced a total of 24 adverse events during the study. No serious events were recorded in this study. Among the events, 19 were deemed mild and 5 were considered moderate. Among the 24 events 19 were possibly related and 5 were unrelated to the drug therapy. Eleven events were reported after the single dose administration of the test product and 13 events were reported after the single dose administration of the reference product.

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Concomitant medication (acetaminophen for back pain)	N/A	027
Food (Subject #21 was given Special K cereal instead of Corn Flakes cereal with his breakfast)	021	N/A
Post-study tests (Subject #25 had post study tests performed on day #30 of the study when all tests should have been performed no later than day #27 of the study)	N/A	025
Blood sampling time deviations (2-48 minute deviation) (Average 10.5 minute deviation, median 4 minutes)	003, 005, 008, 011, 014, 015, 016, 017, 019, 024, 026, 027, 030, 032, 035, 036, 037	005, 006, 011, 012,014, 015, 016, 017, 018, 020, 021, 022, 023, 025, 027, 030, 033, 039, 040
Blood sampling not done (Subjects did not return for follow-up visit)	018, 020, 022, 026	029

Comments on Dropouts/Adverse Events/Protocol Deviations: The number of dropouts, adverse events or the reported protocol deviations are not expected to alter the outcome of the study.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Tacrolimus										
Parameter	**Standard Curve Samples**									
Concentration (ng/ml)	0.100	0.200	0.600	2.5	7.5	12.5	20.0	35.0	45.0	50.0
Inter day Precision (%CV)	3.5	6.8	5.9	5.3	4.0	4.9	3.6	4.1	5.2	4.9
Inter day Accuracy (%Nominal)	98.7	102.3	101.8	96.6	97.4	101.1	98.9	100.5	100.0	102.3
Linearity	0.9945-0.9992									
Linearity Range (ng/ml)	0.100-50.000									
Sensitivity/LOQ (ng/ml)	0.100									

Parameter	**Quality Control Samples**			
Concentration (ng/ml)	0.300	10.000	40.000	**
Inter day Precision (%CV)	11.2	6.8	9.2	**
Inter day Accuracy (%Nominal)	104.6	100.8	101.8	**

Comments on Study Assay Validation: These data are acceptable.

Any interfering peaks in chromatograms?	None identified
Were 20% of chromatograms included?	Yes (Subjects 1-9)
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: Acceptable.

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
SOP #PHP-3004-05	4/4/2006	Retested Samples Due to Poor Pharmacokinetic Fit
SOP #LAP-3001-04	5/17/2005	Sample Coding and Re-Assay

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays: Acceptable

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters Fasting Study TCU-P6-130

Mean concentrations are presented in Table 18 and Figure 1

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	354.06	37.36	129.48	663.78	316.78	36.12	184.84	608.75	1.12
AUCI	ng hr/mL	380.06	37.70	133.28	737.07	342.15	37.18	197.44	653.63	1.11
CMAX	ng/mL	37.63	26.98	12.34	61.26	34.33	29.31	16.02	65.72	1.10
TMAX	hr	1.50	.	0.50	4.10	1.75	.	0.75	3.50	0.86
KE	hr-1	0.02	18.60	0.01	0.03	0.02	15.34	0.01	0.03	1.07
THALF	hr	35.30	21.57	23.88	59.82	37.19	15.19	26.11	49.81	0.95

* Tmax values are presented as median and range.

Table 15. Geometric Means and 90% Confidence Intervals Calculated by the Firm

Tacrolimus Capsules 5mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study #TCU-P6-130				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t} (hr*ng/ml)	331.184	299.186	110.69	(100.47-121.96)
$AUC_{0-\infty}$ (hr*ng/ml)	355.168	322.017	110.29	(100.30-121.28)
C_{max} (ng/ml)	36.181	32.931	109.87	(101.81-118.56)

Table 16. Geometric Means and 90% Confidence Intervals Calculated by the Reviewer

Tacrolimus Capsules 5mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No.TCU-P6-130				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t} (hr*ng/ml)	331.18	299.19	110.69	(100.47-121.96)
$AUC_{0-\infty}$ (hr*ng/ml)	355.17	322.02	110.29	(100.30-121.28)
C_{max} (ng/ml)	36.18	32.93	109.87	(101.81-118.56)

These results are calculated by the reviewer and are in good agreement with those reported by the firm. See additional comments in the "Pharmacokinetic and Statistical Analysis" section below.

Table 17. Additional Study Information, Fasting Study No. TCU-P6-130

Root mean square error, AUC_{0-t}	0.2467	
Root mean square error, $AUC_{0-\infty}$	0.2417	
Root mean square error, C_{max}	0.1938	
	Test	**Reference**
Ratio of $AUC_{0-t}/AUC_{0-\infty}$: Mean (Range)	0.93 (0.84-0.97)	0.93 (0.88-0.96)
Kel and AUC∞ determined for how many subjects?	37	37
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Comments on Pharmacokinetic and Statistical Analysis:
The firm's study design contained an adequate washout to avoid detectable pre-dose concentrations of tacrolimus in all subjects in period II.

The firm's study design contained a sufficient number of time points chosen to observe a C_{max}. No subject vomitted during the study.

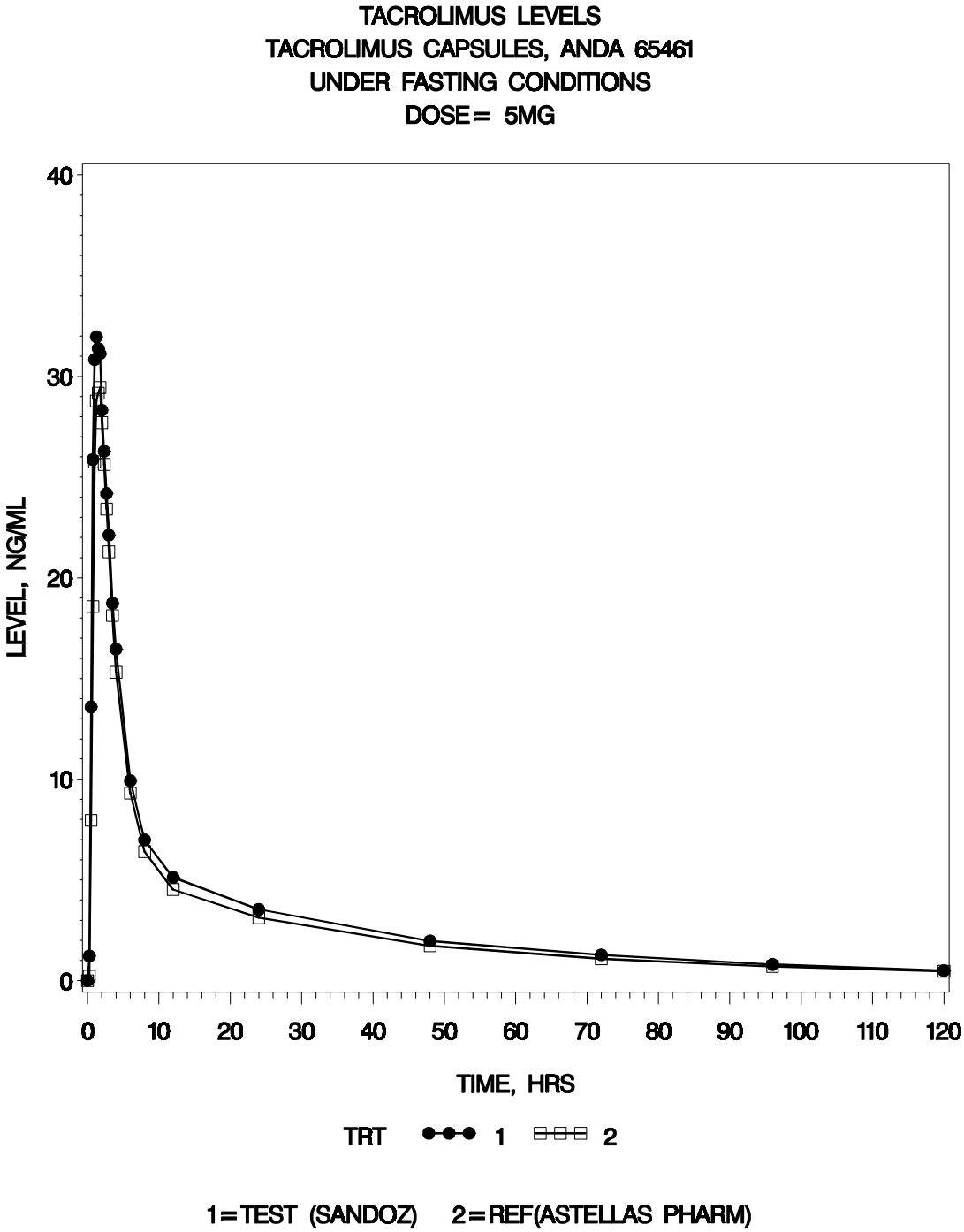
The reviewer agrees with the statistical analysis conducted by the firm.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:
The PK parameters and 90% confidence intervals calculated by the reviewer indicate the dosage form is bioequivalent under fasting conditions.

Table 18. Mean Concentrations, Single-Dose Fasting Bioequivalence Study

	Test (n=37)		Reference (n=37)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.25	1.22	149.92	0.23	151.63	5.42
0.50	13.59	41.79	7.96	79.32	1.71
0.75	25.87	30.88	18.57	51.94	1.39
1.00	30.84	32.98	25.76	39.89	1.20
1.25	31.97	31.29	28.78	35.03	1.11
1.50	31.39	33.70	29.16	35.60	1.08
1.75	31.13	33.57	29.44	34.29	1.06
2.00	28.32	35.32	27.71	33.98	1.02
2.33	26.28	41.01	25.63	38.56	1.03
2.67	24.18	46.96	23.42	40.48	1.03
3.00	22.12	48.01	21.29	41.26	1.04
3.50	18.74	49.40	18.12	41.39	1.03
4.00	16.46	47.82	15.31	41.55	1.08
6.00	9.93	47.85	9.31	49.63	1.07
8.00	6.99	41.75	6.40	45.07	1.09
12.00	5.12	43.90	4.52	44.05	1.13
24.00	3.54	40.58	3.12	40.57	1.13
48.00	1.97	40.88	1.73	42.40	1.14
72.00	1.28	44.94	1.08	44.20	1.18
96.00	0.80	48.61	0.71	46.21	1.13
120.00	0.50	48.38	0.47	48.93	1.06

Figure 1. Mean Concentrations, Single-Dose Fasting Bioequivalence Study



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 19. Study Information

Study Number	Study#TCU-P6-131
Study Title	Bioequivalence Study of Tacrolimus 5mg Capsules of Sandoz Private Limited, India and Prograf® (Tacrolimus) 5mg Capsules of Fujisawa Healthcare Inc., USA in Healthy Male Volunteers in the Fed State
Clinical Site (Name & Address)	Algorithme Pharma Inc. 1200 Beaumont Ave Mount-Royal, Quebec, Canada H3P 3P1
Principal Investigators	Eric Sicard M.D.
Dosing Dates	Period I: 7/29/2006 Period II: 8/19/2006
Analytical Site (Name & Address)	(b) (4)
Analytical Director	
Analysis Dates	August 29th – September 19th 2006
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	53 days (Long Term Storage Stability = 94 days at -20°C)

Table 20. Product Information

Product	Test	Reference
Treatment ID	(A)	(B)
Product Name	Tacrolimus Capsules	Prograf® Capsule
Manufacturer	Sandoz Private Limited	Astellas Pharma
Batch/Lot No.	KW06G36NA	025581
Manufacture Date	07/2006	
Expiration Date		9/2007
Strength	5mg	5mg
Dosage Form	Capsule	Capsule
Bio-Batch Size	(b) (4) capsules	
Production Batch Size	(b) (4) capsules	
Potency (Assay)	(b) (4)%	(b) (4)%
Content Uniformity (mean, %RSD)	104.2% (2.4%)	
Dose Administered	5mg	5mg
Route of Administration	Oral	Oral

Table 21. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	40 normal, healthy male subjects (39 subjects completed)
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	21 days
Randomization Scheme	AB: 1, 3, 5, 8, 9, 12, 13, 15, 17, 20, 21, 24, 25, 28, 29, 31, 34, 36, 37, 39 BA: 2, 4, 6, 7, 10, 11, 14, 16, 18, 19, 22, 23, 26, 27, 30, 32, 33, 35, 38 ,40
Blood Sampling Times	0, 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 14, 16, 24, 48, 72, 96 and 120 hours.
Blood Volume Collected/Sample	Blood was collected (7ml/sample) in K_3 EDTA vacutainers. There were 24 samples per treatment arm and blood was drawn for screening lab assessments. A total of approximately 370 ml of blood was taken from each subject during the course of the study.
Blood Sample Processing/Storage	Blood was collected in pre-cooled K_3 EDTA vacutainers. The blood was separated into duplicate polypropylene culture tubes and frozen in an upright position at -20°C until sent for analysis at the analytical lab.
IRB Approval	Approval, July 13th 2006
Informed Consent	Approval, July 13th 2006
Length of Fasting Before Meal	Following an overnight fast of at least 10 hours, a high calorie, high fat breakfast was consumed by the subjects 30 minutes prior to dosing. The study drug was administered with 240ml of water. The fast was maintained for 4 hours after dosing.
Length of Confinement	≈ 58.5 hours. Subjects checked in about 10.5 hours before dosing and were not allowed to leave the facility until 48 hour post-dose blood draw had been taken.
Safety Monitoring	Blood pressure, heart rate and body temperature were monitored predose. BP and PR were recorded in a seated position at 1.5, 2.5, 4.5 and 8.5 hours post dose.
Standard FDA Meal Used?	Yes**
If No, then meal composition is listed in the table below	**Pieces of toast were replaced with an Englifh Muffin

Comments on Study Design:
Overall, the study design is acceptable.

4.1.2.2 Clinical Results

Table 22. Demographics of Subjects Completing the Bioequivalence Study

Study No. TCU-P6-131			
		Treatment Groups	
		Test Product N =39	Reference Product N =39
Age (years)	Mean ± SD	37 ± 11	37 ± 11
	Range	20 - 61	20 – 61
Age Groups	< 18	0(0%)	0(0%)
	18 – 39	21(54%)	21(54%)
	40 – 64	18(46%)	18(46%)
	65 – 75	0(0%)	0(0%)
	> 75	0(0%)	0(0%)
Sex	Male	39(100%)	39(100%)
	Female	0(0%)	0(0%)
Race	White	28(72%)	28(72%)
	Black	6(15%)	6(15%)
	Asian	1(3%)	1(3%)
	American Native or Alaska Native	3(8%)	3(8%)
	Native Hawaiian or Pacific Islander	0(0%)	0(0%)
	Other	1(3%)	1(3%)
BMI	Mean ± SD	25 ± 3	25 ± 3
	Range	19 - 29	19 – 29
Other Factors		N/A	N/A

Table 23. Dropout Information, Fed Bioequivalence Study

Subject No.	Reason	Period	Replaced?
027	Withdrawn by the physician on 8/19/2006 (before dosing in period II) due to an abnormal lab result (↓ Hgb) and received only one dose of the reference product	washout	No

Table 24. Study Adverse Events, Fed Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study Study No.TCU-P6-131	
	Test	Reference
Gastrointestinal disorders		
Abdominal pain lower	1 (3%)	0 (0%)
Diarrhoea	0 (0%)	1 (3%)
Nausea	0 (0%)	1 (3%)
General disorders and administration site conditions		
Fatigue	0 (0%)	1 (3%)
Venipuncture site bruise	0 (0%)	1 (3%)
Venipuncture site swelling	0 (0%)	1 (3%)
Injury, poisoning and procedural complications		
Injury	0 (0%)	1 (3%)
Investigations		
Blood creatinine increased	1 (3%)	1 (3%)
Musculoskeletal and connective tissue disorders		
Pain in extremity	0 (0%)	1 (3%)
Nervous system disorders		
Dizziness	1 (3%)	1 (3%)
Headache	1 (3%)	2 (5%)
Insomnia	0 (0%)	1 (3%)
Somnolence	3 (8%)	3 (8%)
Syncope vasovagal	0 (0%)	1 (3%)
Respiratory, thoracic and mediastinal disorders		
Rhinorrhoea	1 (3%)	0 (0%)
Skin and subcutaneous tissue disorders		
Photosensitivity reaction	0 (0%)	1 (3%)
Rash	0 (0%)	1 (3%)
Sunburn	0 (0%)	1 (3%)
Total	7 (18%)	14 (35%)

* A total of 17 of the 40 subjects experienced a total of 26 adverse events during the study. No serious events were recorded in this study. Among the events, 25 were deemed mild and 1 was considered moderate. Among the 26 events 18 were possibly related, 2 were unlikely related and 6 were not related to the drug therapy. Eight events were reported after the single dose administration of the test product and 19 events were reported after the single dose administration of the reference product.

Table 25. Protocol Deviations, Fed Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
Concomitant medication (Gramicidin & polymyxin topical cream)	N/AP	026
Xanthines (Subject #12 drank 355ml of Pepsi about 52 hours & 49 minutes after dosing of period I.	012	N/AP
Blood sampling time deviations (2-70 minute deviation)	004, 005, 007, 008,	004, 007, 009, 013,

(Average 7.75 minute deviation, median 3 minutes)	009, 011, 014, 015, 016, 017, 018, 021, 022, 023, 025, 026, 029, 030, 031, 032, 033, 035, 037, 039, 040	016, 021, 022, 023, 024, 025, 027, 028, 029, 030, 032, 034, 035, 036, 038, 039, 040
Blood sampling time not recorded (Exact time of sampling was omitted or inconclusive).	009, 020	N/AP
Blood sampling not done (Subjects did not return for follow-up visits or no sample was obtained)	039	035, 039

Comments on Dropouts/Adverse Events/Protocol Deviations:
The number of dropouts, adverse events or the reported protocol deviations are not expected to alter the outcome of the study.

4.1.2.3 Bioanalytical Results

Table 26. Assay Validation – Within the Fed Bioequivalence Study

Tacrolimus										
Parameter	**Standard Curve Samples**									
Concentration (ng/ml)	0.100	0.200	0.600	2 500	7.500	12.50	20.00	35.00	45.00	50.00
Inter day Precision (%CV)	3.3	6.5	4.6	4.5	3.6	4.1	2.9	4.7	4.1	3.9
Inter day Accuracy (%Nominal)	101.1	99.0	96.8	99.0	98.7	99.2	101.3	102.0	103.2	99.9
Linearity	0.9917-0.9996									
Linearity Range (ng/ml)	0.100-50.00									
Sensitivity/LOQ (ng/ml)	0.100									

Parameter	**Quality Control Samples**			
Concentration (ng/ml)	0.300	10.000	40.000	**
Inter day Precision (%CV)	6.0	4.7	4.0	**
Inter day Accuracy (%Nominal)	98.3	98.3	100.1	**

Comments on Study Assay Validation: These data are acceptable.

Any interfering peaks in chromatograms?	None identified
Were 20% of chromatograms included?	Yes (Subjects 1-8)
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: Acceptable.

Table 27. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
SOP PHP-3004-05	4/4/2006	Retested Samples Due to Poor Pharmacokinetic Fit
SOP #LAP-3001-04	5/17/2005	Sample Coding and Re-Assay

Table 28. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays: Acceptable

4.1.2.4 Pharmacokinetic Results

Table 29. Arithmetic Mean Pharmacokinetic Parameters

Fed Study TCU-P6-131
Mean concentrations are presented in Table 33 and Figure 2

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	ng hr/mL	154.67	35.53	45.82	274.81	161.63	38.51	49.55	377.69	0.96
AUCI	ng hr/mL	169.44	36.00	51.80	306.61	178.09	38.91	53.49	414.57	0.95
CMAX	ng/mL	7.76	32.39	2.34	14.46	8.18	35.75	3.75	14.05	0.95
TMAX	hr	6.00	.	2.00	12.00	5.50	.	2.00	12.00	1.09
KE	hr-1	0.02	15.64	0.01	0.03	0.02	16.14	0.01	0.03	1.04
THALF	hr	36.44	14.80	23.47	55.22	38.01	16.48	27.52	51.57	0.96

* Tmax values are presented as median.

Table 30. Geometric Means and 90% Confidence Intervals Calculated by the Firm

Tacrolimus Capsules 5mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study #TCU-P6-131				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t} (hr*ng/ml)	143.721	149.593	96.07	(92.36-99.94)
$AUC_{0-\infty}$ (hr*ng/ml)	157.135	164.394	95.58	(92.03-99.27)
C_{max} (ng/ml)	7.327	7.633	95.99	(90.11-102.26)

Table 31. Geometric Means and 90% Confidence Intervals Calculated by the Reviewer

Tacrolimus Capsules 5mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study, Study #TCU-P6-131				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC_{0-t} (hr*ng/ml)	143.72	149.59	96.08	(92.36-99.94)
$AUC_{0-\infty}$ (hr*ng/ml)	157.13	164.39	95.58	(92.03-99.27)
C_{max} (ng/ml)	7.33	7.63	96.07	(90.11-102.26)

These results are calculated by the reviewer and are in good agreement with those reported by the firm. See additional comments in the "Pharmacokinetic and Statistical Analysis" section below.

Table 32. Additional Study Information

Root mean square error, AUC_{0-t}	0.1032	
Root mean square error, $AUC_{0-\infty}$	0.0990	
Root mean square error, C_{max}	0.1654	
	Test	**Reference**
Ratio of $AUC_{0-t}/AUC_{0-\infty}$: Mean (Range)	0.91 (0.82-0.97)	0.91 (0.85-0.96)
Kel and AUC∞ determined for how many subjects?	39	39
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Comments on Pharmacokinetic and Statistical Analysis:

The firm's study design contained an adequate washout to avoid detectable pre-dose concentrations of tacrolimus in period II and a sufficient number of time points chosen to observe a C_{max}. No subject vomitted during the study.

The reviewer notes the reduced variability in the AUC estimates when the test dosage form is administered with a high fat meal. The RMSE for both AUC_{0-t} and $AUC_{0-\infty}$ are each approximately 2.4 times lower than those in the fasting study. The n-octanol/water partition coefficient for tacrolimus is >1000, suggesting the compound is lipophilic.[2] The fat in the meal most likely helps to solubilize tacrolimus and thereby reduce the variability associated with the dissolution step prior to absorption.

The reviewer agrees with the statistical analysis conducted by the firm.

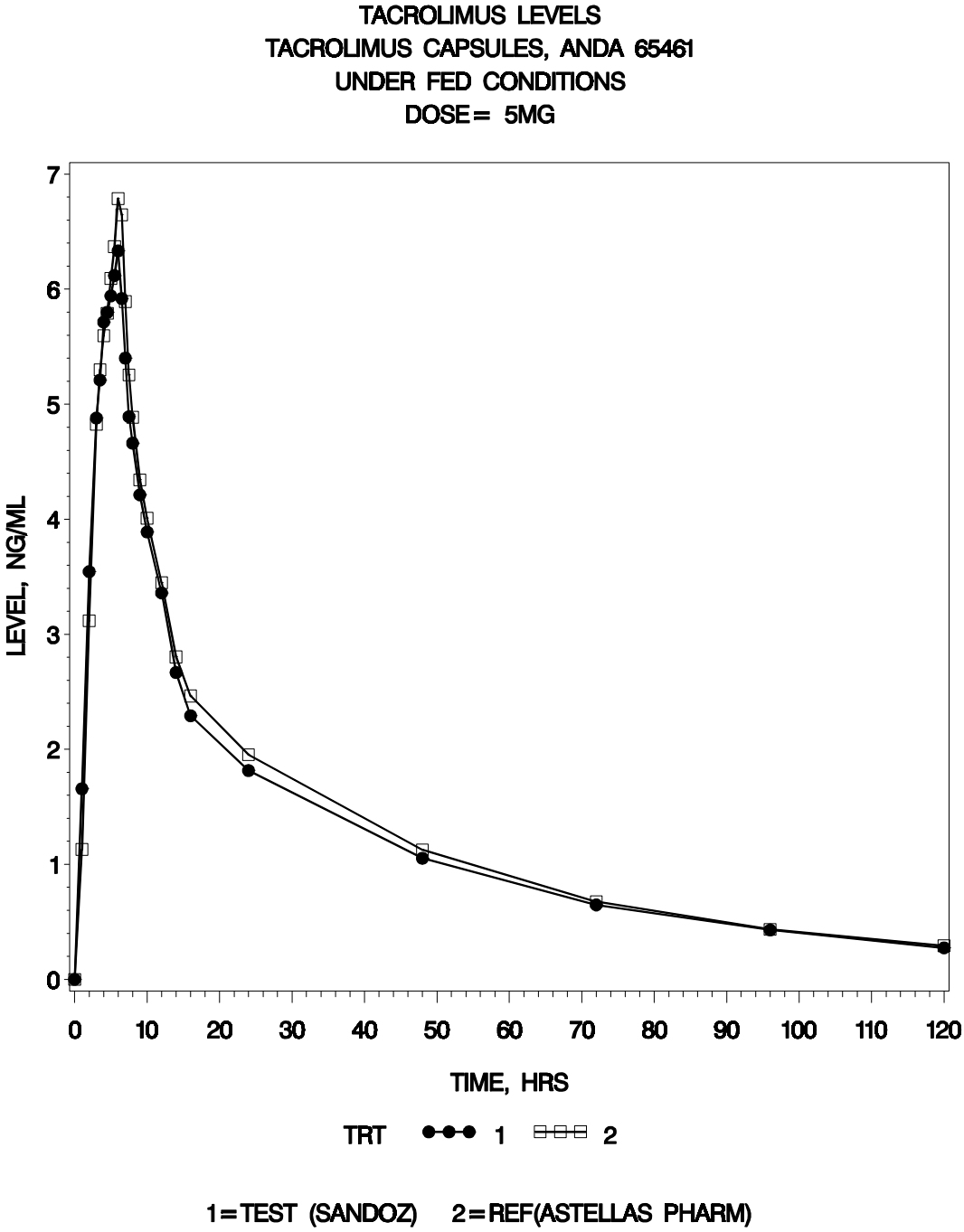
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:
The PK parameters and 90% confidence intervals calculated by the reviewer indicate the dosage form is bioequivalent under fed conditions.

[2] Astellas.com [product monograph for Protopic(tacrolimus)]

Table 33. Mean Concentrations, Single-Dose Fed Bioequivalence Study

	Test (n=39)		Reference (n=39)		Ratio
Time (hr)	Mean (ng/mL)	CV%	Mean (ng/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
1.00	1.66	89.16	1.13	129.61	1.47
2.00	3.55	64.01	3.12	90.72	1.14
3.00	4.88	54.66	4.83	55.65	1.01
3.50	5.21	50.42	5.30	45.98	0.98
4.00	5.71	45.38	5.60	43.07	1.02
4.50	5.80	41.86	5.79	45.24	1.00
5.00	5.94	39.56	6.09	44.15	0.97
5.50	6.12	39.31	6.37	41.25	0.96
6.00	6.33	38.07	6.79	40.00	0.93
6.50	5.92	38.51	6.65	41.91	0.89
7.00	5.40	38.41	5.89	41.34	0.92
7.50	4.89	38.60	5.25	41.76	0.93
8.00	4.66	40.40	4.89	40.80	0.95
9.00	4.21	47.28	4.34	44.22	0.97
10.00	3.89	46.71	4.01	43.36	0.97
12.00	3.36	43.43	3.45	43.57	0.97
14.00	2.67	42.18	2.80	41.32	0.95
16.00	2.29	41.60	2.46	43.17	0.93
24.00	1.82	37.39	1.95	47.21	0.93
48.00	1.05	40.35	1.13	43.94	0.93
72.00	0.65	40.21	0.68	46.62	0.96
96.00	0.43	43.74	0.43	46.45	0.99
120.00	0.27	48.74	0.29	53.40	0.94

Figure 2. Mean Concentrations, Single-Dose Fed Bioequivalence Study



4.2 Formulation Data

Ingredient	Amount (mg) / Capsule			Amount (%) / Capsule		
	0.5 mg	1 mg	5 mg	0.5 mg	1 mg	5 mg
(b) (4)						
Tacrolimus monohydrate (equivalent to Tacrolimus)*	(b) (4)					
Hyperomellose USP ((b) (4))						
Lactose monohydrate NF ((b) (4))**						
Croscarmellose Sodium NF ((b) (4))						
(b) (4) USP***						
(b) (4)****						
(b) (4)						
Lactose monohydrate NF ((b) (4))****						
Magnesium Stearate NF						
Fill Weight						
Encapsulation						
Imprinted Hard gelatin capsule shell						
Total Fill Weight						

Note: Quantity of Lactose Monohydrate (used for (b) (4)) to be adjusted according to Assay value obtained for Tacrolimus (b) (4).

* This quantity is theoretical and based on 100% assay on (b) (4) basis and (b) (4) content of Tacrolimus Monohydrate.

(b) (4)

† The reviewer corrected the values in the table provided by the firm to reflect the % per capsule based on fill weight not total weight of the dosage form.

All excipient concentrations in the finished dosage forms are below the IIG

- Is there an overage of the active pharmaceutical ingredient (API)? No
- If the answer is yes, has the appropriate chemistry division been notified? N/A
- If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted? (No)

Comments on the drug product formulation:

The DBE reviewer concurs with the chemistry reviewer in that no inactive ingredient in the proposed formulation would exceed the IIG limits. All strengths of the dosage form are proportionally formulated.

4.3 Dissolution Data

Dissolution Review Path	DFS N065461 N 000 28-Dec-2006 (Bioequivalence Dissolution Review)

The DBE conducted a first dissolution review before the full ANDA was assigned. The firm developed their own dissolution method with the data summarized in Table 34a below. The original dissolution review (located in DFS) requested that the firm conduct additional dissolution testing using the FDA recommended method. The firm complied with this request and submitted the data. These data are summarized in Table 34b below.

Upon reviewing the dissolution amendment, tacrolimus was not completely released from the dosage form under the FDA recommended dissolution test conditions through 120 minutes of testing. The reviewer notes that in the firm's method, sinkers were employed, the pH controlled at 7.0 and higher stirrer speed used to achieve more favorable results. The ANDA reviewer consulted the DBE Dissolution Focal Point for an opinion regarding the dissolution testing for this ANDA. These recommendations may be found in "4.5 Consult Reviews" of this document.

Based on poor dissolution testing results and the recommendations from the DBE Dissolution Focal Point, the firm will be asked to conduct additional dissolution testing. It is assumed that the firm used a sinker when conducting dissolution testing using their method, based on their "Master Control Procedure". However, when their method was used, the results were not sufficiently discriminatory. Therefore, the firm will be asked to repeat dissolution testing using their own method (with sinkers) at 50 rpm versus (b) (4) rpm. It is hoped that this slower stirrer speed will provide a more meaningful dissolution profile.

The firm will also be asked to repeat dissolution testing using the FDA-recommended method (with sinker) at 50 rpm. It is assumed that sinkers were not used with the FDA method as the use of sinkers was not documented in their dissolution amendment. However, if the firm used a sinker, but omitted its use in the method write up, the firm will be asked to repeat testing with a sinker at 75 rpm. It is hoped that using a sinker will increase dosage form to dissolution media solvent interaction and thereby improve dissolution. If sinkers were used, then an increase in the agitation of the media, by increasing stirrer rpm to 75 rpm versus 50 rpm, may further facilitate dissolution.

The dissolution testing is incomplete pending the firm's response to the deficiency.

Table 34a. Original Dissolution Testing Using the Firm's Dissolution Method

Dissolution Conditions	**Apparatus:**	USP Apparatus Type II (Paddle) with sinker
	Speed of Rotation:	(b) (4) RPM
	Medium:	Buffer pH 7.0
	Volume:	900 ml
	Temperature:	37 ± 0.5°C
Firm's Proposed Specifications	Not less than (b) (4) % (Q) of the labeled amount. After 45 minutes The current FDA specification is NLT (b) (4) % in 90 minutes	
Dissolution Testing Site (Name, Address)	Sandoz Private Limited, M.I.D.C., Plot Nos. 8-A/2 & 8-B,TTC Industrial Area, Kalwe Block, Village Dighe, Navi Mumbai - 400 708, Maharashtra, INDIA	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10	15	30	45	60	Study Report Location
Study Report # NA	Oct.30.2006	Tacrolimus capsules Batch # KW06G38N Mfg Date: July. 2006	0.5 mg Capsule	12	Mean Range %RSD	(b) (4)					Module 5
Study Report # NA	Aug.01.2006	PROGRAF® Batch # 027591 Exp. Date : Aug.2008	0.5 mg Capsule	12	Mean Range %RSD						
Study Report # NA	Oct.30.2006	Tacrolimus capsules Batch # KW06G37N Mfg Date: July. 2006	1 mg Capsule	12	Mean Range %RSD						Module 5
Study Report # NA	Aug.01.2006	PROGRAF® Batch # 027191 Exp. Date : May.2008	1 mg Capsule	12	Mean Range %RSD						
Study Report # NA	July.21.2006	Tacrolimus capsules Batch # KW06G36N Mfg Date: July. 2006	5 mg Capsule	12	Mean Range %RSD						Module 5
Study Report # NA	July.21.2006	PROGRAF® Batch # 025581 Exp. Date : Sep.2007	5 mg Capsule	12	Mean Range %RSD						

Table 34b. Repeated Dissolution Testing Using the FDA Recommended Method

Dissolution Conditions	**Apparatus:**	USP Apparatus Type II (Paddle)
	Speed of Rotation:	50 RPM
	Medium:	Hydroxypropyl cellulose solution (1 in 20,000) pH 4.5 with phosphoric acid
	Volume:	900 ml
	Temperature:	37 ± 0.5°C
Firm's Proposed Specifications	Not Provided The current FDA specification is NLT (b)(4)% in 90 minutes	
Dissolution Testing Site (Name, Address)	Not Provided	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 15	30	60	90	120	Study Report Location
Study Report # NA	Not Provided	Tacrolimus capsules Batch # KW06G38N Mfg Date: July. 2006	0.5 mg Capsule	12	Mean	25	42	57	66	73	Module 5
					Range	(13-33)	(25-54)	(38-67)	(43-82)	(50-86)	
					%RSD	20.0	17.9	13.5	16.2	12.9	
Study Report # NA	Not Provided	PROGRAF® Batch # 027591 Exp. Date : Aug.2008	0.5 mg Capsule	12	Mean	25	58	81	84	88	
					Range	(18-33)	(48-65)	(71-93)	(75-90)	(81-99)	
					%RSD	16.0	9.2	7.1	5.3	5.1	
Study Report # NA	Not Provided	Tacrolimus capsules Batch # KW06G37N Mfg Date: July. 2006	1 mg Capsule	12	Mean	20	35	48	55	60	Module 5
					Range	(16-24)	(26-40)	(37-53)	(45-62)	(51-68)	
					%RSD	12.9	10.7	10.3	9.1	9.5	
Study Report # NA	Not Provided	PROGRAF® Batch # 027191 Exp. Date : May.2008	1 mg Capsule	12	Mean	28	52	76	83	83	
					Range	(18-43)	(43-59)	(70-85)	(71-88)	(73-90)	
					%RSD	24.0	12.4	5.9	5.6	6.8	
Study Report # NA	Not Provided	Tacrolimus capsules Batch # KW06G36N Mfg Date: July. 2006	5 mg Capsule	12	Mean	21	42	59	71	77	Module 5
					Range	(15-25)	(33-50)	(50-65)	(64-78)	(73-83)	
					%RSD	12.7	13.2	7.7	6.0	4.5	
Study Report # NA	Not Provided	PROGRAF® Batch # 025581 Exp. Date : Sep.2007	5 mg Capsule	12	Mean	20	43	70	84	89	
					Range	(4-30)	(22-52)	(50-81)	(71-93)	(83-98)	
					%RSD	35.7	21.9	12.0	7.6	5.0	

Figure 3. Dissolution Profiles

Not Applicable

APPEARS THIS WAY ON ORIGINAL

4.4 Detailed Regulatory History (If Applicable)

Protocol Reviewed
07-022 (Panacea Biotec)
03-059 (Roxane)

Controls Reviewed (Since 2005 or more recent)
05-0739 (Watson)
(b) (4)
07-1257 (Panacea Biotec)
07-1177 (ACIC)
07-0753 (Anchen)
(b) (4)

Other ANDA's
(b) (4)

4.5 Consult Reviews

HI Chris,

A couple of things. The bio seems pretty good so I would not be averse to giving them their proposed method ((b) (4)), but using that method provides non-discriminatory results (i.e. the products dissolve way too quickly). So here are some suggestions:

1. Find out if the firm used a sinker using the FDA-recommended method
    a. If they did, I would suggest that they repeat testing (w/ FDA method) using 75 rpm
    b. If they did not, have them repeat testing (w/ FDA method) using a sinker
2. In addition to #1, they should repeat testing using their proposed method, but at 50 rpm.

Therefore, a total of 2 additional methods should be tried by the firm for all strengths of T & R.

This is just a recommendation, please consult your TL as well.

Thanks,
Paul

From: Jones, Christopher
Sent: Wednesday, October 24, 2007 9:37 AM
To: Seo, Paul
Subject: FW: Dissolution Consult

Looks like I'm going to have an otherwise clean ANDA, what do think about this dissolution testing?

From: Jones, Christopher
Sent: Thursday, October 18, 2007 12:25 PM
To: Seo, Paul
Subject: Dissolution Consult

Paul:

I have a dissolution amendment I'm reviewing that was assigned to me after I received the full ANDA to review. There are some issues with the dissolution testing that I'd like for you take a look at and comment. The drug is Tacrolimus Capsules (ANDA 65-461) and it is a first generic.

The original dissolution reviewer issued a deficiency to the firm because the firm developed their own method and a current FDA method existed. We recommended the firm complete the testing using FDA method. The firm complied and submitted the amendment. Attached are two tables that provide the data using both methods.

The problem I'm encountering is that the firm's test product and the reference product will not meet the FDA recommended specification, with the test product more noticeably deviating from this spec. The firm's original method employed a higher stirrer speed (b) (4) vs 50 rpm) and the medium was modified. The original testing, with more favorable results, used a medium buffered at pH (b) (4) where as the repeat testing with the FDA method used hydroxypropyl cellulose (1:20,000) solution at pH 4.5 (adjusted with H3PO4). Although not noted in the original dissolution review, the firm indicates in the amendment that (b) (4) with the firm's method. Both the test and reference products demonstrate incomplete dissolution at 120 minutes when the firm conducts testing using the FDA method.

I spoke with the Team Leader and he recommended that I consult you. Do you have any preferences or thoughts as to how we should proceed? Could the dosage form have a low density and float

(hence sinkers needed) or could there be an issue with the testing procedure at that facility since both test and reference products did not meet the FDA spec? Maybe there is pH dependent solubility issue for this drug or dosage form or the method is sensitive to stirrer speed. Should we use their method and spec or use the FDA method and change the spec? What do you think? Additionally, after a preliminary review, I have not found any in vivo issues that would suggest the product is not bioequivalent. Let me know what you think once you've had a chance to review.

<< File: DissolutionTestingTables.doc >>

Chris

4.6 SAS Output

4.6.1.1 Fasting Study Concentration Dataset

Obs	SUB	SEQ	PER	TRT	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16	c17	c18	c19	c20	c21	c22
1	1																									(b) (4)
2	1																									
3	2																									
4	2																									
5	3																									
6	3																									
7	4																									
8	4																									
9	5																									
10	5																									
11	6																									
12	6																									
13	7																									
14	7																									
15	8																									
16	8																									
17	9																									
18	9																									
19	10																									
20	10																									
21	11																									
22	11																									
23	12																									
24	12																									
25	13																									

62 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.7 Additional Attachments

None

BIOEQUIVALENCE DEFICIENCY

ANDA: 65-461

APPLICANT: Sandoz Inc.

DRUG PRODUCT: Tacrolimus Capsule
0.5mg, 1mg and 5mg

The Division of Bioequivalence (DBE) has completed its review of your submission acknowledged on the cover sheet. The following deficiency has been identified:

1. The DBE has reviewed all dissolution data submitted thus far. The DBE recommends two additional dissolution tests be conducted. These are summarized below.

- Please repeat dissolution testing using your in house method with sinkers and reduce your stirrer speed from (b) (4) rpm to 50 rpm.

  Apparatus: USP Apparatus II (Paddle) sinker
  Speed: 50 RPM
  Medium: Buffer at pH 7.0
  Volume: 900ml at 37°C

- Please repeat dissolution testing using the FDA-recommended method with sinkers. We assume sinkers were not used as it was not documented in your dissolution amendment dated 7/25/2007. Alternatively, if a sinker was used, but omitted from the method write up, please repeat this testing with sinkers and increase the stirrer speed to 75 rpm versus the 50 rpm currently recommended.

  Apparatus: USP Apparatus II (Paddle) sinker
  Speed: 50 or 75 RPM based on sinker use
  Medium: HPC(1:20,000) pH 4.5 H_3PO_4
  Volume: 900ml at 37°C

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.8 Completed Assignment for 65461 ID: 748

Reviewer: Jones, Christopher **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description: Fasting and fed studies and two dissolution waivers. Additional study amendment not completed by the original dissolution reviewer.

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*		
858	12/28/2006	Bioequivalence Study	Fasting Study	1	1	Edit	Delete
858	12/28/2006	Bioequivalence Study	Fed Study	1	1	Edit	Delete
858	12/28/2006	Other	Dissolution Waiver	1	1	Edit	Delete
858	12/28/2006	Other	Dissolution Waiver	1	1	Edit	Delete
858	7/25/2007	Other	Study Amendment	1	1	Edit	Delete
				Bean Total:	5		

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

/s/

S Christopher Jones
11/6/2007 01:12:30 PM
BIOPHARMACEUTICS

Kuldeep R. Dhariwal
11/6/2007 01:30:41 PM
BIOPHARMACEUTICS

Barbara Davit
11/9/2007 02:37:14 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE DISSOLUTION CHECKLIST

ANDA No.	65-461		
Drug Product Name	Tacrolimus Capsules		
Strength (s)	0.5 mg, 1 mg and 5 mg		
Applicant Name	Sandoz Inc.		
Address	506 Carnegie Center, Suite 400, Princeton, NJ 08540		
Applicant's Point of Contact	Dr. Carmelle Lucas, Director of Regulatory Affairs		
Contact's Phone Number	(609) 627-8854		
Contact's Fax Number	(609) 395-2792		
Submission Date(s)	December 28, 2006		
First Generic	No		
Reviewer	Sikta Pradhan, Ph.D.		
Study Number (s)	**TCU-P6-130**	**TCU-P6-131**	**Bio-waiver request**
Study Type (s)	**Fasting**	**Fed**	**N/A**
Strength(s)	**5 mg Cap.**	**5 mg Cap.**	**0.5 mg and 1 mg Cap**
Clinical Site	Algorithme Pharma Inc.		
Clinical Site Address	1200 Beaumont Ave.		
	Mount-Royal, Quebec, Canada H3P 3H5		
Analytical Site	(b) (4)		
Analytical Address			

Table 1. Submission Content Checklist

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☐	X	☐
Did the firm use the USP dissolution method			☐	X	☐
Did the firm use 12 units of both test and reference in dissolution testing			X	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV)			X	☐	☐
Did the firm conduct dissolution testing with its own proposed method			X	☐	☐
Is FDA method in the public dissolution database (on the web)			X	☐	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	X	☐	☐
		Plasma concentrations	X	☐	☐
	Fed BE study	PK parameters	X	☐	☐
		Plasma concentrations	X	☐	☐
	Other study	PK parameters	☐	☐	X
		Plasma concentrations	☐	☐	X
Are all eight electronic summary biotables present			X	☐	☐
Are electronic summary biotables in pdf format			X	☐	☐

If the answer to either of the last two questions is no, indicate which summary biotables are

- Not present:
- Not in pdf format:

Recommendations

1. The dissolution testing conducted by Sandoz Inc. on its test product, Tacrolimus Capsules, 0.5 mg, 1 mg and 5 mg comparing them to Prograf[R] , 0.5 mg, 1 mg and 5 mg capsules, respectively, using [redacted] (b) (4) is not acceptable to the Division of Bioequivalence. The firm is requested to conduct and submit dissolution testing on the test and reference products (12 units each) using the following FDA-recommended method:

Medium:	Hydroxypropyl cellulose solution (1 in 20,000), pH is adjusted to 4.5 with phosphoric acid.
Volume:	900 mL
USP Apparatus:	# 2 (Paddle) at 50 rpm
Temperature:	37^0 C

2. The Division of Bioequivalence has developed new data summary tables in a concise format consistent with the Common Technical Document (CTD). The firm is requested to provide complete tables and send them with the rest of the bioequivalence submission. The tables are available in Word and PDF format under the title "Model Bioequivalence Data Summary Tables" in our website at http://www.fda.gov/cder/ogd/index.htm. To improve the efficiency of the Division, these tables should be provided in the ANDA submission.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 65-461 APPLICANT: Sandoz Inc.

DRUG PRODUCT: Tacrolimus Capsules, 0.5 mg, 1 mg and 5 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies and the waiver request will be conducted later. The following deficiencies have been identified:

1. Your dissolution testing is not acceptable to the Division of Bioequivalence. Please conduct and submit dissolution testing on the test and reference products (12 units each) using the following FDA-recommended method:

Medium:	Hydroxypropyl cellulose solution (1 in 20,000), pH is adjusted to 4.5 with phosphoric acid.
Volume:	900 mL
Apparatus:	USP # 2 (Paddle) at 50 rpm
Temperature	37 ^{0} C

2. The Division of Bioequivalence has developed new data summary tables in a concise format consistent with the Common Technical Document (CTD). Please provide complete tables and send them with the rest of the bioequivalence submission. The tables are available in Word and PDF format under the title "Model Bioequivalence Data Summary Tables" in our website at http://www.fda.gov/cder/ogd/index.htm. To improve the efficiency of the Division, these tables should be provided in the ANDA submission.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA #65-461

DISSOLUTION - INCOMPLETE Submission date: December 28, 2006

[NOTE: The in vitro testing is incomplete. The fasting and fed BE studies and waiver request are pending review]

1. BDI-DISSOLUTION (Dissolution Data) Strength: 0.5 mg, 1 mg and 5 mg
Outcome: IC

Outcome Decisions: IC – Incomplete

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

/s/

Sikta Pradhan
6/27/2007 04:46:30 PM
BIOPHARMACEUTICS

Yi Zhang
6/27/2007 04:50:35 PM
BIOPHARMACEUTICS
On behalf of Yih Chain Huang

Barbara Davit
6/28/2007 06:56:05 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-461

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 65-461 Applicant Sandoz Inc.
Drug Tacrolimus Capsules Strength(s) 0.5 mg, 1 mg, and 5 mg

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. **Martin Shimer** Chief, Reg. Support Branch	Date 3 Sept 2008/12/12/08 Initials MHS	Date _____ Initials _____

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant Notify patent holder/NDA holder Yes ☐ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Has case been settled: Yes ☐ No ☐
Is applicant eligible for 180 day Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval

Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
RLD = _____ NDA# _____
Date Checked _____
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐
Date settled:

Comments: ANDA submitted on 12/29/2006. BOS=Prograf NDA 50708, no unexpired patents cert provided-firm will carve out the ODE(prophylaxis of Organ Rejection in patients receiving heart transplants). ANDA ack for filing on 12/29/2006(LO dated 4/6/2007). There are no patents which preclude approval of this ANDA-ODE has been omitted from labeling. ANDA is eligible for Full Approval.

****There is a pending CP 07P-0358 which must be answered prior to issuance of an approval action.

Update 12/12/08-Despite the change in statute there remain no patents listed for this drug product which could preclude approval of this ANDA. Applicant has omittted claims associated with ODE. ANDA remains eligible for full approval.

2. **Project Manager**, Roberta Szydlo Team 6 Review Support Branch	Date 9/3/08 Initials rts	Date 8/10/09 Initials rts

Original Rec'd date 12/28/06
Date Acceptable for Filing 12/29/06
Patent Certification (type) 1
Date Patent/Exclus.expires
Citizens' Petition/Legal Case Yes ☒ No ☐
(If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
Priority Approval Yes ☒ No ☐
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio review tabbed Yes ☒ No ☐
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments: HI Roberta

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 4/18/07
Date of Office Bio Review 4/15/08
Date of Labeling Approv. Sum 6/9/09
Date of Sterility Assur. App. NA
Methods Val. Samples Pending Yes ☐ No ☐
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

You can fax the letter and inform Sandoz.

Thanks
Gary

From: Drew, Carol E
Sent: Monday, August 10, 2009 8:50 AM
To: Buehler, Gary J

Cc: Lynn, Steven J
Subject: RE: tacrolimus

yes, I just got confirmation that the faxes when through...

From: Buehler, Gary J
Sent: Monday, August 10, 2009 8:42 AM
To: Drew, Carol E
Cc: Lynn, Steven J
Subject: FW: tacrolimus

HI Carol

Can we contact Sandoz and fax the letter now?

Dave:

Can you review the proposed press release for Tacrolimus?

Bob

From: Szydlo, Roberta
Sent: Tuesday, March 10, 2009 3:14 PM
To: West, Robert L
Subject: FW: ANDA 65-461, Tacrolimus, Sandoz - Press release

Hi Bob,

I sent the email below way back when to Cec. I don't think that I ever received any feedback regarding the draft of the press release. Should we skip the PR for this one?

Thanks,
Roberta

From: Szydlo, Roberta
Sent: Wednesday, September 03, 2008 3:54 PM
To: Parise, Cecelia M
Cc: West, Robert L
Subject: RE: ANDA 65-461, Tacrolimus, Sandoz

Hi Cec,

Attached please find the draft of the press release.

Thanks,
Roberta

3. Labeling Endorsement

Reviewer:	Labeling Team Leader:
Date 9/3/08;7/22/09	Date 9/3/08
Name/Initials rts for AV; rts for AP	Name/Initials rts for av

Comments:
There should be an approval summary with a submission date of June 3, 2009 AP@. It is current for now. There are two pending supplement seen in comis for the RLD. There is no REMS currently.

From: Szydlo, Roberta
Sent: Wednesday, July 22, 2009 10:50 AM
To: Payne, Angela
Subject: Tacrolimus

Hi Angela,

The CP for tarcrolimus may be answered this Friday allowing us to approve ANDA 65-461 from Sandoz on the same day. Is there a REMS associated with these? The latest approval summary for this ANDA is dated 3/5/09 in DFS. Is it still good to go?

Thanks,
Roberta

Hi Roberta

The labeling is still okay for approval - I am acting for Lillie this week.

Adolph

From: Szydlo, Roberta
Sent: Wednesday, September 03, 2008 10:23 AM
To: Vezza, Adolph E
Subject: Labeling concurrence, ANDA 65-461, Tacrolimus Capsules, Sandoz

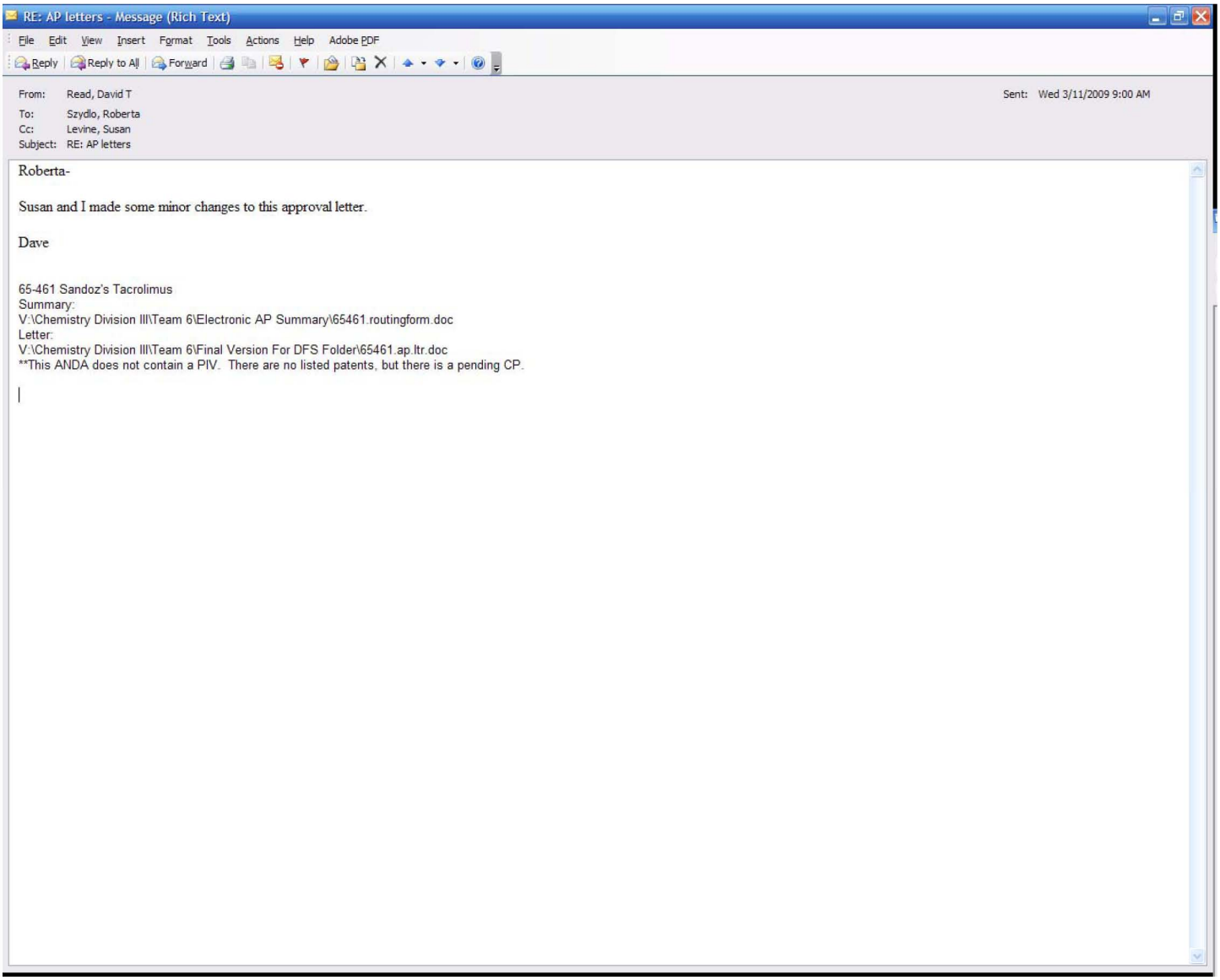
Hello Adolph,

Attached are the approval letter and most recent labeling approval summary for ANDA 65-461, Tacrolimus Capsules 0.5 mg, 1 mg, and 5 mg, Sandoz Inc. Please provide final labeling concurrence for full approval. If there is an acting labeling TL please forward this due to Lillie's absence.

<< File: 65461.ap.ltr.pdf >> << File: 65461.label.pdf >>

Thank you,
Roberta

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 3/11/09
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initialsrs for DR
Comments:



RE: AP letters - Message (Rich Text)

File Edit View Insert Format Tools Actions Help Adobe PDF

Reply | Reply to All | Forward

From: Read, David T
Sent: Wed 3/11/2009 9:00 AM
To: Szydlo, Roberta
Cc: Levine, Susan
Subject: RE: AP letters

Roberta-

Susan and I made some minor changes to this approval letter.

Dave

65-461 Sandoz's Tacrolimus
Summary:
V:\Chemistry Division III\Team 6\Electronic AP Summary\65461.routingform.doc
Letter:
V:\Chemistry Division III\Team 6\Final Version For DFS Folder\65461.ap.ltr.doc
**This ANDA does not contain a PIV. There are no listed patents, but there is a pending CP.

5. Div. Dir./Deputy Dir. Date10/27/08;11/6/08
Chemistry Div. III InitialsDSG;VAS
Comments:cmc acceptable

6. Frank Holcombe **First Generics Only** Date2/10/09
Assoc. Dir. For Chemistry InitialsRAR
Comments: (First generic drug review)
CMC acceptable, Calculations documented for the 2 tautomeric forms. For Frank,

7. Vacant Date
Deputy Dir., DLPS Initials

8. Peter Rickman Date7/22/2009
Director, DLPS Initialswpr
Para.IV Patent Cert: Yes No ;Pending Legal Action: Yes No ; Petition: Yes No
Comments:ANDA submitted on 12/29/2006. BOS=Prograf NDA 50708; There are no unexpired patents for this product; applicant will carve out the ODE (prophylaxis of organ rejection in patients receiving heart transplants). ANDA ack for filing on

12/29/2006(LO dated 4/6/2007). Labeling acceptable 6/3/2009 per AP Summary; Bio acceptable 4/15/2008; EER acceptable 4/18/2007.

****There is a pending CP 07P-0358 which must be answered prior to issuance of an approval action.

RLD labeling checked for updates by Angela Payne on 8/32009, no updates to RLD labeling.

Okay for Full Approval

OR

8. Robert L. West Date _____
Deputy Director, OGD Initials _____
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Press Release Acceptable ☐
Comments:

9. Gary Buehler Date _____
Director, OGD Initials _____
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Team Roberta Szydlo Date8/10/09
Review Support Branch Initials rts

_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
8:55amTime notified of approval by phone
8:55amTime approval letter faxed

FDA Notification:
8/10/09Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
8/10/09Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

EER DATA:

APPEARS THIS WAY ON ORIGINAL

COMIS TABLE:

ORANGE BOOK PRINT OFF:

APPEARS THIS WAY ON ORIGINAL

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
ANDA 65461	ORIG 1		TACROLIMUS

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

/s/

ROBERTA T SZYDLO
08/10/2009

MINOR AMENDMENT

ANDA 65-461

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Sandoz Inc. TEL: 609-627-8854

ATTN: Carmelle Lucas, Ph.D. FAX: 609-395-2792

FROM: Roberta Szydlo PROJECT MANAGER: (240) 276-8476

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 28, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Tacrolimus Capsules, 0.5 mg, 1 mg and 5 mg.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__**4**__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

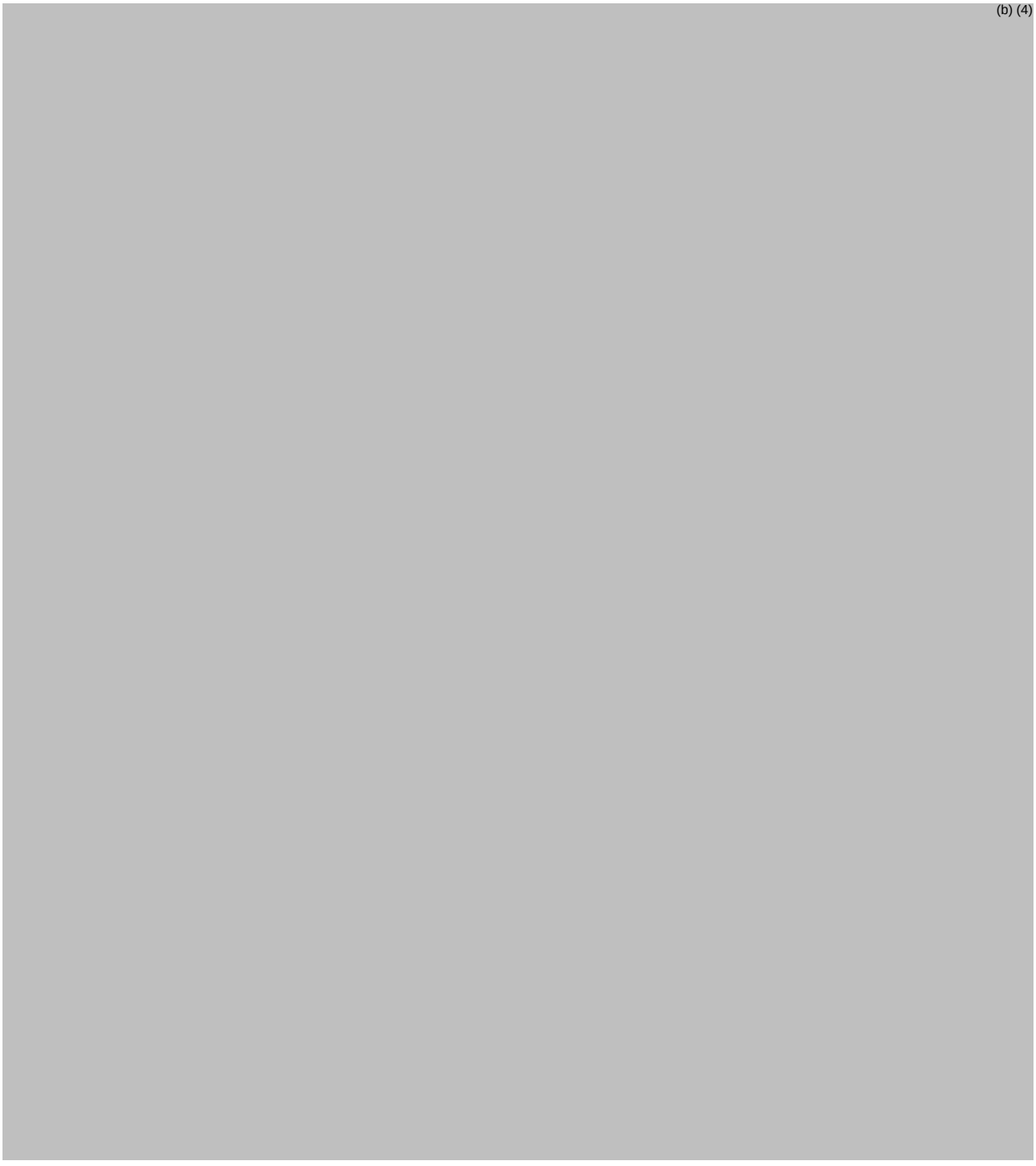
ANDA: 65-461 APPLICANT: Sandoz Inc.

DRUG PRODUCT: Tacrolimus Capsules, 0.5 mg, 1 mg, and 5 mg

The deficiencies presented below represent MINOR deficiencies:

A. Deficiencies:

(b) (4)



B. (b) (4)

Sincerely yours,

{See appended electronic signature page}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Susan Zuk

2/28/2008 03:16:13 PM

BIOEQUIVALENCY AMENDMENT

ANDA 65-461

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Sandoz Inc. TEL: 609-627-8854

ATTN: Carmelle Lucas, Ph.D. FAX: 609-395-2792

FROM: Christina Thompson PROJECT MANAGER: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on December 28, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Tacrolimus Capsules 0.5 mg, 1 mg, and 5 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __**1**__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

In an effort to improve document flow and availability to review staff, please submit your response in electronic PDF format, with a signed cover letter and 356h form.

BIOEQUIVALENCE DEFICIENCY

ANDA: 65-461

APPLICANT: Sandoz Inc.

DRUG PRODUCT: Tacrolimus Capsule
0.5mg, 1mg and 5mg

The Division of Bioequivalence (DBE) has completed its review of your submission acknowledged on the cover sheet. The following deficiency has been identified:

1. The DBE has reviewed all dissolution data submitted thus far. The DBE recommends two additional dissolution tests be conducted. These are summarized below.

- Please repeat dissolution testing using your in house method with sinkers and reduce your stirrer speed from (b)(4) rpm to 50 rpm.

  Apparatus: USP Apparatus II (Paddle) sinker
  Speed: 50 RPM
  Medium: Buffer at pH 7.0
  Volume: 900ml at 37°C

- Please repeat dissolution testing using the FDA-recommended method with sinkers. We assume sinkers were not used as it was not documented in your dissolution amendment dated 7/25/2007. Alternatively, if a sinker was used, but omitted from the method write up, please repeat this testing with sinkers and increase the stirrer speed to 75 rpm versus the 50 rpm currently recommended.

  Apparatus: USP Apparatus II (Paddle) sinker
  Speed: 50 or 75 RPM based on sinker use
  Medium: HPC(1:20,000) pH 4.5 H_3PO_4
  Volume: 900ml at 37°C

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Barbara Davit
11/19/2007 04:15:00 PM
Signing for Dale P Conner

MINOR AMENDMENT

ANDA 65-461

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Sandoz Inc. TEL: 609-627-8854

ATTN: Carmelle Lucas, Ph.D. FAX: 609-395-2792

FROM: Roberta Szydlo PROJECT MANAGER: (301) 827-5743

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 28, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Tacrolimus Capsules 0.5 mg, 1 mg, and 5 mg.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__**3**__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 65-461 APPLICANT: Sandoz, Inc.

DRUG PRODUCT: Tacrolimus Capsules, 0.5 mg, 1 mg, and 5 mg

The deficiencies presented below represent MINOR deficiencies:

A. Deficiencies:

(b) (4)

(b) (4)

B.

Sincerely yours,

{See appended electronic signature page}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA
ANDA Duplicate
DIV FILE
Field Copy

Endorsement Block:

B. Endorsement Block

Reviewer /MBennett/6/26/2007; 7/2/2007
Team Leader/SZuk/6/29/07
Project Manager/RSzydlo/7/3/07

F/T by/

V:\Chemistry Division III\Team 6\Final Version For DFS Folder\65461.R01.NA.doc

TYPE OF LETTER: Not Approvable

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

/s/

Susan Zuk
7/3/2007 11:13:14 AM

BIOEQUIVALENCY AMENDMENT

ANDA 65-461

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Sandoz Inc. TEL: 609-627-8854

ATTN: Carmelle Lucas, Ph.D. FAX: 609-395-2792

FROM: Beth Fabian-Fritsch PROJECT MANAGER: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on December 28, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Tacrolimus Capsules, 0.5 mg, 1 mg and 5 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __**2**__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCIES

ANDA: 65-461 APPLICANT: Sandoz Inc.

DRUG PRODUCT: Tacrolimus Capsules, 0.5 mg, 1 mg and 5 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence studies and the waiver request will be conducted later. The following deficiencies have been identified:

1. Your dissolution testing is not acceptable to the Division of Bioequivalence. Please conduct and submit dissolution testing on the test and reference products (12 units each) using the following FDA-recommended method:

Medium:	Hydroxypropyl cellulose solution (1 in 20,000), pH is adjusted to 4.5 with phosphoric acid.
Volume:	900 mL
Apparatus:	USP # 2 (Paddle) at 50 rpm
Temperature	37 ^{0} C

2. The Division of Bioequivalence has developed new data summary tables in a concise format consistent with the Common Technical Document (CTD). Please provide complete tables and send them with the rest of the bioequivalence submission. The tables are available in Word and PDF format under the title "Model Bioequivalence Data Summary Tables" in our website at http://www.fda.gov/cder/ogd/index.htm. To improve the efficiency of the Division, these tables should be provided in the ANDA submission.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Barbara Davit
6/29/2007 05:23:29 PM
Signing for Dale P Conner

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ *****

ANDA #: 65-461 **FIRM NAME**: SANDOZ INC.

PIV: NO **Electronic or Paper Submission:** CTD FORAMT PAPER

RELATED APPLICATION(S): NA

First Generic Product Received? YES PER MARTY

1/20/07

DRUG NAME: TACROLIMUS
DOSAGE FORM: CAPSULES,
0.5 MG, 1 MG AND 5 MG

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☐ **BCE**	☐
☐ **BST**	☒ **BDI**	

Random Queue: 6
Chem Team Leader: Susan Zuk PM: Ryan Nguyen Labeling Reviewer: Jacqueline Council

Letter Date: DECEMBER 28, 2006 **Received Date**: DECEMBER 29, 2006

Comments: EC- 3 YES **On Cards:** YES
Therapeutic Code: 5010400 IMMUOMODULATORS

Archival copy: CTD FORAMT **Sections** I
Review copy: YES E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Iain Margand	**Recommendation:**
Date 4/5/07	☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: _____	**Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:

SEE DBE FIRST GENERIC REVIEW ATTACHED

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2** **Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: DECEMBER 28, 2006	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) or Disclosure Statement (Form FDA 3455) YES	☒
1.3.5	**1.3.5.1** **Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations N **1.3.5.2** **Patent Certification** 1. Patent number(s) N/A 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☒ PII ☐ PIII ☐ PIV ☐ No Relevant Patents ☐ 3. Expiration of Patent(s): NA a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES ODE exp. 3/29/13 – will carve out	☒
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient Y b. Type III DMF authorization letter(s) for container closure Y 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A	☒

1.12.11	**Basis for Submission** NDA# : 50-708 Ref Listed Drug: PROGRAF Firm: ASTELLAS PHARMA US INC. ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same except for carved out ODE 2. Active ingredients Tacrolimus 3. Inactive ingredients 4. Route of administration Oral 5. Dosage Form Capsule 6. Strength 0.5mg, 1mg, 5mg	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): Paper, YES	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) Y **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained Y **1.14.1.3** 1 package insert (content of labeling) submitted electronically Y ***Was a proprietary name request submitted? No (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained Y **1.14.3.3** 1 RLD label and 1 RLD container label Y	☒

ACCEPTABLE

2.3	**Quality Overall Summary** **E-Submission: X___PDF (archive) X__ Word Processed e.g., MS Word** A model Quality Overall Summary for an immediate release table and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ **Question based Review (QbR) X_____ YES ____ NO** **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** **2.3.S.1** **General Information** **2.3.S.2** **Manufacture** **2.3.S.3** **Characterization** **2.3.S.4** **Control of Drug Substance** **2.3.S.5** **Reference Standards or Materials** **2.3.S.6** **Container Closure System** **2.3.S.7** **Stability** **2.3.P** **Drug Product** **2.3.P.1** **Description and Composition of the Drug Product** **2.3.P.2** **Pharmaceutical Development** **2.3.P.2.1** **Components of the Drug Product** **2.3.P.2.1.1** **Drug Substance** **2.3.P.2.1.2** **Excipients** **2.3.P.2.2** **Drug Product** **2.3.P.2.3** **Manufacturing Process Development** **2.3.P.2.4** **Container Closure System** **2.3.P.3** **Manufacture** **2.3.P.4** **Control of Excipients** **2.3.P.5** **Control of Drug Product** **2.3.P.6** **Reference Standards or Materials** **2.3.P.7** **Container Closure System** **2.3.P.8** **Stability**	☒

2.7	**Clinical Summary (Bioequivalence)** **E-Submission: X___PDF (archive) ____ Word Processed e.g., MS Word** **2.7.1** **Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1** **Background and Overview** **2.7.1.2** **Summary of Results of Individual Studies** **2.7.1.3** **Comparison and Analyses of Results Across Studies** 1. Summary Bioequivalence tables: Table 1. Summary of Comparative Bioavailability (BA) Studies Table 2. Statistical Summary of the Comparative BA Data Table 4. Summary of In Vitro Dissolution Studies **2.7.1.4** **Appendix**	☒

MODULE 3

3.2.S DRUG SUBSTANCE

ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1** **Nomenclature** **3.2.S.1.2** **Structure** **3.2.S.1.3** **General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Addresses of bulk manufacturers Y 2. Manufacturing Responsibilities Y 3. Type II DMF number for API DMF# 19979 4. CFN or FEI numbers	☒
3.2.S.3	**Characterization**	☒

3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1** **Specification** Testing specifications and data from drug substance manufacturer(s) Y **3.2.S.4.2** **Analytical Procedures** Y **3.2.S.4.3** **Validation of Analytical Procedures** **1.** Spectra and chromatograms for reference standards and test samples Y 2. Samples-Statement of Availability and Identification of: a. Drug Substance Y b. Same lot number(s) Y **3.2.S.4.4** **Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) Y 2. Applicant certificate of analysis Y **3.2.S.4.5** **Justification of Specification** Y	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems**	☒
3.2.S.7	**Stability**	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1) Unit composition Y 2) Inactive ingredients are appropriate per IIG Y – see attached	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report	☒
3.2.P.3	**Manufacture** **3.2.P.3.1** **Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. Function or Responsibility YES No testing of API or Drug Product 4. CFN or FEI numbers **3.2.P.3.2** **Batch Formula** Batch Formulation Y **3.2.P.3.3** **Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process Y 2. Master Production Batch Record(s) for largest intended production runs (no more than (b) (4) x pilot batch) with equipment specified see sec. 3.2.R.1.P.1.2 0.5mg – (b) (4) caps 3. If sterile product: Aseptic fill / Terminal sterilization N/A 1mg – caps 4. Reprocessing Statement Y 5mg – caps **3.2.P.3.4** **Controls of Critical Steps and Intermediates** Y **3.2.P.3.5** **Process Validation and/or Evaluation** 1. Microbiological sterilization validation N/A 2. Filter validation (if aseptic fill) N/A	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified Y **3.2.P.4.1** **Specifications** 1. Testing specifications (including identification and characterization) Y 2. Suppliers' COA (specifications and test results) Y **3.2.P.4.2** **Analytical Procedures** Y **3.2.P.4.3** **Validation of Analytical Procedures** N/A **3.2.P.4.4** **Justification of Specifications** Applicant COA Y	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1** **Specification(s)** Y **3.2.P.5.2** **Analytical Procedures** Y **3.2.P.5.3** **Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form Y 2. Same lot numbers Y **3.2.P.5.4** **Batch Analysis** 0.5 mg – KW06G38N Certificate of Analysis for Finished Dosage Form 1mg – KW06G37N **3.2.P.5.5** 5mg – KW06G36N **Characterization of Impurities** Y **3.2.P.5.6** **Justification of Specifications** Y	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) Y 2. Components Specification and Test Data Y 3. Packaging Configuration and Sizes (b) (4) cc, (b) (4) cc plastic bottles 4. Container/Closure Testing Y 5. Source of supply and suppliers address Y	☒
3.2.P.8	**3.2.P.8.1** **Stability (Finished Dosage Form)** 1. Stability Protocol submitted Y 2. Expiration Dating Period 24 months bottles, 3 months bulk **3.2.P.8.2** **Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments Y **3.2.P.8.3** **Stability Data** 0.5 mg – KW06G38N 1. 3 month accelerated stability data Y 1mg – KW06G37N 2. Batch numbers on stability records the same as the test batch 5mg – KW06G36N	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S** **Executed Batch Records for drug substance (if available) N/A** **3.2.R.2.S** **Comparability Protocols N/A** **3.2.R.3.S** **Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation see attached Theoretical Yield Actual Yield Packaged Yield **3.2.R.1.P.2** **Information on Components** N/A **3.2.R.2.P** **Comparability Protocols** N/A **3.2.R.3.P** **Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

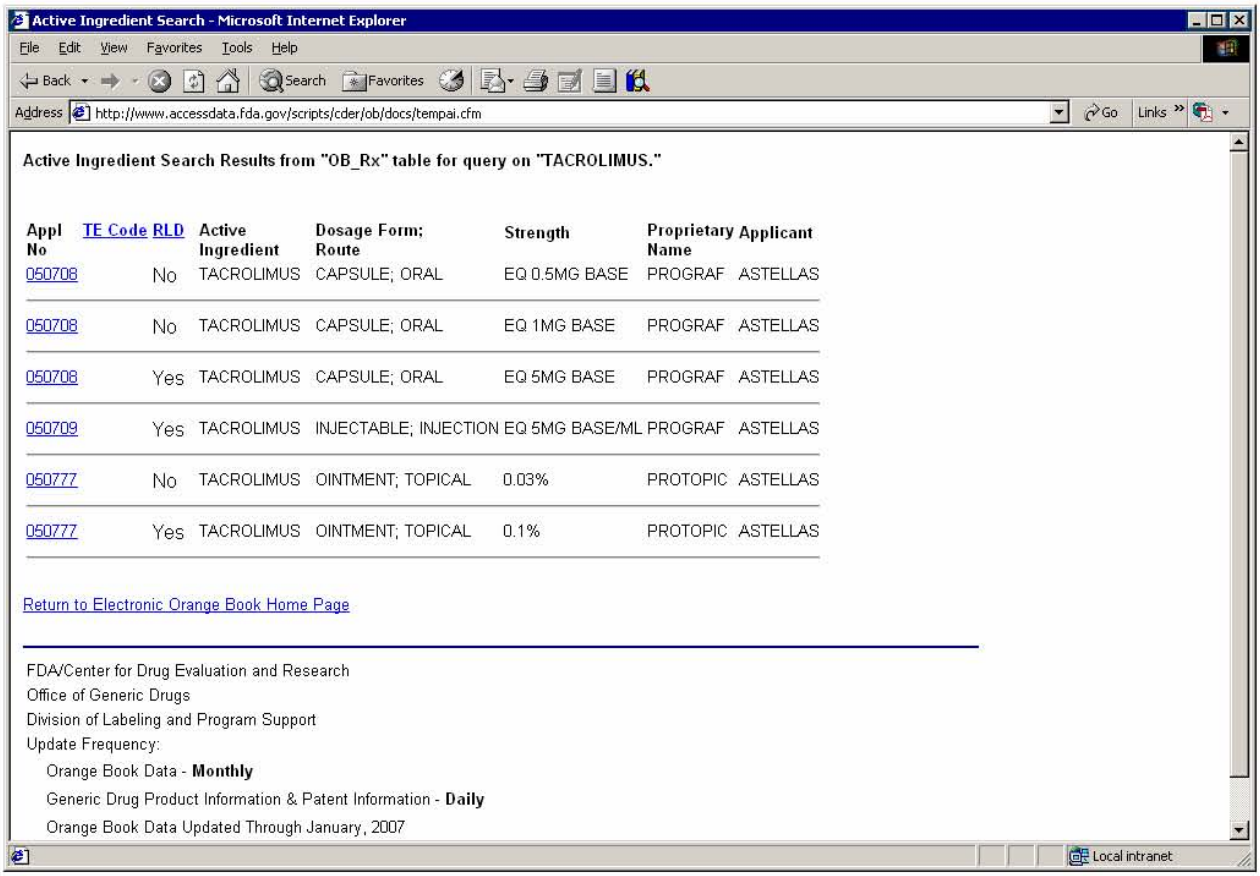
MODULE 5

CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☒
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) Strengths are proportional b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) N/A **2. Lot Numbers of Products used in BE Study(ies):** 5mg – KW06G36NA **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒
	5.3.1.2 ELECTRONIC **Comparative BA/BE Study Reports** 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) Y 2. Summary Bioequivalence tables: Table 6. Demographic Profile of Subjects Completing the Comparative BA Study Y Table 7. Incidence of Adverse Events in Individual Studies Y Table 8. Reanalysis of Study Samples Y **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 4. Summary of In Vitro Dissolution Studies Y Table 5. Formulation Data Y **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 3. Bioanalytical Method Validation Y **5.3.7** **Case Report Forms and Individual Patient Listing**	☒

5.4	**Literature References**	
	Possible Study Types:	
Study Type	**IN-VIVO PK STUDY(IES) (**i.e., fasting/fed/sprinkle) FASTING AND FED ON 5 MG 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) SEE ATTACHED 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: YES	☒
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES) (**i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% or 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

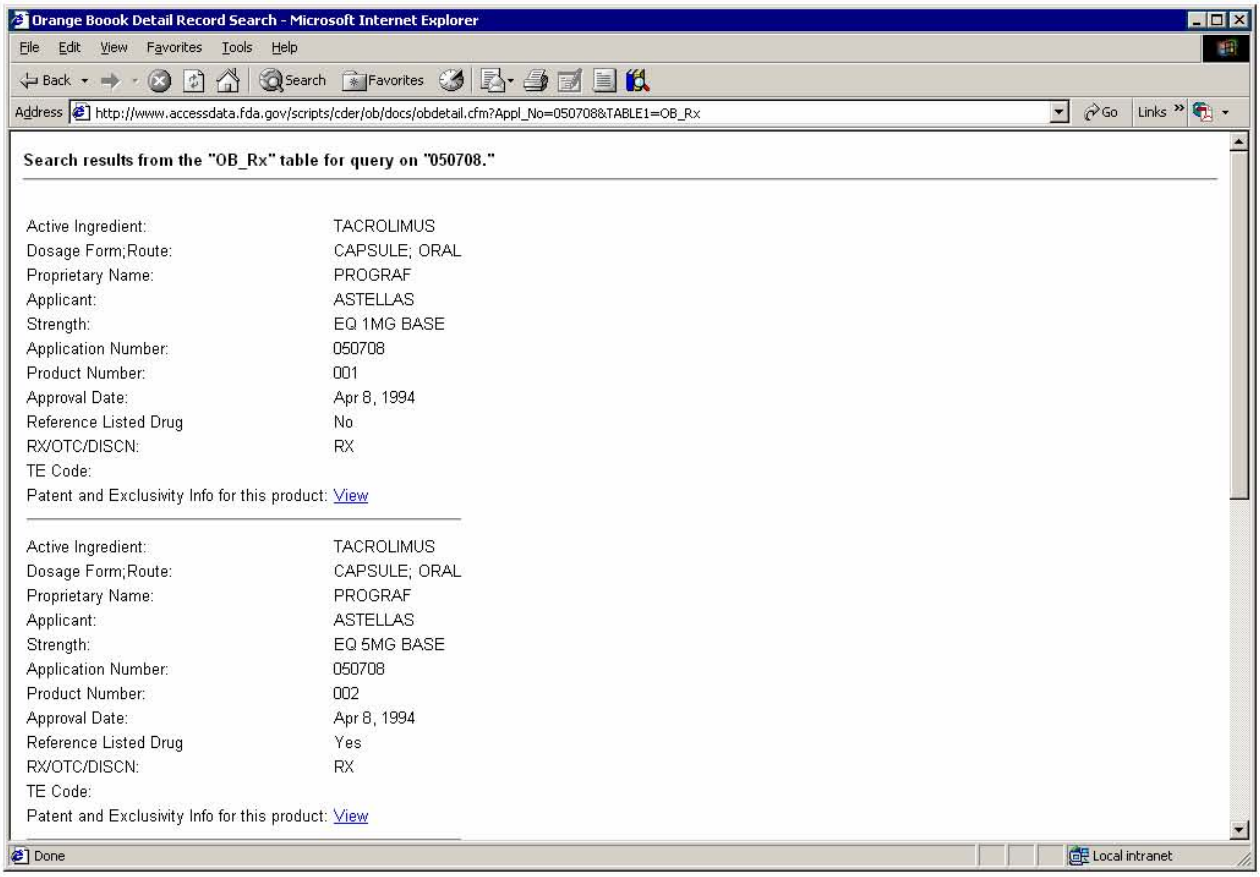


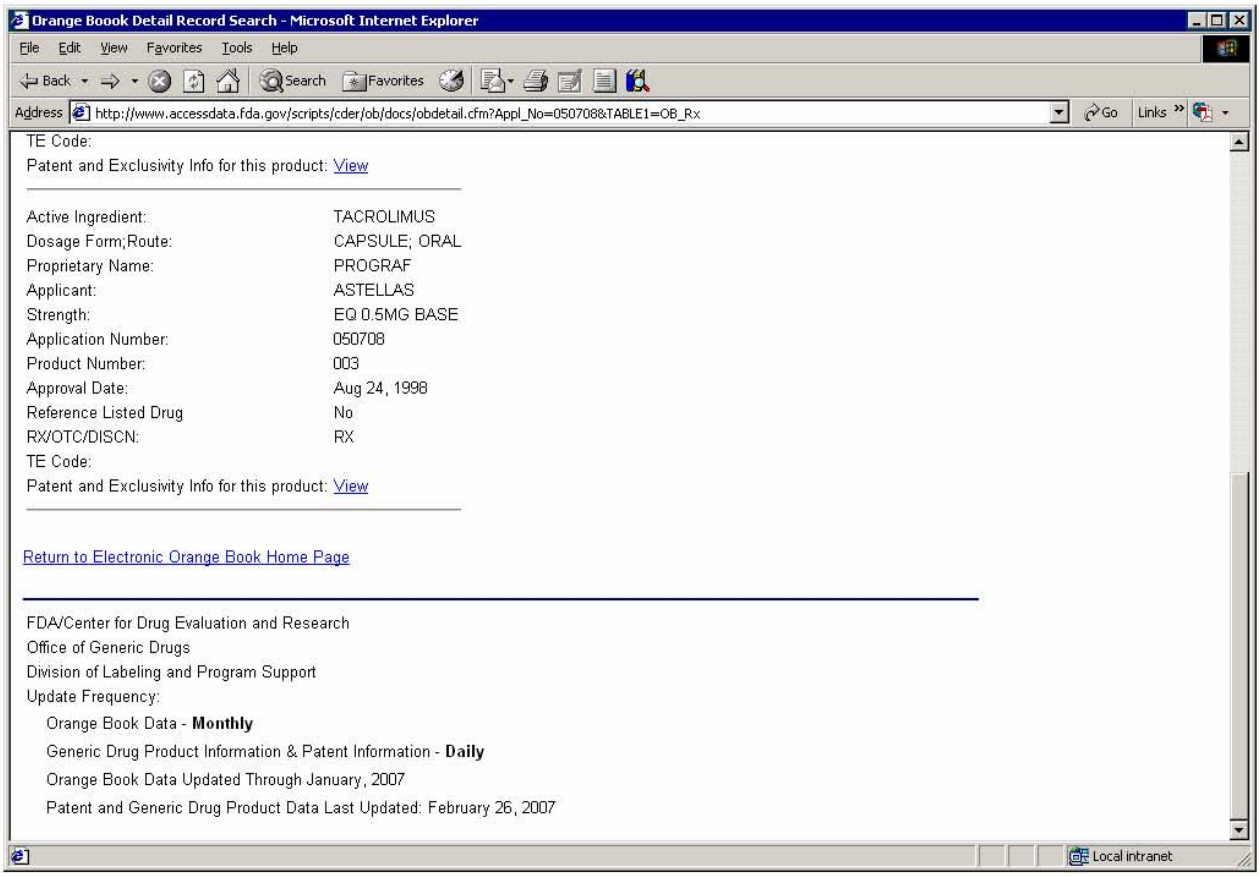
Active Ingredient Search Results from "OB_Rx" table for query on "TACROLIMUS."

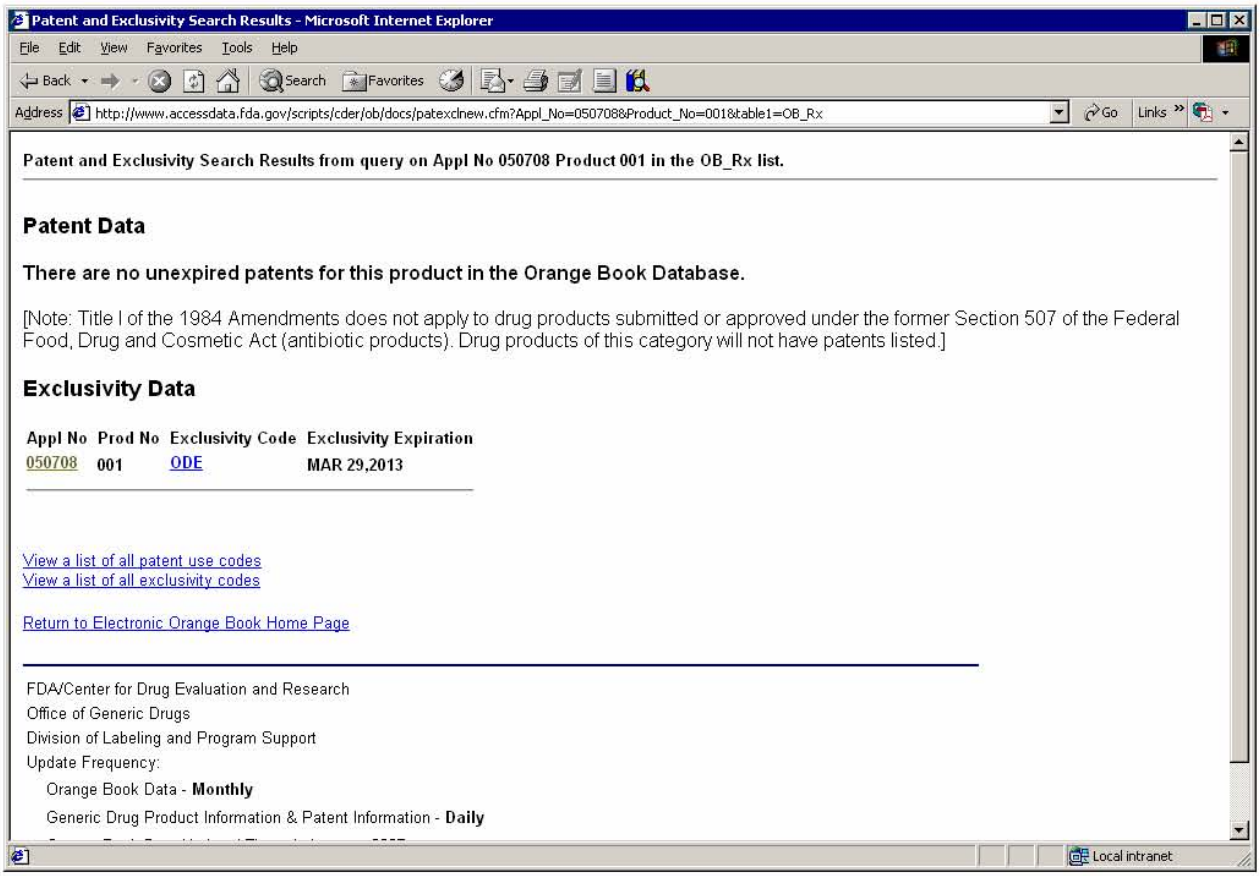
Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
050708		No	TACROLIMUS	CAPSULE; ORAL	EQ 0.5MG BASE	PROGRAF	ASTELLAS
050708		No	TACROLIMUS	CAPSULE; ORAL	EQ 1MG BASE	PROGRAF	ASTELLAS
050708		Yes	TACROLIMUS	CAPSULE; ORAL	EQ 5MG BASE	PROGRAF	ASTELLAS
050709		Yes	TACROLIMUS	INJECTABLE; INJECTION	EQ 5MG BASE/ML	PROGRAF	ASTELLAS
050777		No	TACROLIMUS	OINTMENT; TOPICAL	0.03%	PROTOPIC	ASTELLAS
050777		Yes	TACROLIMUS	OINTMENT; TOPICAL	0.1%	PROTOPIC	ASTELLAS

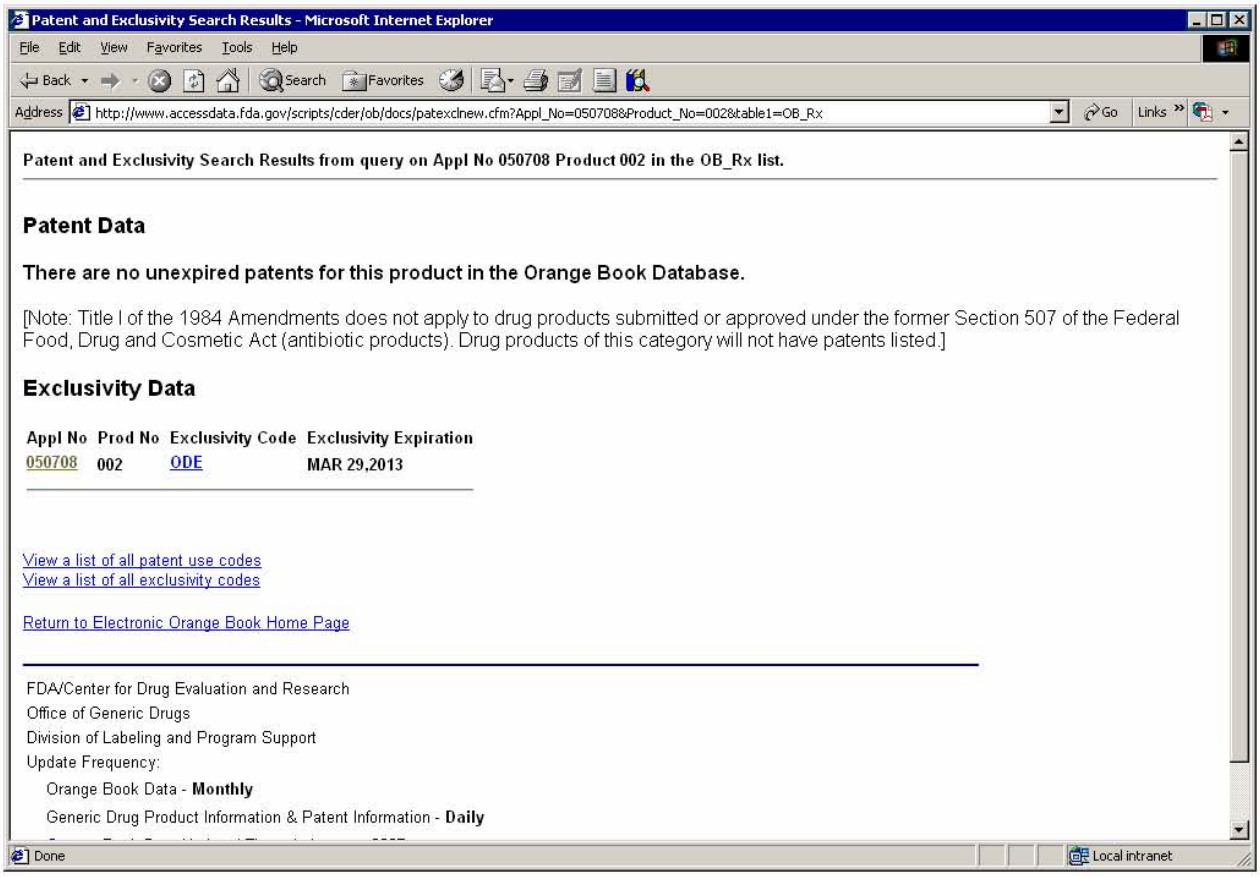
Return to Electronic Orange Book Home Page

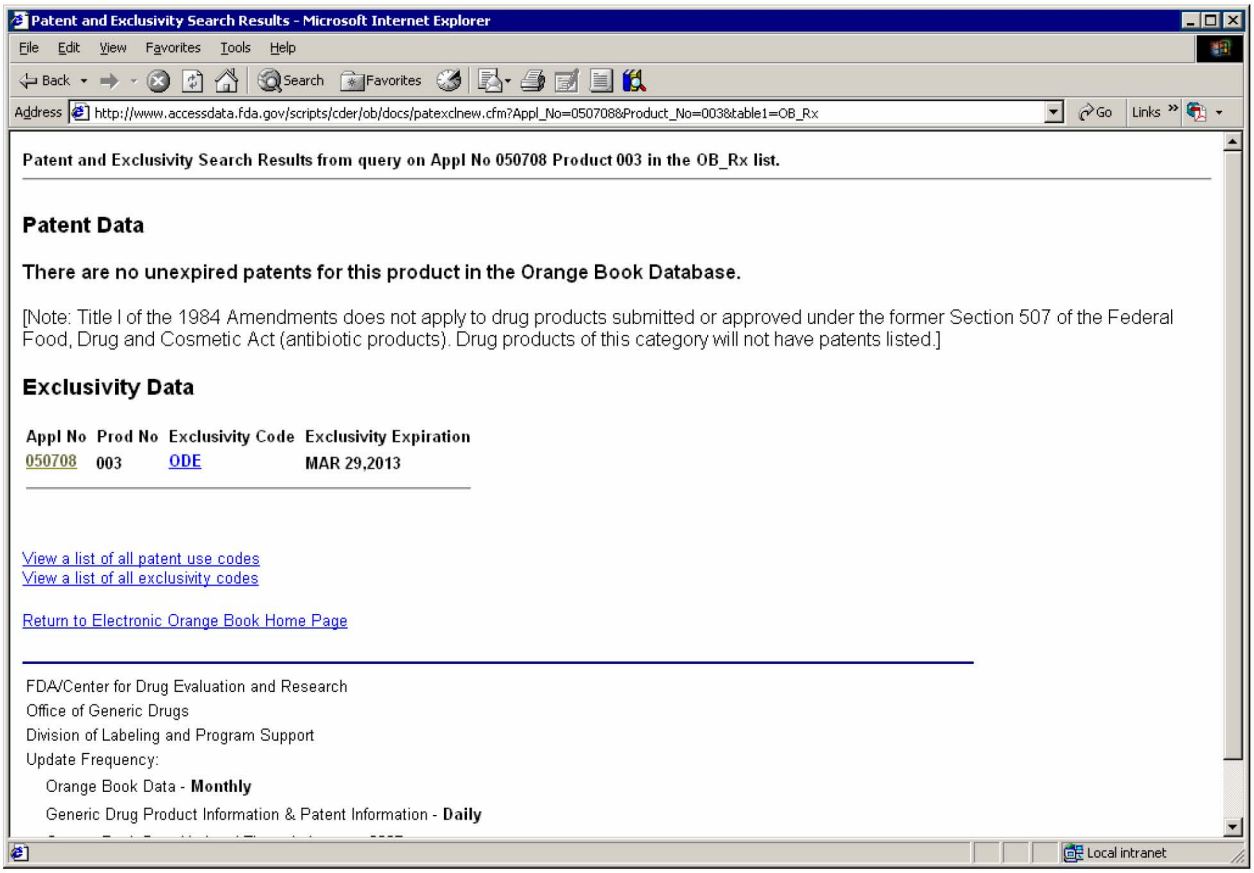
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through January, 2007

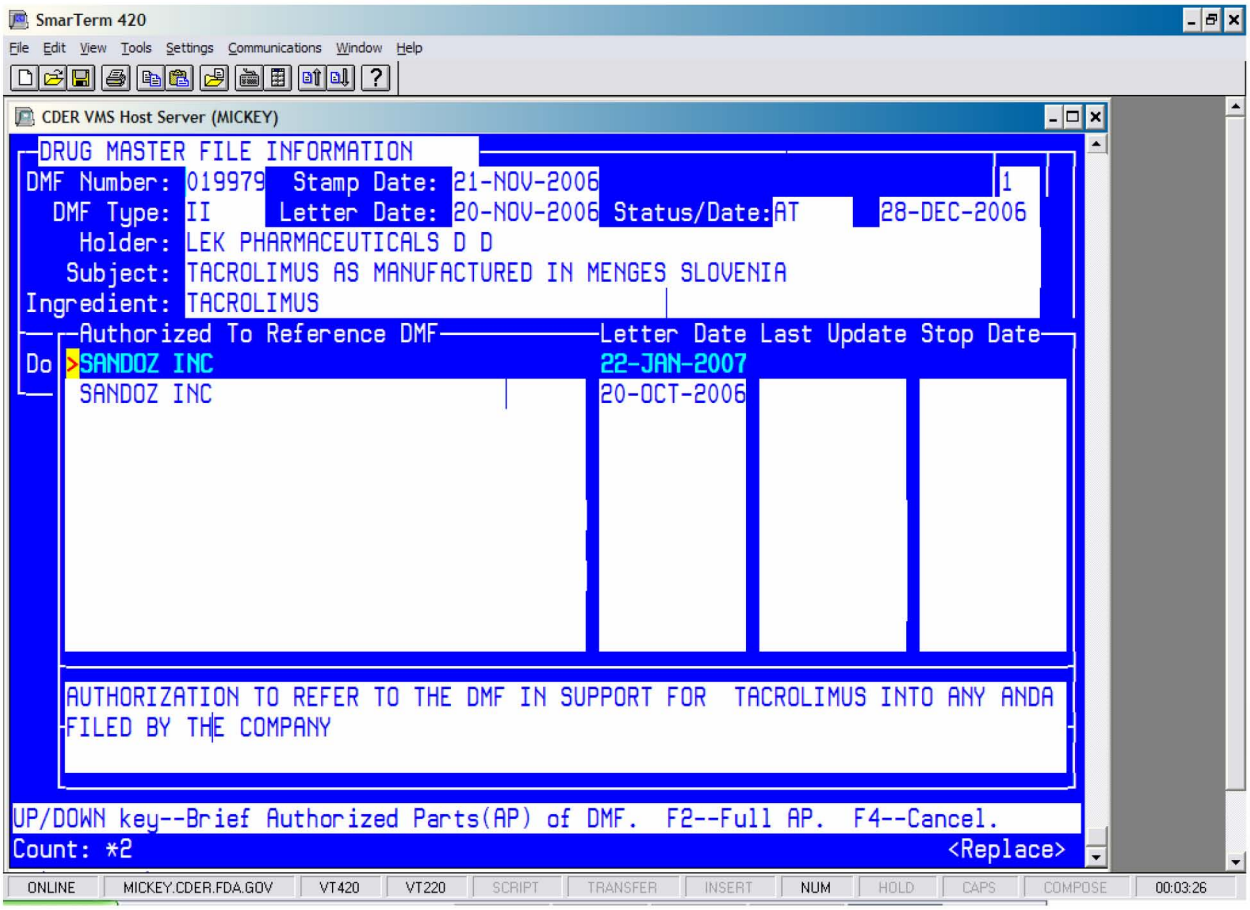

Orange Boook Detail Record Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=050708&TABLE1=OB_Rx
Go Links
Search results from the "OB_Rx" table for query on "050708."
Active Ingredient: TACROLIMUS
Dosage Form;Route: CAPSULE; ORAL
Proprietary Name: PROGRAF
Applicant: ASTELLAS
Strength: EQ 1MG BASE
Application Number: 050708
Product Number: 001
Approval Date: Apr 8, 1994
Reference Listed Drug No
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Active Ingredient: TACROLIMUS
Dosage Form;Route: CAPSULE; ORAL
Proprietary Name: PROGRAF
Applicant: ASTELLAS
Strength: EQ 5MG BASE
Application Number: 050708
Product Number: 002
Approval Date: Apr 8, 1994
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Done
Local intranet


Orange Boook Detail Record Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=050708&TABLE1=OB_Rx
Go Links
TE Code:
Patent and Exclusivity Info for this product: View
Active Ingredient: TACROLIMUS
Dosage Form;Route: CAPSULE; ORAL
Proprietary Name: PROGRAF
Applicant: ASTELLAS
Strength: EQ 0.5MG BASE
Application Number: 050708
Product Number: 003
Approval Date: Aug 24, 1998
Reference Listed Drug No
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through January, 2007
Patent and Generic Drug Product Data Last Updated: February 26, 2007
Local intranet


Patent and Exclusivity Search Results - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=050708&Product_No=001&table1=OB_Rx
Go Links
Patent and Exclusivity Search Results from query on Appl No 050708 Product 001 in the OB_Rx list.
Patent Data
There are no unexpired patents for this product in the Orange Book Database.
[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]
Exclusivity Data
Appl No Prod No Exclusivity Code Exclusivity Expiration
050708 001 ODE MAR 29,2013
View a list of all patent use codes
View a list of all exclusivity codes
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Local intranet


Patent and Exclusivity Search Results - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=050708&Product_No=002&table1=OB_Rx
Go Links
Patent and Exclusivity Search Results from query on Appl No 050708 Product 002 in the OB_Rx list.
Patent Data
There are no unexpired patents for this product in the Orange Book Database.
[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]
Exclusivity Data
Appl No Prod No Exclusivity Code Exclusivity Expiration
050708 002 ODE MAR 29,2013
View a list of all patent use codes
View a list of all exclusivity codes
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Done
Local intranet


Patent and Exclusivity Search Results - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=050708&Product_No=003&table1=OB_Rx
Go Links
Patent and Exclusivity Search Results from query on Appl No 050708 Product 003 in the OB_Rx list.
Patent Data
There are no unexpired patents for this product in the Orange Book Database.
[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]
Exclusivity Data
Appl No Prod No Exclusivity Code Exclusivity Expiration
050708 003 ODE MAR 29,2013
View a list of all patent use codes
View a list of all exclusivity codes
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Local intranet


SmarTerm 420
File Edit View Tools Settings Communications Window Help
CDER VMS Host Server (MICKEY)
DRUG MASTER FILE INFORMATION
DMF Number: 019979 Stamp Date: 21-NOV-2006 1
DMF Type: II Letter Date: 20-NOV-2006 Status/Date: AT 28-DEC-2006
Holder: LEK PHARMACEUTICALS D D
Subject: TACROLIMUS AS MANUFACTURED IN MENGES SLOVENIA
Ingredient: TACROLIMUS
Authorized To Reference DMF Letter Date Last Update Stop Date
Do >SANDOZ INC 22-JAN-2007
SANDOZ INC 20-OCT-2006
AUTHORIZATION TO REFER TO THE DMF IN SUPPORT FOR TACROLIMUS INTO ANY ANDA FILED BY THE COMPANY
UP/DOWN key--Brief Authorized Parts(AP) of DMF. F2--Full AP. F4--Cancel.
Count: *2
<Replace>
ONLINE MICKEY.CDER.FDA.GOV VT420 VT220 SCRIPT TRANSFER INSERT NUM HOLD CAPS COMPOSE 00:03:26

Qualitative and quantitative composition for Tacrolimus Capsules is tabulated below:

Ingredient	Quantity per unit (mg)			Function
	0.5 mg	1 mg	5 mg	
[redacted]				
Tacrolimus monohydrate [redacted] (equivalent to Tacrolimus)*				
Hypromellose USP ([redacted])				
Lactose monohydrate NF [redacted])**				
Croscarmellose Sodium NF ([redacted])				
[redacted] USP***				
Total weight of [redacted] ****				
[redacted]				
Lactose monohydrate NF ([redacted])****				
Magnesium Stearate NF				
Fill Weight				
Encapsulation				
Imprinted Hard gelatin capsule shell				
HGC size "4" with white coloured opaque body imprinted with "643" in black and ivory coloured cap imprinted with " " in black				
HGC size "4" with white coloured opaque body imprinted with "644" in black and light brown coloured cap imprinted with " " in black.				
HGC size "3" with white coloured opaque body imprinted with "645" in black and Swedish orange coloured cap imprinted with " " in black.				
Total Weight				--

Note: Quantity of Lactose Monohydrate (used for [redacted]) to be adjusted according to Assay value obtained for Tacrolimus [redacted].

* This quantity is theoretical and based on 100% assay on [redacted].

** [redacted].

*** [redacted].

**** Above mentioned quantity of Tacrolimus [redacted] and Lactose monohydrate is based on 100 % Assay value of Tacrolimus [redacted].

Inactive Ingredients for ANDA 65-461

(b) (4)	ORAL; TABLET	(b) (4)
LACTOSE MONOHYDRATE	ORAL; TABLET	(b) (4)
CROSCARMELLOSE SODIUM	ORAL; TABLET	(b) (4)
MAGNESIUM STEARATE	ORAL; TABLET	(b) (4)

Inactive ingredients are acceptable per IIG.

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 65-461 **FIRM NAME** **Sandoz Inc.**

DRUG NAME Tacrolimus Capsules, 0.5 mg, 1 mg and 5 mg

DOSAGE FORM **Tablets**
SUBJ: Request for examination of: Bioequivalence Study and Request for Waiver

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☒	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

_____ Date: _____
Reviewer

Shiriniwas Nerurkar Date: _____
Team Leader

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐			
Assay Methodology	☒	☐			
Procedure SOP	☒	☐			
Methods Validation	☒	☐			
Study Results Ln/Lin	☒	☐			
Adverse Events	☒	☐			
IRB Approval	☒	☐			
Dissolution Data	☒	☐			
Pre-screening of Patients	☒	☐			
Chromatograms	☒	☐			
Consent Forms	☒	☐			
Composition	☒	☐			
Summary of Study	☒	☐			CTD tables in EDR
Individual Data & Graphs, Linear & Ln	☒	☐			
PK/PD Data Disk Submitted)	☒	☐			Yes in EDR
Randomization Schedule	☒	☐			
Protocol Deviations	☒	☐			
Clinical Site	☒	☐			
Analytical Site	☒	☐			
Study Investigators	☒	☐			

Medical Records	☒	☐			
Clinical Raw Data	☒	☐			
Test Article Inventory	☐	☒			
BIO Batch Size	☒	☐			In module 2
Assay of Active Content Drug	☒	☐			
Content Uniformity	☒	☐			
Date of Manufacture	☒	☐			
Exp. Date of RLD	☒	☐			
BioStudy Lot Numbers	☒	☐			
Statistics	☒	☐			
Summary results provided by the firm indicate studies pass BE criteria	☒	☐			
Waiver requests for other strengths / supporting data	☒	☐			

Additional Comments regarding the ANDA:

1. The DBE has reviewed many control documents including #04-016 (the first inquiry) 04-123 (from Sandoz) and 06-0596 (the most recent one) for this drug product. The DBE recommends a single-dose fasting and a single-dose fed bioquivalence study on the 5 mg strength. The 0.5 mg and 1 mg strengths are eligible for waiver. The parent compound, Tacrolimus in whole blood should be measured. The dissolution testing should be conducted using the method listed in the public Dissolution Methods Database.

2. The firm has submitted a single-dose, fasting and a single-dose, fed biequivalence study comparing Sandoz's Tacrolimus Capsules, 5 mg with the RLD, Astellas's Prograf Capsules, 5 mg. The parent compound, Tacrolimus in whole blood were measured. The firm also requested waivers of in vivo studies for the lower strengths, 0.5 mg and 1 mg. The firm did not use the FDA-recommended dissolution method.

Tacrolimus 5 mg (1 x 5 mg) Geometric LS Means, Ratio and 90% Confidence Intervals				
Fasted Bioequivalence Study (TCU-P6-130)				
Parameter	Test*	Reference*	Ratio (%)	90% C.I. (%)
C_{max}	36.181	32.931	109.87	101.81 - 118.56
AUC_T	331.184	299.186	110.69	100.47 – 121.96
AUC_∞	355.168	322.017	110.29	100.30 – 121.28
Fed Bioequivalence Study (TCU-P6-131)				
Parameter	Test*	Reference*	Ratio (%)	90% C.I. (%)
C_{max}	7.327	7.633	95.99	90.11 – 102.26
AUC_T	143.721	149.593	96.07	92.36 – 99.94
AUC_∞	157.135	164.394	95.58	92.03 – 99.27

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞.

Tacrolimus Capsules 0.5 mg

Batch No	KW06G38N
Theoretical Batch Size	(b) (4) kg ((b) (4) Capsules)

- (b) (4):

Sr. No.	Title	Quantity
A	Theoretical Batch Size (Kg)	(b) (4)
B	Total Yield of (b) (4) (Kg)	
C	Quantity of Samples (if any) (Kg)	
D	Rejects (Kg)	
E	% Yield (b/a x 100)	
F	**% Reconciliation (b + c + d) / a x 100**	

- **Inspected Tacrolimus Capsules 0.5 mg**

Sr. No.	Title	Quantity
A	Theoretical Wt. of Filled capsules (Kg)	(b) (4)
B	Target average Wt. of Filled capsules (mg)	
C	Theoretical No. of filled capsules (Nos)	
D	Actual wt. of filled capsule (Kg)	
E	Average wt of filled capsule (mg)	
F	Quantity of filled capsules (Nos) (D/E)x1000x1000	
G	Percentage yield (F/C)x100	
H	Samples if any (Nos)	
I	Rejects (Kg)	
J	**% Reconciliation (F + H + I) / C x 100**	

- **Details of All Packs:**

Sr. No.	Pack	Qty. Transferred to Warehouse	Sample Quantity	Rejects
1.	C- 10 (Blister)			
2.	C- 100 (Bottle)			
3.	(b) (4)			
4.	C-100 (Prototype bulk)			
5.	Bulk Ship			
	Total			

- **Reconciliation:**

Sr. No.	Title	Quantity No. of units
A	Theoretical Manufacturing Batch Size	(b) (4)
B	Qty transferred to packing	
C	Total Qty. transferred to warehouse	
D	Total sample qty	
E	Total Rejects	
F	Packaging yield {(C + D)/B X 100} %	
G	Batch yield {(C + D)/A X 100} %	
H	**% Reconciliation {(C + D + E) / B x 100} %**	

Tacrolimus Capsules 1 mg

Batch No	KW06G37N
Theoretical Batch Size	(b) (4) kg (b) (4) Capsules)

- (b) (4):

Sr. No.	Title	Quantity
A	Theoretical Batch Size (Kg)	(b) (4)
B	Total Yield of (b) (4), (Kg)	
C	Quantity of Samples (if any) (Kg)	
D	Rejects (Kg)	
E	% Yield (b/a x 100)	
F	**% Reconciliation (b + c + d) / a x 100**	

- **Inspected Tacrolimus Capsules 1 mg**

Sr. No.	Title	Quantity
A	Theoretical Wt. of Filled capsules (Kg)	(b) (4)
B	Target average Wt. of Filled capsules (mg)	
C	Theoretical No. of filled capsules (Nos)	
D	Actual wt. of filled capsule (Kg)	
E	Average wt of filled capsule (mg)	
F	Quantity of filled capsules (Nos) (D/E)x1000x1000	
G	Percentage yield (F/C)x100	
H	Samples if any (Nos)	
I	Rejects (Kg)	
J	**% Reconciliation (F + H + I) / C x 100**	

- **Details of All Packs:**

Sr. No.	Pack	Qty. Transferred to Warehouse	Sample Quantity	Rejects
6.	C- 10 (Blister)			
7.	C- 100 (Bottle)			
8.	(b) (4)			
9.	C-100 (Prototype bulk)			
10.	Bulk Ship			
	Total			

- **Reconciliation:**

Sr. No.	Title	Quantity No. of units
A	Theoretical Manufacturing Batch Size	
B	Qty transferred to packing	
C	Total Qty. transferred to warehouse	
D	Total sample qty	
E	Total Rejects	
F	Packaging yield {(C + D)/B X 100} %	
G	Batch yield {(C + D)/A X 100} %	
H	**% Reconciliation {(C + D + E) / B x 100} %**	

Tacrolimus Capsules 5 mg

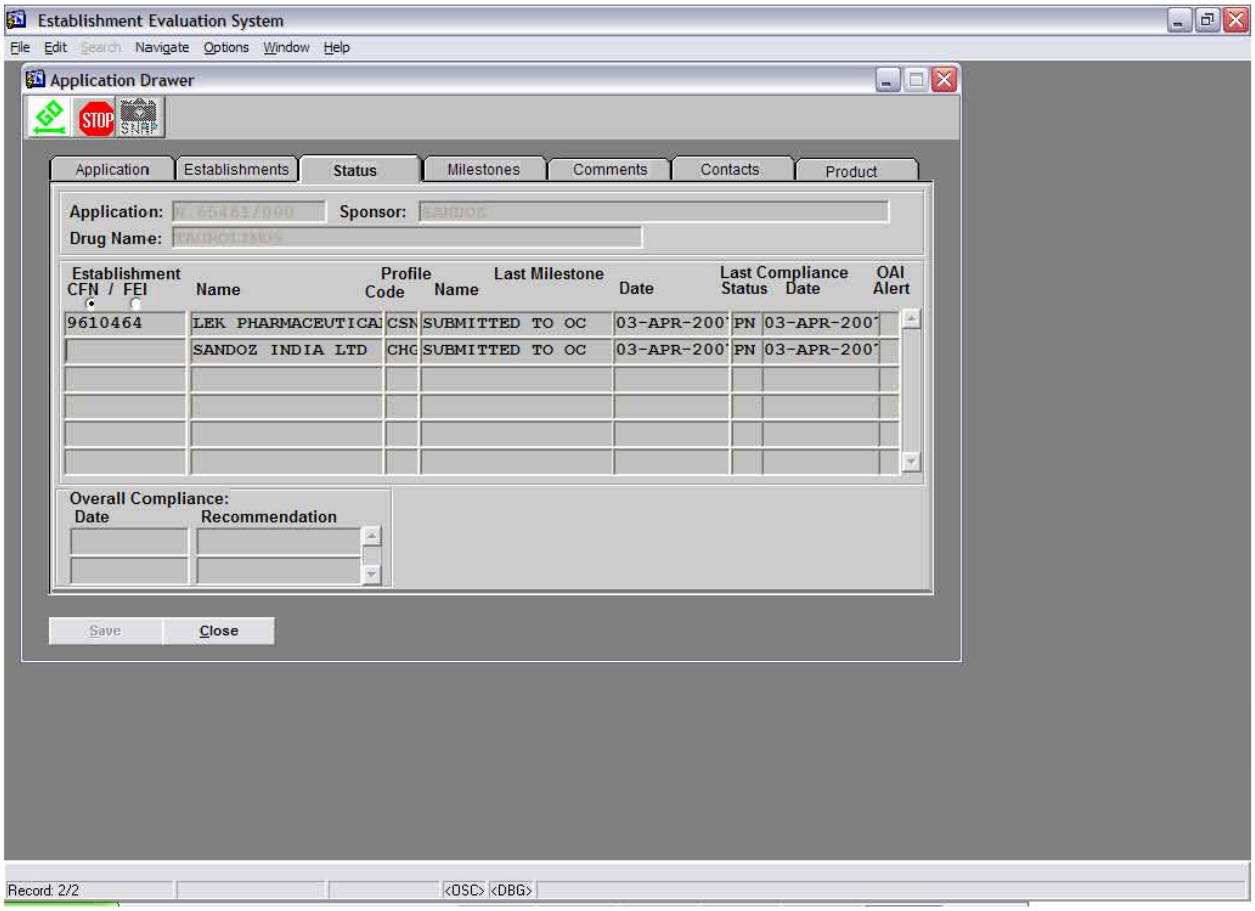
Batch No	KW06G36N
Theoretical Batch Size	(b) (4) kg ((b) (4) Capsules)

- (b) (4):

Sr. No.	Title	Quantity
A	Theoretical Batch Size (Kg)	(b) (4)
B	Total Yield o (b) (4) (Kg)	
C	Quantity of Samples (if any) (Kg)	
D	Rejects (Kg)	
E	% Yield (b/a x 100)	
F	**% Reconciliation (b + c + d) / a x 100**	

- **Inspected Tacrolimus Capsules 0.5 mg**

Sr. No.	Title	Quantity
A	Theoretical Wt. of Filled capsules (Kg)	(b) (4)
B	Target average Wt. of Filled capsules (mg)	
C	Theoretical No. of filled capsules (Nos)	
D	Actual wt. of filled capsule (Kg)	
E	Average wt of filled capsule (mg)	
F	Quantity of filled capsules (Nos) (D/E)x1000x1000	
G	Percentage yield (F/C)x100	
H	Samples if any (Nos)	
I	Rejects (Kg)	
J	**% Reconciliation (F + H + I) / C x 100**	


Establishment Evaluation System
File Edit Search Navigate Options Window Help
Application Drawer
STOP
SNAP
Application
Establishments
Status
Milestones
Comments
Contacts
Product
Application:
Sponsor:
Drug Name:
Establishment CFN / FEI
Name
Profile Code
Last Milestone Name
Date
Last Compliance Status
Compliance Date
OAI Alert
9610464
LEK PHARMACEUTICA
CSN
SUBMITTED TO OC
03-APR-200
PN
03-APR-200
SANDOZ INDIA LTD
CHG
SUBMITTED TO OC
03-APR-200
PN
03-APR-200
Overall Compliance:
Date
Recommendation
Save
Close
Record: 2/2
<OSC>
<DBG>

- **Reconciliation:**

Sr. No.	Pack	Qty. Transferred to Warehouse	Sample Quantity	Rejects
1.	C- 10 (Blister)		(b) (4)	
2.	C- 100 (Bottle)			
3.	(b) (4)			
4.	C-100 (Prototype bulk)			
5.	Bulk Ship			
	Total			

- **Details of All Packs:**

Sr. No.	Title	Quantity No. of units
A	Theoretical Manufacturing Batch Size	(b) (4)
B	Qty transferred to packing	
C	Total Qty. transferred to warehouse	
D	Total sample qty	
E	Total Rejects	
F	Packaging yield {(C + D)/B X 100} %	
G	Batch yield {(C + D)/A X 100} %	
H	**% Reconciliation {(C + D + E) / B x 100} %**	

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

/s/

Martin Shimer

4/6/2007 08:04:27 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 65-461

Sandoz Inc.
Attention: Carmelle Lucas, Ph.D.
506 Carnegie Center
Suite 400
Princeton, NJ 08540

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Tacrolimus Capsules, 0.5 mg, 1 mg and 5 mg

DATE OF APPLICATION: December 28, 2006

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 29, 2006

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Ryan Nguyen
Project Manager
301-827-5737

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Martin Shimer
4/6/2007 08:03:27 AM
Signing for Wm Peter Rickman

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 65-461 **FIRM NAME Sandoz Inc.**

DRUG NAME Tacrolimus Capsules, 0.5 mg, 1 mg and 5 mg

DOSAGE FORM Tablets
SUBJ: Request for examination of: Bioequivalence Study and Request for Waiver

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☒	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

_____ Date: _____
Reviewer

Shiriniwas Nerurkar Date: _____
Team Leader

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐			
Assay Methodology	☒	☐			
Procedure SOP	☒	☐			
Methods Validation	☒	☐			
Study Results Ln/Lin	☒	☐			
Adverse Events	☒	☐			
IRB Approval	☒	☐			
Dissolution Data	☒	☐			
Pre-screening of Patients	☒	☐			
Chromatograms	☒	☐			
Consent Forms	☒	☐			
Composition	☒	☐			
Summary of Study	☒	☐			CTD tables in EDR
Individual Data & Graphs, Linear & Ln	☒	☐			
PK/PD Data Disk Submitted)	☒	☐			Yes in EDR
Randomization Schedule	☒	☐			
Protocol Deviations	☒	☐			
Clinical Site	☒	☐			
Analytical Site	☒	☐			
Study Investigators	☒	☐			

Medical Records	☒	☐			
Clinical Raw Data	☒	☐			
Test Article Inventory	☐	☒			
BIO Batch Size	☒	☐			In module 2
Assay of Active Content Drug	☒	☐			
Content Uniformity	☒	☐			
Date of Manufacture	☒	☐			
Exp. Date of RLD	☒	☐			
BioStudy Lot Numbers	☒	☐			
Statistics	☒	☐			
Summary results provided by the firm indicate studies pass BE criteria	☒	☐			
Waiver requests for other strengths / supporting data	☒	☐			

Additional Comments regarding the ANDA:

1. The DBE has reviewed many control documents including #04-016 (the first inquiry) 04-123 (from Sandoz) and 06-0596 (the most recent one) for this drug product. The DBE recommends a single-dose fasting and a single-dose fed bioquivalence study on the 5 mg strength. The 0.5 mg and 1 mg strengths are eligible for waiver. The parent compound, Tacrolimus in whole blood should be measured. The dissolution testing should be conducted using the method listed in the public Dissolution Methods Database.

2. The firm has submitted a single-dose, fasting and a single-dose, fed biequivalence study comparing Sandoz's Tacrolimus Capsules, 5 mg with the RLD, Astellas's Prograf Capsules, 5 mg. The parent compound, Tacrolimus in whole blood were measured. The firm also requested waivers of in vivo studies for the lower strengths, 0.5 mg and 1 mg. The firm did not use the FDA-recommended dissolution method.

APPEARS THIS WAY ON ORIGINAL

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

/s/

Shriniwas G. Nerurkar

3/9/2007 01:29:19 PM

M E M O R A N D U M

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

DATE : February 26, 2007

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 65-461 for Tacrolimus Capsules, 0.5 mg, 1 mg and 5 mg to determine if the application is substantially complete for filing.

Sandoz Inc. has submitted ANDA 65-461 for Tacrolimus Capsules, 0.5 mg, 1 mg and 5 mg. It is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Sandoz Inc. on December 28, 2006 for its Tacrolimus product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

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

/s/

Eda Howard
2/27/2007 07:16:04 AM
APPLICATIONS EXA

SANDOZ

Frank J. DellaFera
President and CEO

Phone: 609.627.8506
Fax: 609.627.8684
Email: frank.dellafera@sandoz.com

October 30, 2008

N/MC

Gary J. Buehler, R.Ph., Director
Office of Generic Drugs (HFD-600)
U.S. Food and Drug Administration
7500 Standish Place, Room 150
Rockville, MD 20855-2793

Re: **Controlled Correspondence ANDA 65-461**
Tacrolimus Capsules, 0.5, 1, and 5 mg
Request for Immediate Final Action on Pending ANDA for First-Time Generic for Off-Patent Tacrolimus RLD, Prograf

Dear Mr. Buehler:

In follow-up to our letters of June 3 and October 10, 2008 (copies enclosed) regarding request for immediate final action on pending ANDA for first-time generic for off-patent tacrolimus RLD, Prograf, we are requesting a face-to-face meeting with you in your offices. In addition to myself, also participating in this meeting will be our Vice President Regulatory Affairs, Kalpana Rao.

We are proposing the dates of November 12-14 or November 17 and 18, 2008 for your consideration. Please kindly confirm what date and time would work best for you, and we will make ourselves available.

Looking forward to your response.

Best regards,

Frank J. DellaFera
President and CEO

Enclosures (2)

Sandoz

506 Carnegie Center, Suite 400
Princeton, NJ 08540
www.us.sandoz.com

SANDOZ

Frank J. DellaFera
President and CEO *ad interim*

Phone: 609.627.8506
Fax: 609.627.8684
Email: frank.dellafera@sandoz.com

NEW CORRESP

N/mc

October 10, 2008

Gary J. Buehler, R.Ph.
Director
Office of Generic Drugs (HFD-600)
U.S. Food and Drug Administration
7500 Standish Place, Room 150
Rockville, Maryland 20855-2793

Gerald F. Masoudi, Esq.
Chief Counsel
Food and Drug Administration
5600 Fishers Lane
Room 605
Rockville, MD 20857-0001

Re: **Controlled Correspondence ANDA 65-461**
Tacrolimus Capsules, 0.5, 1, and 5 mg
Request for Immediate Final Action on Pending ANDA for First-Time Generic for Off-Patent Tacrolimus RLD, Prograf

Dear Messrs. Buehler and Masoudi:

As a follow-up to our June 3, 2008 letter to Mr. Buehler (copy enclosed), I am writing to address the persisting deferral of final action on Sandoz's pending ANDA No. 65-461 for tacrolimus capsules, 0.5, 1, and 5 mg (the "Sandoz ANDA")--a first-time generic for the blockbuster reference listed drug Prograf®, which went off-patent six (6) months ago. To our knowledge, there is no legitimate basis preventing OGD from taking final action on this application. We believe the application contains all the necessary chemistry, bioequivalence and labeling data and information to establish the approvability of Sandoz's first-generic tacrolimus product.

Basing final action on the bioequivalence data in the Sandoz ANDA is entirely consistent with the healthy-volunteer bioequivalence data on the Prograf RLD that is discussed in the Prograf labeling. Accordingly, as set forth in our prior letter and below, we request that OGD promptly finalize their substantive review of the Sandoz ANDA and issue final approval if, as we believe, the ANDA establishes approvability of this important generic product.

RECEIVED
OCT 14 2008
OGD

Sandoz

506 Carnegie Center, Suite 400
Princeton, NJ 08540
www.us.sandoz.com

While the incumbent marketing the off-patent brand RLD Prograf has reiterated various arguments outside the context of the Sandoz ANDA, their positions are without merit and have been soundly and consistently rejected by the Agency many times before --including, most notably, in the context of comparable generic immunosuppressant therapies for transplant recipients. The Agency dismissed the very same arguments some ten years ago at a time when they were then open to debate; and with the Agency and transplant physicians and patients having experienced the reality and benefit of bioequivalent immunosuppressant therapy such as Eon cyclosporine, there is no basis to give such arguments new consideration. To the contrary, the anti-competitive arguments being advanced to maintain Astellas's unwarranted monopoly provide no basis for deferring final action on the Sandoz ANDA. The approval of the ANDA would allow American patients access to a lower-cost generic version of an off-patent blockbuster drug that benefited the brand RLD holder with nearly (b) (4) in U.S. sales in 2007. We are concerned that if there is deferral of OGD's final action, it is plainly inconsistent with Congressional intent embodied in the new citizen petition provisions enacted in FDAAA, which expressly prohibit baseless delays in ANDA reviews and approvals.

As stated in our prior letter, FDA previously notified Sandoz that the bioequivalence and proposed labeling sections of the Sandoz ANDA are acceptable. Following submission of our June 3rd letter, some questions have been raised regarding the CMC section of the Sandoz ANDA, all of which Sandoz promptly addressed and all of which Sandoz understands have been fully resolved. The events proceeded as follows:

- 6/9/2008: Minor CMC deficiency letter sent to Sandoz.
- 6/20/2008: Sandoz responded to 6/9/2008 minor CMC deficiency letter.
- 6/27/2008: Sandoz requested its 6/20/2008 response be classified as a telephone amendment.
- 7/15/2008: FDA raised several CMC questions by telephone.
- 7/21/2008: Sandoz submitted telephone amendment responding to 7/15/2008 questions.
- 8/7/2008: FDA raised additional CMC questions by telephone.
- 8/8/2008: Sandoz submitted telephone amendment responding to 8/7/2008 questions.
- 8/14/2008: FDA raised additional CMC questions by telephone.
- 8/25/2008: Sandoz submitted telephone amendment responding to 8/14/2008 questions.

The questions regarding the Sandoz ANDA submission came to a close with our final telephone amendment on August 25th. Now, over six weeks have passed since Sandoz submitted its last telephone amendment on August 25, 2008, and FDA has not raised any additional CMC concerns. In light of all other FDA communications, Sandoz reasonably believes that it has addressed all open CMC questions and that the Sandoz ANDA is prepared for final action, but final action has not been taken. This situation is particularly surprising in light of the fact that FDA informed Sandoz long ago that the Sandoz ANDA, as a first generic, had been afforded expedited regulatory review.

The data in the Sandoz ANDA establish that Sandoz' tacrolimus product is bioequivalent to the RLD. Those bioequivalence data meet the statutory requirements as well as the requirements in FDA's implementing regulations, and the data are entirely consistent with FDA's tacrolimus bioequivalence guidance. Undoubtedly, that is why FDA previously communicated to Sandoz that the bioequivalence portion of the Sandoz ANDA is acceptable. Similarly, the labeling section of the Sandoz ANDA demonstrates that the labeling of the Sandoz tacrolimus product is "the same as" the labeling of the Prograf RLD, thus warranting FDA's prior communication to Sandoz that the labeling portion of its ANDA is acceptable. Finally, as indicated above, Sandoz has every reason to believe that the CMC portion of its ANDA is acceptable. All that is left is for OGD to issue its final action on the ANDA to Sandoz.

Any further delay in this last remaining step in the approval process is unwarranted. Any suggestion that the current and longstanding standards for approval of a generic tacrolimus product--e.g., contentions that tacrolimus is an NTI drug or that clinical studies in patients should be required--have long since been resolved by FDA for immunosuppressants generally and for tacrolimus in particular. First and foremost, there is nothing in the labeling of Prograf to even suggest that tacrolimus is an NTI drug, nor are we aware of anything in its regulatory history indicating that FDA has ever considered Prograf an NTI drug. FDA has cleared tacrolimus assays as Class II medical devices for the quantitative determination of tacrolimus concentrations as an aid in the management of transplant patients receiving tacrolimus, and any monitoring that physicians believe is necessitated to tailoring of dosing can be addressed with the readily-available assays. Second, and perhaps more importantly, the sound bioequivalence data in the Sandoz ANDA demonstrating the bioequivalence of the Sandoz product to the Prograf RLD is not the first tacrolimus bioequivalence data the Agency has considered for purposes of approval. As set forth in the current Prograf labeling, Astellas itself has secured FDA review and action on tacrolimus products based on bioequivalence data: "A single dose study conducted in 32 healthy volunteers established the bioequivalence of the 1 mg and 5 mg capsules. Another single dose study in 32 healthy volunteers established the bioequivalence of the 0.5 mg and 1 mg." Bioequivalence data has been appropriate for FDA action on Prograf, and it is at least as appropriate for action on the Sandoz ANDA. To do otherwise would overturn a myriad of well-reasoned and entirely appropriate Agency precedents that have consistently rejected anti-generic NTI arguments advanced by RLD holders seeking to extend their monopolies through artificial barriers to entry.

In conclusion, FDA has all the data and information it needs or has required of Sandoz to proceed immediately to final action on the Sandoz ANDA. Accordingly, we trust that OGD will proceed with final action on the application forthwith.

To support the Agency in that course of action, we would request an opportunity to discuss this critically-important matter with you and your staffs at your earliest convenience. We will call your offices to schedule a mutually-convenient time for a telephone conference or meeting. In the meantime, we appreciate the Agency's urgent attention to this matter.

We appreciate your treating this document as containing confidential, commercial and trade secret information provided solely for use by Government Regulatory Authorities. This document is not authorized for public disclosure.

Respectfully submitted,

Frank J. Della Fera
President and CEO *ad interim*

Enclosure

cc: Robert West (by electronic mail, robert.west@fda.hhs.gov, w/ enclosure)
Cecilia Parise (by electronic mail, cecelia.parise@fda.hhs.gov, w/ enclosure)
Roberta Szydlo (by electronic mail, roberta.szydlo@fda.hhs.gov, w/ enclosure)
Elizabeth Dickinson, Esq. (by electronic mail, elizabeth.dickinson@fda.hhs.gov, w/ enclosure)
Jane Axelrad, Esq. (by electronic mail, jane.axelrad@fda.hhs.gov, w/ enclosure)

SANDOZ

Bernhard Hampl, Ph.D.
President and CEO

Tel + 1 609 627 8502
Fax + 1 609 627 8684
e-mail: bernhard.hampl@sandoz.com

BY OVERNIGHT DELIVERY

June 3, 2008

N/mc

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2793

Re: CONTROLLED CORRESPONDENCE, ANDA 65-461
(Tacrolimus Capsules, 0.5, 1, and 5mg)

Dear Mr. Buehler:

We are writing with regard to our pending ANDA 65-461 for tacrolimus capsules, 0.5, 1, and 5mg, (the "Sandoz ANDA") based on the reference listed drug Prograf®. For the reasons discussed below, we request that your office promptly continue with substantive review of the Sandoz ANDA and, upon completion, issue final approval. Further, Sandoz is requesting FDA to timely address pending Citizen Petition 2007P-0358, if resolution is deemed necessary (though certainly not required) by FDA before issuing final approval of the Sandoz ANDA.

Background

Prograf®. Astellas Pharma US, Inc. (formerly Fujisawa) first received approval for NDA 050708 (Prograf capsules) on April 8, 1994. Because the active pharmaceutical ingredient in Prograf capsules, tacrolimus, is an "old" antibiotic, there is no exclusivity or Orange Book patent that limits FDA's authority to issue final approval of the Sandoz ANDA. *See, e.g.,* FDA's *Guidance for Industry and Reviewers: Repeal of Section 507 of the Federal Food, Drug & Cosmetic Act* (revised 5/1998). Final approval of the Sandoz ANDA would permit much-

Sandoz

506 Carnegie Center, Suite 400
Princeton, NJ 08540

www.us.sandoz.com

needed generic competition for Prograf, an important drug which cost consumers nearly (b) (4) in 2007[1].

In relevant part, the chronology of the **Sandoz ANDA** is as follows:

- [**12/28/06**]: Sandoz submits its ANDA for Tacrolimus capsules to the Office of Generic Drugs at FDA (OGD)
- [**04/11/07**]: OGD accepts the Sandoz ANDA for filing and substantive review.
- [**07/01/07, 11/20/07**]: OGD notifies Sandoz bioequivalence deficiencies.
- [**07/25/07, 12/31/07**]: Sandoz response to bioequivalence deficiencies to OGD.
- [**10/01/07, 12/05/07**]: OGD notifies Sandoz labeling deficiencies
- [**10/23/07, 01/04/08**]: Sandoz responses to labeling deficiencies to OGD.
- [**07/05/07**]: OGD notifies Sandoz of a minor CMC deficiency.
- [**08/08/07**]: Sandoz response to the minor CMC deficiency to OGD.
- [**02/28/07**]: OGD notifies Sandoz of a minor CMC deficiency
- [**03/07/08**]: Sandoz response to the minor CMC deficiency to OGD
- [**03/20/08**]: Sandoz submits a gratuitous amendment to OGD
- [**03/06/08**]: OGD notifies Sandoz that bioequivalence section of ANDA is acceptable.
- [**01/07/08**]: OGD notifies Sandoz that proposed labeling is acceptable (verbal)

Upon submission of the last CMC amendment, Sandoz believes that it has addressed all open questions proffered by OGD and further believes that the Sandoz ANDA is in condition for final approval. That is, the product described in the Sandoz ANDA is bioequivalent to the reference listed drug and meets the chemistry and labeling requirements as promulgated by FDA. Lastly, in addition to the above-referenced OGD/Sandoz correspondence, OGD recently informed Sandoz that its ANDA, as a first-generic, was afforded expedited regulatory review.

Astella's Citizen's Petition. Astellas Pharma US, Inc. ("Astellas") submitted Citizen Petition 2007P-0358 on September 21, 2007.[2] In accordance with the Food, Drug & Cosmetic Act (as amended), in relevant part, and 21 CFR 10.30, FDA is required to respond to such petitions within 180 days. However, much like historical actions FDA has chosen not to act decisively by either affirming or denying the petition within such 180 day period. Rather, FDA has chosen to fall behind 21 CFR 10.30(e) (2) (iii) by providing only "a tentative response". Our review of the public docket identifies only this cursory response from FDA as to Astellas's Petition.[3]

---

[1] 2007 IMS data.

[2] FDA's acknowledgement letter dated September 24, 2007, states that Astellas' Petition was submitted on September 21, 2007 and deemed filed three days later.

[3] FDA initially assigned Astellas' Petition docket number 2007P-0358/CP1, which (for whatever reason) was subsequently changed to 2007P-0111 at or about the time of the migration of all dockets to regulations.gov. A search of both docket numbers at the new site does not reveal the tentative response from FDA but only the petition itself, some but not all of the exhibits to the petition, as well as other (unrelated) papers regarding a Pfizer petition on Lotrel®, which had previously been assigned docket number 2007P-0111.

Impact of Unresolved Citizen's Petition. Failure by FDA to timely address and resolve Citizen's Petition results in delays in ANDA approval and benefits to the US public. Sandoz is concerned that FDA may be deprioritizing its review of our CMC amendment and delaying final approval of the Sandoz ANDA in the face of the pending citizen's petition. We make this statement as near 90 days have elapsed between the submission of our CMC amendment and the date of this letter and OGD still has not picked up this amendment for review. We believe that such practice is not in keeping with the precepts of an expedited review schedule.

Moreover, resolution of the petition is not required before approving the Sandoz ANDA. *See, e.g.* *Biovail Corp. v. U.S. Food & Drug Admin.*, 448 F. Supp.2d 154, 162 (D. D.C. 2006) [noting the lack of any "legal authority for the proposition that (FDA) must rule on citizen petitions prior to approving an ANDA"]. Lastly, any delay of review of the Sandoz ANDA provides Astellas the precise underlying relief sought by their petition – a delay in generic competition for Prograf.

Impact of New Legislation. Not coincidentally, Astellas's petition was filed a mere *three days* before the Food and Drug Administration Amendments Act was signed into law on September 27, 2007. The FDAAA added new section 505(q) to the FDC Act, which imposes new requirements to ensure prompt agency decision-making on citizen petitions that seek to block or delay generic drug approvals. Although the FDAAA did not include a transitional provision or specific effective date provision for new section 505(q), FDA has interpreted the provision as only applying to citizen petitions submitted to FDA on or after September 27, 2007. *See* Docket No. 2007P-0316, February 26, 2008 FDA letter to Teva Pharmaceuticals USA at 1, n.1.

We respectfully submit that FDA's interpretation is unlawful and contrary to the plain language of the law and the spirit of Congress. That is, Congress could have used language in the FDAAA to expressly exempt petitions filed before the enactment date. It did not. And absent such an express exemption or limitation, the most reasonable (*i.e.*, plain) interpretation of the FDAAA is that the new law applies to *all* pending petitions. But instead, FDA's interpretation clearly conflicts with the Congressional intent behind the FDAAA, namely to minimize delays in generic drug approvals caused by ostensibly merit less citizen petitions. Therefore, we request that FDA apply the requirements of new section 505(q) of the FDC Act to Astellas's petition.

When applied, section 505(q) requires FDA not to delay approval (and thus review) of a pending ANDA (such as ours), unless FDA determines such delay is "necessary to protect the public health." If FDA determines that resolution of the issues raised by Astellas' Petition is so necessary (and we submit it is not), then FDA is required to provide Sandoz, within thirty days of its determination, with: (1) notice of FDA's determination; (2) clarification of the information that such Sandoz should submit such that FDA may promptly review the petition; and (3) a brief summary of the substantive issues raised in the petition that led to FDA's determination. *See* 21 U.S.C. § 355(q) (1)(B). To date, we have not received any of this information.

For these reasons, Sandoz respectfully requests that FDA honor the expedited, first-generic review of the Sandoz ANDA and timely grant final approval, as warranted.

We appreciate the agency's attention to this request. We would be pleased to discuss this matter with you.

Respectfully submitted,

Bernhard Hampl, Ph.D.
Chief Executive Officer & President

cc: Robert West (by electronic mail: robert.west@fda.hhs.gov)
Cecilia Parise (by electronic mail: cecelia.parise@fda.hhs.gov)
Roberta Szydlo (by electronic mail; roberta.szydlo@fda.hhs.gov)
Gerald Masoudi, Esq. (by electronic mail: gerald.masoudi@fda.hhs.gov)
Elizabeth Dickinson, Esq. (by electronic mail: elizabeth.dickinson@fda.hhs.gov)
Jane Axelrad, Esq. (by electronic mail: jane.axelrad@fda.hhs.gov)

SANDOZ

Sandoz Inc.
506 Carnegie Center
Princeton, NJ 08540

Tel 609-627-8859 (Direct)
Tel: 609-627-8500 (General)
Fax : 609-395-2792

March 20, 2008

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ORIG AMENDMENT
N/AA

- GRATUITOUS AMENDMENT -

Re: **TACROLIMUS CAPSULES, 0.5 mg, 1 mg and 5 mg**
ANDA# 65-461

Dear Sirs:

We are herewith submitting a "GRATUITOUS AMENDMENT" document to our pending application for **TACROLIMUS CAPSULES, 0.5 mg, 1 mg and 5 mg (ANDA# 65-461)** as required under 21 CFR 314.120.

Reference is made to our response submitted on March 7, 2008, to the minor deficiency letter dated February 28, 2008.

We refer to our response to question #7 wherein we tightened the assay specifications for release and stability. We would like to revise this specification as given below:

Assay	Release specification	Shelf life specification
As per Response submitted on March 7, 2008	(b) (4) of the declared content	(b) (4) of the declared content
Proposed	(b) (4) of the declared content	(b) (4) of the declared content

RECEIVED
MAR 21 2008
OGD

Sandoz Inc.
506 Carnegie Center
Suite 400
Princeton, NJ 08540

Tel: 609-627-8500 (General)
Fax: 609-395-2792

SANDOZ

For any communication regarding this ANDA application, please contact Dr. Carmelle Lucas, at (609) 627-8854 (phone) or (609) 395-2792 (facsimile).

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed stamped envelope.

Sincerely,

Lalitha Subramanian

SANDOZ

Lalitha Subramanian
Regulatory Affairs

Sandoz Inc.
506 Carnegie Center
Princeton, NJ 08540

Tel 609-627-8859 (Direct)
Tel: 609-627-8500 (General)
Fax 609-395-2792

ORIGINAL

January 19, 2007

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

65-461

ORIG AMENDMENT
NDMC

- CORRESPONDENCE TO THE APPLICATION-NEW INFORMATION -

Re: **TACROLIMUS CAPSULES**
0.5 mg, 1 mg and 5 mg

Dear Sirs:

We have herewith enclosed a "*CORRESPONDENCE TO THE APPLICATION*" document submitted in duplicate for our pending application for **TACROLIMUS CAPSULES, 0.5 mg, 1 mg and 5 mg** as required under 21 CFR 314.120.

Please note that the firm has now received, from the holder of the Drug Master File (DMF), a copy of the DMF referral letter for the active pharmaceutical ingredient with the DMF# 19979. A copy of this referral letter is provided towards the application.

The firm has submitted an additional copy of this correspondence to the Office of Generic Drugs, Food and Drug Administration. We hereby certify that this additional copy (field copy) is a true copy of the Archival and Review copies submitted.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed stamped envelope.

Sincerely,

Lalitha Subramanian

RECEIVED
JAN 22 2007
OGD / CDER

SANDOZ

Lalitha Subramanian
Regulatory Affairs
Associate IV

Sandoz Inc
506 Carnegie Center
Princeton, NJ 08540

Tel: 609-627-8859 (Direct)
Tel: 609-627-8500 (General)
Fax: 609-395-2792

July 16, 2007

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

. NEW CORRESP

N/Rec

- CORRESPONDENCE TO THE APPLICATION -

Re: **TACROLIMUS CAPSULES**
0.5 mg, 1 mg and 5 mg
ANDA# 65-461

Dear Sirs:

We have herewith enclosed a "*CORRESPONDENCE TO THE APPLICATION*" document submitted in duplicate for our pending application for **TACROLIMUS CAPSULES, 0.5 mg, 1 mg and 5 mg** as required under 21 CFR 314.120.

Reference is made to the telephone correspondence from Ms. Roberta Szydlo (FDA) on July 16, 2007.

We have enclosed the corrected and most updated attachments to the 356h form in this submission. This will replace the attachments to the 356h form that we submitted with the original ANDA application dated December 28, 2006.

The firm has submitted an additional copy of this correspondence to the Office of Generic Drugs, Food and Drug Administration. We hereby certify that this additional copy (field copy) is a true copy of the Archival and Review copies submitted.

Please acknowledge receipt of this document by signing and dating the enclosed copy of the cover letter and return it in the self-addressed stamped envelope.

Sincerely,

Lalitha Subramanian

RECEIVED

JUL 17 2007

OGD