DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-708/S-026
NDA 50-709/S-020

Astellas Pharma US, Inc.
Attention: Donald E. Baker, J.D.
Senior Director, Regulatory Affairs
Three Parkway North
Deerfield, IL 60015-2548

Dear Dr. Baker:

Please refer to your supplemental new drug applications, dated October 28, 2005, received October 31, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Supplement Number	Name of Drug Product
50-708	S-026	Prograf® (tacrolimus) Capsules, 0.5 mg, 1 mg, and 5 mg
50-709	S-020	Prograf® (tacrolimus) Injection, 5 mg/mL

We acknowledge receipt of your submission dated April 10, 2006 and April 26, 2006.

These "Changes Being Effected" supplemental new drug applications provide for the following changes to the package insert (additions are double underlined and deletions are in strikethrough):

1. An improved drawing of the chemical structure of tacrolimus replaced the previous chemical structure in the **DESCRIPTION** section of the labeling.

2. Lansoprazole was added to the **PRECAUTIONS/ Drugs that May Alter Tacrolimus Concentrations/*_Drugs That May Increase Tacrolimus Blood Concentrations_** subsection of the labeling as follows:

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

**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.

3. Minor typographical errors were corrected in the labeling.

We have completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text. The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).
The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: ***Providing Regulatory Submissions in Electronic Format - NDAs*** (January 1999) and ***Providing Regulatory Submissions in Electronic Format – Content of Labeling*** (February 2004). The guidances specify that labeling be submitted in *pdf* format. To assist in our review of the FPL and future submissions, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper. For administrative purposes, these submissions should be designated "**FPL for approved supplements NDA 50-708/S-026 and NDA 50-709/S-020**." Approval of these submissions by the FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this Division and two copies of both the promotional materials and the package inserts directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you issue a letter communicating important information about these drug products (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH
Food and Drug Administration
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Rebecca D. Saville, Pharm.D., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure