DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 50-722/S-028
NDA 50-723/S-027
NDA 50-758/S-026
NDA 50-759/S-033

SUPPLEMENT APPROVAL

Roche Palo Alto, LLC.
c/o Genentech, Inc.
Attention: Becky Prokipcak
Regulatory Agent of behalf of Roche
1 DNA Way MS #241B
South San Francisco, CA 94080-4900

Dear Ms. Prokipcak:

Please refer to your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

NDA Number	Drug Product	Supplement Number	Date of Supplement	Date of Receipt
50-722	CellCept® (mycophenolate mofetil) Capsules, 250 mg	S-028	January 13, 2012	January 17, 2012
50-723	CellCept® (mycophenolate mofetil) Tablets, 500 mg	S-027	January 13, 2012	January 17, 2012
50-758	CellCept® (mycophenolate mofetil hydrochloride for injection) Intravenous, 500 mg/ 20 mL	S-026	January 13, 2012	January 17, 2012
50-759	CellCept® (mycophenolate mofetil for oral suspension) Oral Suspension, 200 mg/mL	S-033	January 13, 2012	January 17, 2012

We also acknowledge your amendments dated May 31 and June 13, 2012.

These "Prior Approval" supplemental new drug applications propose changes to the CellCept labeling to include updated pregnancy information.

The following changes were observed:
(~~strikethrough text~~ = deletions, <u>underlined text</u> = additions)

1. Boxed warning

WARNING: EMBRYOFETAL TOXICITY, MALIGNANCIES AND SERIOUS INFECTIONS

Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Females of reproductive potential (FRP) must be counseled regarding pregnancy prevention and planning (see **WARNINGS and PRECAUTIONS**).

Immunosuppression may lead to increased susceptibility to infection and possible development of lymphoma. Only physicians experienced in immunosuppressive therapy and management of renal, cardiac or hepatic transplant patients should ~~use~~ prescribe CellCept. 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 (**see WARNINGS and PRECAUTIONS**).

~~Female users of childbearing potential must use contraception. Use of CellCept during pregnancy is associated with increased risks of pregnancy loss and congenital malformations.~~

2. **WARNINGS**

WARNINGS
(see boxed WARNING)
Embryofetal Toxicity

Mycophenolate mofetil (MMF) can cause fetal harm when administered to a pregnant female. Use of MMF during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney (see **PRECAUTIONS: Pregnancy).**

Pregnancy Exposure Prevention and Planning

Females of reproductive potential must be made aware of the increased risk of first trimester pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention and planning. For recommended pregnancy testing and contraception methods (see **PRECAUTIONS: Pregnancy Exposure Prevention and Planning.**

3. **WARNING/Pregnancy: Teratogenic Effects:** Pregnancy Category D:

~~**Pregnancy: Teratogenic Effects:** Pregnancy Category D~~

~~Mycophenolate mofetil (MMF) can cause fetal harm when administered to a pregnant woman. Use of MMF during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs,~~

heart, esophagus, and kidney. In the National Transplantation Pregnancy Registry (NTPR), there were data on 33 MMF-exposed pregnancies in 24 transplant patients; there were 15 spontaneous abortions (45%) and 18 live-born infants. Four of these 18 infants had structural malformations (22%). In postmarketing data (collected 1995-2007) on 77 women exposed to systemic MMF during pregnancy, 25 had spontaneous abortions and 14 had a malformed infant or fetus. Six of 14 malformed offspring had ear abnormalities. Because these postmarketing data are reported voluntarily, it is not always possible to reliably estimate the frequency of particular adverse outcomes. These malformations seen in offspring were similar to findings in animal reproductive toxicology studies. For comparison, the background rate for congenital anomalies in the United States is about 3%, and NTPR data show a rate of 4-5% among babies born to organ transplant patients using other immunosuppressive drugs.

In animal reproductive toxicology studies, there were increased rates of fetal resorptions and malformations in the absence of maternal toxicity. Female rats and rabbits received mycophenolate mofetil (MMF) doses equivalent to 0.02 to 0.9 times the recommended human dose for renal and cardiac transplant patients, based on body surface area conversions. In rat offspring, malformations included anophthalmia, agnathia, and hydrocephaly. In rabbit offspring, malformations included ectopia cordis, ectopic kidneys, diaphragmatic hernia, and umbilical hernia.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. In certain situations, the patient and her healthcare practitioner may decide that the maternal benefits outweigh the risks to the fetus. Women using CellCept at any time during pregnancy should be encouraged to enroll in the National Transplantation Pregnancy Registry.

Pregnancy Exposure Prevention

Women of childbearing potential should have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 1 week prior to beginning therapy. CellCept therapy should not be initiated until a negative pregnancy test report is obtained.

Women of childbearing potential (including pubertal girls and peri-menopausal women) taking CellCept must receive contraceptive counseling and use effective contraception. The patient should begin using her two chosen methods of contraception 4 weeks prior to starting CellCept therapy, unless abstinence is the chosen method. She should continue contraceptive use during therapy and for 6 weeks after stopping CellCept. Patients should be aware that CellCept reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness (see **PRECAUTIONS: Information for Patients** and **PRECAUTIONS: Drug Interactions: Oral Contraceptives**).

4. **PRECAUTIONS**

PRECAUTIONS

Pregnancy Exposure Prevention and Planning

Females of reproductive potential must be made aware of the increased risk of first trimester pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention and planning.

Females of reproductive potential include girls who have entered puberty and all women who have a uterus and have not passed through menopause. Menopause is the permanent end of menstruation and fertility. Menopause should be clinically confirmed by a patient's healthcare practitioner. Some commonly used diagnostic criteria include 1) 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or 2) postsurgical from a bilateral oophorectomy.

Pregnancy Testing

To prevent unplanned exposure during pregnancy, females of reproductive potential should have a serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL immediately before starting CellCept. Another pregnancy test with the same sensitivity should be done 8 to 10 days later. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient.

In the event of a positive pregnancy test, females should be counseled with regard to whether the maternal benefits of mycophenolate treatment may outweigh the risks to the fetus in certain situations.

Contraception

Females of reproductive potential taking CellCept must receive contraceptive counseling and use acceptable contraception (see **Table 8** for acceptable contraception methods). Patients must use acceptable birth control during entire CellCept therapy, and for 6 weeks after stopping CellCept, unless the patient chooses abstinence (she chooses to avoid heterosexual intercourse completely).

Patients should be aware that CellCept reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness (see **PRECAUTIONS: Information for Patients** and **PRECAUTIONS: Drug Interactions: Oral Contraceptives**).

Table 1 Acceptable Contraception Methods for Females of Reproductive Potential
Pick from the following birth control options:

Option 1 Methods to Use Alone	• Intrauterine devices (IUDs) • Tubal sterilization • Patient's partner had a vasectomy

OR

Option 2	**Hormone Methods** choose 1		**Barrier Methods** choose 1
Choose One Hormone Method *AND* **One Barrier Method**	**Estrogen and Progesterone** Oral Contraceptive Pill Transdermal patch Vaginal ring **Progesterone-only** Injection Implant	*AND*	Diaphragm with spermicide Cervical cap with spermicide Contraceptive sponge Male condom Female condom

OR

Option 3	**Barrier Methods** choose 1		**Barrier Methods** choose 1
Choose One Barrier Method from each column *(must choose two methods)*	Diaphragm with spermicide Cervical cap with spermicide Contraceptive sponge	*AND*	Male condom Female condom

Pregnancy Planning

For patients who are considering pregnancy, consider alternative immunosuppressants with less potential for embryofetal toxicity. Risks and benefits of CellCept should be discussed with the patient.

Gastrointestinal Disorders

Gastrointestinal bleeding (requiring hospitalization) has been observed in approximately 3% of renal, in 1.7% of cardiac, and in 5.4% of hepatic transplant patients treated with CellCept 3 g daily. In pediatric renal transplant patients, 5/148 cases of gastrointestinal bleeding (requiring hospitalization) were observed.

Gastrointestinal perforations have rarely been observed. Most patients receiving CellCept were also receiving other drugs known to be associated with these complications. Patients with active peptic ulcer disease were excluded from enrollment in studies with mycophenolate mofetil. Because CellCept has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, hemorrhage, and perforation, CellCept should be administered with caution in patients with active serious digestive system disease.

Patients with Renal Impairment

Subjects with severe chronic renal impairment (GFR <25 mL/min/1.73 m^2) who have received single doses of CellCept showed higher plasma MPA and MPAG AUCs relative to subjects with lesser degrees of renal impairment or normal healthy volunteers. No data are available on the safety of long-term exposure to these levels of MPAG. Doses of CellCept greater than 1 g administered twice a day to renal transplant patients should be avoided and they should be carefully observed (see **CLINICAL PHARMACOLOGY: Pharmacokinetics** and **DOSAGE AND ADMINISTRATION**).

No data are available for cardiac or hepatic transplant patients with severe chronic renal impairment. CellCept may be used for cardiac or hepatic transplant patients with severe chronic renal impairment if the potential benefits outweigh the potential risks.

In patients with delayed renal graft function posttransplant, mean MPA AUC(0-12h) was comparable, but MPAG AUC(0-12h) was 2-fold to 3-fold higher, compared to that seen in posttransplant patients without delayed renal graft function. In the three controlled studies of prevention of renal rejection, there were 298 of 1483 patients (20%) with delayed graft function. Although patients with delayed graft function have a higher incidence of certain adverse events (anemia, thrombocytopenia, hyperkalemia) than patients without delayed graft function, these events were not more frequent in patients receiving CellCept than azathioprine or placebo. No dose adjustment is recommended for these patients; however, they should be carefully observed (see **CLINICAL PHARMACOLOGY: Pharmacokinetics** and **DOSAGE AND ADMINISTRATION**).

Infections in Cardiac Transplant Patients

In cardiac transplant patients, the overall incidence of opportunistic infections was approximately 10% higher in patients treated with CellCept than in those receiving azathioprine therapy, but this difference was not associated with excess mortality due to infection/sepsis among patients treated with CellCept (see **ADVERSE REACTIONS**).

There were more herpes virus (H. simplex, H. zoster, and cytomegalovirus) infections in cardiac transplant patients treated with CellCept compared to those treated with azathioprine (see **ADVERSE REACTIONS**).

Concomitant Medications

It is recommended that CellCept not be administered concomitantly with azathioprine because both have the potential to cause bone marrow suppression and such concomitant administration has not been studied clinically.

In view of the significant reduction in the AUC of MPA by cholestyramine, caution should be used in the concomitant administration of CellCept with drugs that interfere with enterohepatic recirculation because of the potential to reduce the efficacy of CellCept (see **PRECAUTIONS: Drug Interactions**).

Patients with HGPRT Deficiency

On theoretical grounds, because CellCept is an IMPDH (inosine monophosphate dehydrogenase) inhibitor, it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

Immunizations

During treatment with CellCept, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective (see **PRECAUTIONS: Drug Interactions: Live Vaccines**).

Phenylketonurics

CellCept Oral Suspension contains aspartame, a source of phenylalanine (0.56 mg phenylalanine/mL suspension). Therefore, care should be taken if CellCept Oral Suspension is administered to patients with phenylketonuria.

Information for Patients

See Medication Guide

- Inform females of reproductive potential that use of CellCept during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, and advise them as to the appropriate steps to manage these risks, including that they must use acceptable contraception (see **WARNINGS: Embryofetal Toxicity, PRECAUTIONS: Pregnancy Exposure Prevention and Planning).**
- Discuss pregnancy testing, pregnancy prevention and planning with females of reproductive potential. In the event of a positive pregnancy test, females should be counseled with regard to whether the maternal benefits of mycophenolate treatment may outweigh the risks to the fetus in certain situations.

- Females of reproductive potential must use acceptable birth control during entire CellCept therapy and for 6 weeks after stopping CellCept, unless the patient chooses to avoid heterosexual intercourse completely (abstinence) (see **PRECAUTIONS: Pregnancy Exposure Prevention and Planning, Table 8)**.
- For patients who are considering pregnancy, discuss appropriate alternative immunosuppressants with less potential for embryofetal toxicity. Risks and benefits of CellCept should be discussed with the patient.
- Give patients complete dosage instructions and inform them about the increased risk of lymphoproliferative disease and certain other malignancies.
- Inform patients that they need repeated appropriate laboratory tests while they are taking CellCept.
- Advise patients that they should not breastfeed during CellCept therapy.
- ~~Inform women of childbearing potential that use of CellCept in pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of birth defects, and that they must use effective contraception.~~
- ~~Discuss pregnancy plans with female patients of childbearing potential.~~
  - ♦ ~~Any female of childbearing potential must use highly effective (two methods) contraception 4 weeks prior to starting CellCept therapy and continue contraception until 6 weeks after stopping CellCept treatment, unless abstinence is the chosen method (see **WARNINGS: Pregnancy**).~~
  - ♦ ~~A patient who is planning a pregnancy should not use CellCept unless she cannot be successfully treated with other immunosuppressant drugs.~~

5. **PRECAUTIONS/Oral Contraceptives**

Oral Contraceptives

A study of coadministration of CellCept (1 g bid) and combined oral contraceptives containing ethinylestradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg to 0.20 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.10 mg) was conducted in 18 women with psoriasis over 3 consecutive menstrual cycles. Mean AUC(0-24h) was similar for ethinylestradiol and 3-keto desogestrel; however, mean levonorgestrel AUC(0-24h) significantly decreased by about 15%. There was large inter-patient variability (%CV in the range of 60% to 70%) in the data, especially for ethinylestradiol. Mean serum levels of LH, FSH and progesterone were not significantly affected. CellCept may not have any influence on the ovulation-suppressing action of the studied oral contraceptives. ~~However,~~ It is recommended ~~that oral~~ to co-administer CellCept with hormonal contraceptives ~~are coadministered with CellCept with caution~~(eg, birth control pill, transdermal patch, vaginal ring, injection, and implant) with caution, and additional ~~birth control~~ barrier contraceptive

methods must be ~~considered~~ used (see ~~**WARNINGS: Pregnancy**~~ **PRECAUTIONS: Pregnancy Exposure Prevention and Planning**).

6. **PRECAUTIONS/Pregnancy**

Pregnancy

~~**Teratogenic Effects:**~~ Pregnancy Category D. (See **WARNINGS**)

Use of MMF during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney. In animal studies, congenital malformations and pregnancy loss occurred when pregnant rats and rabbits received mycophenolic acid at dose multiples similar to and less than clinical doses. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Risks and benefits of CellCept should be discussed with the patient. When appropriate, consider alternative immunosuppressants with less potential for embryofetal toxicity. In certain situations, the patient and her healthcare practitioner may decide that the maternal benefits outweigh the risks to the fetus. For those females using CellCept at any time during pregnancy and those becoming pregnant within 6 weeks of discontinuing therapy, the healthcare practitioner should report the pregnancy to the Mycophenolate Pregnancy Registry (1-800-617-8191). The healthcare practitioner should strongly encourage the patient to enroll in the pregnancy registry. The information provided to the registry will help the healthcare community better understand the effects of mycophenolate in pregnancy.

In the National Transplantation Pregnancy Registry (NTPR), there were data on 33 MMF-exposed pregnancies in 24 transplant patients; there were 15 spontaneous abortions (45%) and 18 live-born infants. Four of these 18 infants had structural malformations (22%). In postmarketing data (collected 1995-2007) on 77 females exposed to systemic MMF during pregnancy, 25 had spontaneous abortions and 14 had a malformed infant or fetus. Six of 14 malformed offspring had ear abnormalities. Because these postmarketing data are reported voluntarily, it is not always possible to reliably estimate the frequency of particular adverse outcomes. These malformations are similar to findings in animal reproductive toxicology studies. For comparison, the background rate for congenital anomalies in the United States is about 3%, and NTPR data show a rate of 4-5% among babies born to organ transplant patients using other immunosuppressive drugs.

In animal reproductive toxicology studies, there were increased rates of fetal resorptions and malformations in the absence of maternal toxicity. Female rats and rabbits received mycophenolate mofetil (MMF) doses equivalent to 0.02 to 0.9 times the recommended human dose for renal and cardiac transplant patients, based on body surface area conversions. In rat offspring, malformations included anophthalmia, agnathia, and hydrocephaly. In rabbit

offspring, malformations included ectopia cordis, ectopic kidneys, diaphragmatic hernia, and umbilical hernia.

7. The tables in the CellCept labeling have been revised as follows:

Table 9~~2~~ Adverse Events in Controlled Studies in Prevention of Renal, Cardiac or Hepatic Allograft Rejection (Reported in ≥20% of Patients in the CellCept Group)

Table 3~~9~~ Viral and Fungal Infections in Controlled Studies in Prevention of Renal, Cardiac or Hepatic Transplant Rejection

Table 4~~10~~ Adverse Events Reported in 3% to <20% of Patients Treated With CellCept in Combination With Cyclosporine and Corticosteroids

8. **PRECAUTIONS/Postmarketing Experience**:

Postmarketing Experience
Congenital Disorders: Embryofetal Toxicity: Congenital malformations ~~including ear malformations~~ and an increased incidence of first trimester pregnancy loss have been reported ~~in offspring of patients exposed~~ following exposure to mycophenolate mofetil during pregnancy (see **~~WARNINGS~~PRECAUTIONS**: **Pregnancy**).

9. **DOSAGE AND ADMINISTRATION/CellCept Capsules, Tablets, and Oral Suspension**:

CellCept Capsules, Tablets, and Oral Suspension
The initial oral dose of CellCept should be given as soon as possible following renal, cardiac or hepatic transplantation. Food had no effect on MPA AUC, but has been shown to decrease MPA C_{max} by 40%. Therefore, it is recommended that CellCept be administered on an empty stomach. However, in stable renal transplant patients, CellCept may be administered with food if necessary.

Patients should be instructed to take a missed dose as soon as they remember, except if it is near the next scheduled dose, and then continue to take CellCept at the usual times.

10. **Medication Guide**

Reference of "healthcare provider" replaced with "doctor" throughout the medication guide.

What is the most important information I should know about CellCept?
CellCept can cause serious side effects:

- **~~Possible~~ Increased risk of loss of a pregnancy (miscarriage) and higher risk of birth defects.** ~~Women~~ Females who take CellCept during pregnancy have a higher risk of

~~losing a pregnancy (~~miscarriage~~)~~ during the first 3 months (first trimester), and a higher risk that their baby will be born with birth defects

If you are a female ~~and are able to~~ who can become pregnant:

- your ~~healthcare provider~~ doctor must talk with you about ~~effective~~ acceptable birth control methods (contraceptive counseling) to use while taking CellCept.
- you should have ~~a negative~~ one pregnancy test immediately ~~within 1 week~~ before starting CellCept and another pregnancy test 8 ~~you start~~ to ~~take CellCept~~ 10 days laters. Pregnancy tests should be repeated during routine follow-up visits with your doctor. Talk to your doctor about the results of all of your pregnancy tests.
- you must use ~~2 different types of effective~~ acceptable birth control ~~at the same time, for 4 weeks before you start taking CellCept,~~ during your entire CellCept therapy and for 6 weeks after stopping CellCept, unless at any time you choose to avoid sexual intercourse ~~completely~~ (abstinence) with a man completely. CellCept decreases blood levels of the hormones in birth control pills that you take by mouth. Birth control pills may not work as well while you take CellCept, and you could become pregnant. If you take birth control pills while using CellCept you must also use another form of birth control. Talk to your doctor about other birth control methods that you can use while taking CellCept.

If you plan to become pregnant, talk with ~~your healthcare provider~~ doctor. Your ~~healthcare provider~~ doctor will decide if other medicines to prevent rejection may be right for you.

If you become pregnant while taking CellCept, do not stop taking CellCept. Call your doctor right away. In certain situations, you and your ~~healthcare provider~~ doctor may decide that taking CellCept is more important to your health than the possible risks to your unborn baby.

- **~~If you get pregnant while taking CellCept, do not stop taking CellCept. Call your healthcare provider right away.~~** You and your ~~healthcare provider~~ doctor should report ~~any cases of pregnancies to~~ your pregnancy to Mycophenolate Pregnancy Registry (1-800-617-8191).

The purpose of this registry is to gather information about the health of you and your baby.

~~- FDA MedWatch at 1-800-FDA-1088~~
~~- Roche Professional Drug Safety at 1-800-526-6367~~

~~Talk to your healthcare provider about joining the National Transplantation Pregnancy Registry at 1-877-955-6877.~~

What is CellCept?

CellCept is a prescription medicine to prevent rejection (antirejection medicine) in people who have received a kidney, heart or liver transplant. Rejection is when the body's immune system perceives the new organ as a "foreign" threat and attacks it.

CellCept is used with other medicines called cyclosporine (Sandimmune®, Gengraf®, Neoral®) and corticosteroids. ~~These medicines work together to prevent rejection to your transplanted organ.~~

Who should not take CellCept?

Last bullet:

- **are breastfeeding <u>or plan to breastfeed</u>.** It is not known if CellCept passes into breast milk. You and your ~~healthcare provider~~ doctor will decide if you will take CellCept or breastfeed. ~~You should not do both without first talking with your healthcare provider.~~

How should I take CellCept?

Third bullet:

- If you miss a dose of CellCept, or are not sure when you took your last dose, take the regular amount of CellCept prescribed as soon as you remember. If it is time for your next dose, skip the missed dose <u>and take your next dose at your normal scheduled time.</u> Do not take 2 doses at the same time. Call your ~~healthcare provider~~ doctor if you are not sure what to do.

What are the possible side effects of CellCept?

Last paragraph:

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088 or to ~~Roche Professional Drug Safety at 1-800-526-6367~~ Genentech at 1-888-835-2555.

General Information about CellCept

2nd paragraph

This Medication Guide summarizes the most important information about CellCept. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about CellCept that is written for healthcare professionals. For more information, call ~~1-800-526-6367~~ <u>1-888-835-2555</u> or visit www.~~rocheusa~~<u>gene</u>.com/<u>gene</u>/products/<u>information/</u>cellcept

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

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, please contact Hyun J. Son Pharm.D., Safety Regulatory Project Manager, at (301)796-1600.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, M.D., MPH
Deputy Director for Safety
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

OZLEM A BELEN
06/22/2012