DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-083/S-012
NDA 21-110/S-011

Wyeth Pharmaceuticals
Attention: Patricia Kuker Staub, RPh, JD, Associate Director II
Worldwide Regulatory Affairs
Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Staub:

Please refer to your supplemental new drug applications dated September 19, 2002, received September 23, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rapamune® (sirolimus) Oral Solution, 1 mg/mL and Rapamune® (sirolimus) Tablets, 1 mg.

These "Changes Being Effected (CBE)" supplemental new drug applications provide for the following changes to the Rapamune® package insert. Added text is noted by double underline and deleted text is noted by ~~strikethrough~~:

1. PRECAUTIONS

- In the **General** subsection, the following paragraph was added to the end of the subsection. The same paragraph already appears in the **ADVERSE REACTIONS** section:

> ***Interstitial Lung Disease***
> Cases of interstitial lung disease (including pneumonitis, and infrequently bronchiolitis obliterans organizing pneumonia [BOOP] and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred in patients receiving immunosuppressive regimens including Rapamune. In some cases, the interstitial lung disease has resolved upon discontinuation or dose reduction of Rapamune. The risk may be increased as the trough Rapamune level increases (see **ADVERSE REACTIONS**).

2. OVERDOSAGE

- The first paragraph was revised to read:

> ~~There is minimal experience with overdose. During clinical trials, there were two accidental Rapamune ingestions, of 120 mg and 150 mg. One patient, receiving 150 mg, experienced an episode of transient atrial fibrillation. The other patient experienced no~~

~~adverse effects.~~ Reports of overdose with Rapamune have been received; however, experience has been limited. In general, the adverse effects of overdose are consistent with those listed in the **ADVERSE REACTIONS** section (see **ADVERSE REACTIONS**).

We have completed the review of these applications and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the final printed labeling submitted September 19, 2002. Accordingly, these applications are approved effective on the date of this letter.

If a letter communicating important information about these drugs products (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call Robin Anderson, Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
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/

Marc Cavaille Coll
1/31/03 08:55:00 AM
Signing for Dr. Renata Albrecht