DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-527/S-024, S-026, S-031

Wyeth Pharmaceuticals
Attention: Jennifer D. Norman, R.Ph.
Associate Director, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Norman:

Please refer to your supplemental new drug applications dated November 5, 2001, received November 7, 2001, (S-024) April 30, 2002, received May 1, 2002, (S-026) and February 11, 2003 received February 13, 2003, (S-031) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PREMPRO™/PREMPHASE® (conjugated estrogens/medroxyprogesterone acetate tablets).

We acknowledge receipt of your submissions dated October 15, 2002, March 13, April 2 and 7, and May 28 and 30, 2003 to S-024. Your March 13, 2003 submission constituted a complete response to our approvable letter of August 28, 2002.

We acknowledge receipt of your submissions dated November 27and December 5, 2002, April 2 and 7, and May 28 and 30, 2003 to S-026. Your November 27, 2002 submission constituted a complete response to our approvable letter of July 24, 2002.

We also acknowledge receipt of your submissions dated May 22, 28 and 30, 2003 to S-031.

These supplemental new drug applications provide for:

1. An additional strength of PREMPRO™ (0.3 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate) continuous combined regimen for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause, and the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. (S-024)

2. The use of PREMPRO™ (0.45 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate and 0.3 mg conjugated estrogens/1.5 mg medroxyprogesterone acetate) for the prevention of postmenopausal osteoporosis. (S-026)

3. To provide for revisions in the text of the **DESCRIPTION, CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, HOW SUPPLIED** and **PATIENT INFORMATION** sections of the direction circular. (S-031)

We 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 (attached).

We remind you of our agreements that were made in your submission dated April 2, 2003. These agreements are listed below.

1. You have agreed to an interim release and stability specification for CE dissolution at the (b)(4) timepoint. This interim acceptance criterion is (b)(4)---
2. You have committed to a Dissolution Surveillance Program for the dissolution of conjugated estrogens in the PREMPRO ™ 0.3 mg/1.5 mg drug product. In this commitment, every packaged lot will be tested for CE dissolution at six-month intervals. This surveillance program will be performed through expiration of the product.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this/these submission(s) should be designated "FPL for approved supplement NDA 20-527/S-024, S-026 and S-031." Approval of these submissions by 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 this product. 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 insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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 Kassandra Sherrod, R.Ph., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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

/s/

Daniel A. Shames

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