DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-040/S-001, 002, 005, 007, 009

King Pharmaceuticals
Attention: Karen C. Baker
Manager, Regulatory Affairs
501 Fifth Street
Bristol, TN 37620

Dear Ms. Baker:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prefest (estradiol and norgestimate) dated December 15, 1999, received December 16, 1999 (S-001); May 31, 2000, received June 1, 2000 (S-002): October 23, 2000, received October 24, 2000 (S-005); March 8, 2001, received March 9, 2001 (S-007); and July 2, 2001, received July 3, 2001 (S-009).

We acknowledge receipt of your submissions dated December 21, 1999 (S-001), March 13, 2001 (S-007), and February 7, 2003 (S-001, 002, 005, 007, 009).

Your submission of February 7, 2003 constituted a complete response to our January 15, 2002 approvable letter. This submission also responds to our letter of March 8, 2002 requesting revision of the **CLINICAL STUDIES, Control of Uterine Bleeding** subsection of the package insert and to our letter of January 3, 2003 requesting labeling revisions based on the results of the Women's Health Initiative (WHI) trial.

These "Changes Being Effected" supplemental new drug applications provide for the following:

1. Revisions to the **PRECAUTIONS** and **ADVERSE REACTIONS** sections of the package insert (addition of information on endometrial hyperplasia) (S-001).

2. Revisions to the **WARNINGS** section of package insert (update of information on breast cancer) and revisions to the **USES OF ESTROGEN** (revision of information on osteoporosis), **RISK OF ESTROGENS AND/OR PROGESTINS** (update of information on breast cancer), and **OTHER INFORMATION** (information on body weight and blood levels of progestin) sections of the patient information insert (S-002).

3. Revisions to the **WARNINGS** and **PRECAUTIONS** section of the package insert (update of information on breast cancer and coronary heart disease) and to the **RISK OF ESTROGENS AND/OR PROGESTINS** section of the patient information insert (update to the **Cancer of the Breast** subsection) in response to the August 16, 2000 letter requesting labeling revisions based on the results of the Heart and Estrogen/Progestin Replacement Study (HERS) (S-005).

4. Replacement of the term "17$-estradiol" with "estradiol" throughout the package insert and the

patient information insert, except under the **DESCRIPTION** section (per your agreement in supplement 004, submitted August 30, 2000 and acknowledged and retained on October 31, 2001) and replacement of "TM" with "®" throughout the package insert and the patient information insert (S-007).

5. Revisions to the **CLINICAL PHARMACOLOGY** section (revision of the **Drug-Drug Interactions** subsection to add information about St. John's wort) and to the **ADVERSE REACTIONS** section (addition of information on uterine bleeding; revision of *Genitourinary System* related to vaginal spotting, bleeding or hemorrhage) of the package insert and to the **INTRODUCTION** section of the patient information insert (addition of information on menstrual-like bleeding patterns) (S-009).

We completed our review of these supplemental new drug applications as amended. They are approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on February 7, 2003.

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 the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call George Lyght, Regulatory Project Manager, at (301) 827-5424.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Acting Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
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/

Daniel A. Shames
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