NDA 21-065
NDA [……..]

Parke-Davis Pharmaceutical Research
Attention: Mary E. Taylor, M.P.H.
Director, Worldwide Regulatory Affairs
2800 Plymouth Road
P.O. Box 1047
Ann Arbor, MI 48105-1047

Dear Ms. Taylor:

Please refer to your new drug applications NDA 21-065 and [……] dated December 16, 1998, received December 17, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for *femhrt*™ (norethindrone acetate and ethinyl estradiol) tablets.

We acknowledge receipt of your submissions dated December 16, 1998, March 30, April 15, June 7, and 24, July 8, 20, and 29, August 3, 6, and 31, September 3, 17, 22, 28(2), 29(2), and 30, and October 1, 4, 7, 8(4), 11, 12(4), 13, 14, and 15.

These new drug applications provide for the use of *femhrt*™ tablets in women with an intact uterus for the treatment of moderate to severe vasomotor symptoms associated with menopause and for prevention of osteoporosis. [……]

We have completed our review of these applications, as amended, and have concluded that adequate information has been presented to demonstrate that the 1/5 dose of *femhrt*™ is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved for the 1/5 dose of *femhrt*™ effective on the date of this letter.

[……]

[…….]

Optimally, drugs used to prevent osteoporosis are administered at the lowest effective dose. [……..]

The final printed labeling (FPL) must be identical to the submitted draft labeling (physician and patient package inserts submitted October 15, 1999, and carton labels submitted October 12, 1999). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

All promotional materials, including launch materials must utilize the new tradename, *femhrt*™, with the same size font and color. All secondary packaging materials including boxes and cartons must be

changed to *femhrt*™ at launch. The packaging for foil pouches and blister packages may signify **AfemHRT@** for six months or until supply has been depleted whichever comes first.

Please submit 20 copies of the FPL to the Division of Reproductive and Urologic Drug Products 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 submission should be designated "FPL for approved NDA 21-065." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitment specified in your submission dated October 1, 1999. This commitment, along with any completion dates agreed upon, is listed below.

> You agreed to collect [……] data on tablets from at least ten commercial batches and establish […..] specification for release of the drug product. These data and your proposed specification should be submitted in a AChanges Being Effected@ Supplement.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit four copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit two copies to the Division of Reproductive and Urologic Drug Products and two copies of both the promotional materials and the package insert directly to:

> Division of Drug Marketing, Advertising, and Communications, HFD-40
> Food and Drug Administration
> 5600 Fishers Lane
> Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA as set forth under 21 CFR 314.80 and 314.81. To comply with these regulations, all 7-day and 15-day alert reports, periodic adverse drug experience (ADE) reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA 21-065 for this drug product at the Division of

Reproductive and Urologic Drug Products, not to NDA […….]. In the future, no submissions should be made to NDA [……]

If you have any questions, contact Dornette Spell-LeSane, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

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

Sincerely,

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research