DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-166

Solvay Pharmaceuticals
Attention: Cicely N. Vaughn, MPH
Manager, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Ms. Vaughn:

Please refer to your new drug application (NDA) dated August 13, 1999, received August 16, 1999 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Estrogel 0.06% (estradiol gel).

We note that, during the initial review of this application, it became subject to the provisions of the Application Integrity Policy (AIP), and as such, our normal substantive scientific review could not be continued. We also reference the Agency's April 9, 2003, letter, in which Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, notified you that the substantive scientific review of Solvay's applications could be resumed. Therefore, the 10-month standard review clock for this application started on April 9, 2003, resulting in a PDUFA goal date of February 9, 2004.

We also acknowledge receipt of your submissions dated September 20 and 28, October 28, November 9 and 23, and December 8, 1999, January 6, 12, and 21, March 28, April 5, 21, and 25, May 11, October 18, and November 6, 2000, July 18, 2001, June 26, 2002, May 19, June 16 and 19, August 1 and 13, September 26, October 21, 22, and 23 (3), November 7, 19, and 25, December 10 and 22, 2003, January 7, 9, 15 and 27, February 2, 4, 6 (2) and 9 (2), 2004.

This new drug application provides for the use of Estrogel 0.06% (estradiol gel) for the indications of:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (package insert and patient package insert) and the immediate container and carton labels submitted February 2, 2004. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved drug.

Please submit an electronic version of the FPL 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 but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this

submission. "FPL for approved NDA 21-166." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submissions dated February 9, 2004. These commitments are listed below:

1. Solvay Pharmaceuticals commits to design and conduct a Phase IV clinical trial study to find the lowest effective dose of Estrogel 0.06% for the indications of:

Treatment of moderate to severe vasomotor symptoms associated with the menopause.
Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.

The following is the timeline for this commitment:

Protocol Submission:	Within 6 months of the date of the receipt of this action letter.
Study Start:	Within 6 months of the protocol agreement with the Division of Reproductive and Urologic Drug Products (DRUDP).
Final Report Submission:	Within 6 months of the study completion.

2. Solvay Pharmaceuticals commits to design and conduct a Phase IV study to establish an in-vitro release rate specification:

The following is the timeline for this commitment:

Protocol Submission:	Within 2 months of the receipt of this action letter.
Study Start:	Within 2 months of reaching the protocol agreement with DRUDP.
Final Report Submission:	Within 1 year of the receipt of this action letter.

Submit the clinical protocol to your IND for this product. Submit the chemistry, manufacturing, and controls protocol and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for the clinical study, number of patients entered into the study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

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

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 call George Lyght, R.Ph., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

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

Enclosure: Physician Insert and Patient Package Insert

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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