CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-187

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-187

Organon, Inc.
Attention: Edwina Muir
Director, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Dear Ms. Muir:

Please refer to your new drug application (NDA) dated December 28, 1999, received December 28, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring).

We acknowledge receipt of your submissions dated March 8 and 11, April 21 and 27 (2), June 1 and 9, July 6, August 10, 11 and 29 (2), September 20, October 6, 11, 19 (2), 24 and 27, November 1 and 14, December 13, 14, 20, 21, 22 (2) and 28, 2000; and January 11, February 28, April 20 and 30, June 21, July 19, August 2 and September 13, 27, and 28 (2), 2001. Your submission of August 2, 2001 constituted a complete response to our April 27, 2001 action letter.

This new drug application provides for the use of NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring) for the prevention of pregnancy in women who elect to use this product as a method of contraception.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert) and the immediate container and carton labeling submitted September 28, 2001. 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 copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). 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. 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 21-187." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated September 27, 2001. These commitments are listed below.

1. Initiate study 34232 as per the protocol previously submitted.

Protocol Submission:	Submitted the protocol on April 20, 2001
Study Start:	Within six months of the date of this letter
Final Report Submission:	Within six months of study completion

2. Submit a plan for follow-up of all spontaneous reports of pregnancy with NuvaRing® use to obtain information regarding duration of fetal exposure to NuvaRing® for each pregnancy and pregnancy outcomes, including live births, stillbirths, premature births, spontaneous abortions, and congenital anomalies. The plan, including 6 month intervals for submitting data and a 5 year time span for follow-up post approval.

Protocol Submission:	Within six months of the date of this letter
Study Start:	First day of marketing the product
Final Report Submission:	Within six months following the five year reporting period

We also remind you of your agreement to provide a non-automated alternative for the *in vitro* release analytical method that would allow validation of the methodology.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols 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 clinical studies, number of patients entered into each 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."**

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.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

In addition, please submit three 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 send one copy 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-42
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 set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Jennifer Mercier, B.S., Regulatory Project Manager, at (301) 827-4260.

Sincerely,
{See appended electronic signature page}

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-187

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 21-187

Organon, Inc.
Attention: Edwina Muir
Director, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange, NJ 07052

APR 27 2001

Dear Ms. Muir:

Please refer to your new drug application (NDA) dated December 28, 1999, received December 28, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring).

We acknowledge receipt of your submissions dated March 8 and 11, April 21 and 27 (2), June 1 and 9, July 6, August 10, 11 and 29 (2), September 20, October 6, 11, 19 (2), 24 and 27, November 1 and 14, December 13, 14, 20, 21, 22 (2) and 28, 2000; and January 11, and February 28, 2001. Your submission of February 28, 2001 constituted a complete response to our December 22, 2000 action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as enclosed.

We remind you of your postmarketing study commitments in your submission dated December 13, 2000. These commitments are listed below.

(1) Conduct a clinical study to determine serum etonogestrel and ethinyl estradiol concentrations, and ovulation inhibition, after multiple doses of a commercially available, oil-based anti-mycotic preparation. A placebo arm with an oil-based vehicle should also be considered. A micronazole nitrate preparation will be used for this purpose (since this was the product which was noted to cause an increase in the AUC value for both ethinyl estradiol and etonogestrel following a single dose exposure.

Protocol Submission: Within 6 months of NuvaRing® approval

(2) Conduct a clinical study to determine the effect of tampon use on serum concentration of etonogestrel and ethinyl estradiol.

Protocol Submission: Within 6 months of NuvaRing® approval

(3) For postmarketing safety reports of pregnancy following NuvaRing® exposure, the sponsor will attempt to obtain information on the outcome of all such pregnancies including live births, miscarriages (spontaneous abortions), septic abortions, premature births, congenitial anomalies and duration of fetal exposure to NuvaRing®.

(4) Provide a non-automated alternative for the *in vitro* release analytical method that would allow validation of the methodology. The alternative must mimic the principles and procedures of the automated method in a manner that can be duplicated by our chemists in their laboratories.

Final Report Submission: Within 12 months of NuvaRing® approval

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL, ten of which individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   - Present tabulations of the new safety data combined with the original NDA data.

   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Jennifer Mercier, B.S., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-187

Organon, Inc.
Attention: Edwina Muir
Director, Regulatory Affairs
375 Mt. Pleasant Avenue
West Orange, NJ 07052

Dear Ms. Muir:

Please refer to your new drug application (NDA) dated December 28, 1999, received December 28, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NuvaRing® (etonogestrel/ethinyl estradiol) Ring.

We acknowledge receipt of your submissions dated March 8 and 11, April 21 and 27 (2), June 1 and 9, July 6, August 10, 11 and 29 (2), September 20, October 6, 11, 19 (2), 24 and 27, November 1 and 14, and December 13, 14, and 20, 2000

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as enclosed.

We remind you of your postmarketing study commitments in your submission dated December 13, 2000. These commitments are listed below.

1. Provide a non-automated alternative for the *in vitro* release analytical method that would allow validation of the methodology. The alternative must mimic the principles and procedures of the automated method in a manner that can be duplicated by our chemists in their laboratories.

   Final Report Submission: Within 12 months of the date of this letter

2. Conduct a clinical study to determine serum etonogestrel and ethinyl estradiol concentrations, and ovulation inhibition, after multiple doses of a commercially available, oil-based anti-mycotic preparation. A placebo arm with an oil-based vehicle should also be considered. A micronazole nitrate preparation will be used for this purpose (since this was the product which was noted to cause an increase in the AUC value for both ethinyl estradiol and etonogestrel following a single dose exposure).

   Protocol Submission: Within 6 months of the date of this letter.

3. Conduct a clinical study to determine the effect of tampon use on the serum concentration of etonogestrel and ethinyl estradiol.
   Protocol Submission: Within 6 months of the date of this letter.

4. For postmarketing safety reports of pregnancy following Nuvaring exposure, Organon will attempt to obtain information on the outcome of all such pregnancies including live births, premature births, miscarriages (spontaneous abortions), septic abortions, congenital anomalies and duration of fetal exposure to Nuvaring.

Please submit 20 paper copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   - Present tabulations of the new safety data combined with the original NDA data.

   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated

estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Jennifer Mercier, B.S., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure