CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-781

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 4, 1998

FROM: Diane Moore
Division of Reproductive and Urologic Drug Products (HFD-580)
FAX: (301) 827-4267

SUBJECT: Pediatric Pediatric labeling for Prometrium NDA 19-781

TO: File

This drug is indicated for the treatment of secondary amenorrhea in premenopausal women who have previously had their menses. It is not appropriate for use in children of any age. Therefore, pediatric studies are not needed.

cc:
HFD-580

/S/ 5/6/98

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

/BLA #_NDA 19-781_____ Supplement # _____Circle one: SE1 SE2 SE3 SE4 SE6

HFD-580____ Trade and generic names/dosage form: _Prometrium (progesterone USP) 100 mg_____Action: [AP] AE NA

Applicant _Schering-Plough Research Institute_____ Therapeutic Class_____3S_____

Indication(s) previously approved __none_____
Pediatric information in labeling of approved indication(s) is adequate _X_ inadequate __
Proposed indication in this application__Treatment of secondary amenorrhea in premenopausal women_____

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTINS IN RELATION TO THE PROPOSED INDICATION.
IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) _X__ No (Sign and return the form)
WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)
___Neonates (Birth-1 month) __ Infants (1month-2yrs) __Children (2-12yrs) ___ Adolescents (12-16 yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing.
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

_X__ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? _X__ Yes ___ No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from __medical review_____ (e.g., medical review, medical officer, team leader)

/S/ Project Manager 5/11/98
Signature Of Preparer And Title Date

CC: ORIG NDA/BLA # _NDA 19-781_____
HFD-580_____/DIV FILE
NDA/BLA ACTION PACKAGE
HFD-006/ KROBERTS

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

Group Leader Memorandum

NDA:	**19-781**
Drug and indication:	**Prometrium™ (progesterone) for treatment of secondary amenorrhea**
Dose:	**Four 100 mg capsules daily for ten days**
Applicant:	**Schering Corporation**
Submission received:	**September 30, 1987**
Resubmissions received:	**March 17, 1989 and February 8, 1996**
Date of MO review:	**October 8, 1996**
Date of Memorandum:	**February 6, 1997**

In this application, the sponsor requests approval for Prometrium™, a micronized, oral formulation of progesterone, for the treatment of secondary amenorrhea in premenopausal women. This application's complex regulatory history and the division's rationale for approving this application merit comment.

As detailed by Dr. Cropp in the medical officer's review, almost ten years have elapsed since the original submission of this application and this regulatory action. After the application was refused for filing in 1987 due to the lack of clinical studies for the intended indication, the application was resubmitted in 1989 containing the results of a small, single center study of women with secondary amenorrhea who were randomized to receive either 200 mg or 300 mg of micronized progesterone, or placebo. A subsequent not approvable letter of August 17, 1990 stated that there was insufficient evidence of efficacy because only the 300 mg dose was found to be superior to placebo, and because published articles did not provide further support that micronized progesterone was an adequate progestational agent. In the meeting that followed this action (July 2, 1990), it was agreed that the sponsor would need to demonstrate that the 300 mg dose induces endometrial secretory changes. It was also suggested at this time that the sponsor study the effect on the endometrium of higher doses of micronized progesterone because of concerns that the product was a poor progestational agent.

The most recent resubmission contains the results of a dose-ranging, placebo-controlled study to establish the rate of endometrial secretory transformation in estrogen primed post-menopausal women. The results of this study suggest that the 400 mg dose is more effective than the 300 mg dose based on higher rates of complete secretory transformation and withdrawal bleeding following treatment with the 400 mg dose. This data would therefore suggest that the 400 mg/day dose would be a more effective treatment for secondary

amenorrhea. However, because adequate dose-finding studies were not conducted during the development of this product, there is no data on the safety or efficacy of the 400 mg dose in the intended population.

This deficiency was discussed with the sponsor in a meeting on December 4, 1996. In subsequent internal discussions, consensus was reached that this application is approvable in light of the following considerations:

1) The effectiveness of progestins for this indication is well established;
2) It is reasonable to expect that the safety profile of the 400 mg daily dose will be similar in post-menopausal and pre-menopausal women;
3) The 400 mg dose should be at least equally efficacious as the 300 mg dose at inducing withdrawal bleeding in premenopausal women;
4) The sponsor has addressed the deficiencies in the August 17, 1990 not approvable letter in a manner that is consistent with the division's guidance at that time;
5) The sponsor has committed to conducting a phase IV study

and

6) Until the phase IV study has been completed and reviewed, only the 400 mg dose would be recommended in the package insert because of safety concerns that the 300 mg dose does not induce sufficient endometrium transformation.

Because of the need for extensive revisions to the proposed package insert an approvable letter will be issued.

/S/

Heidi M. Jolson, M.D., M.P.H.
Deputy Division Director, HFD-580

cc:
NDA19-781
HFD-580/LRarick/CCropp/HJolson

c:\h\19781.gl

NDA 19-781
Prometrium (Progesterone USP) Capsules 100 mg
Schering Corporation

Division Director's Memo

The application will be signed off at the Division level. No memo is necessary.

13. PATENT INFORMATION

Please reference our February 8, 1996 submission to our NDA 19-781 (PROMETRIUM Capsules), pages 1 of Section 13, Volume 2.2. There are no changes to the patent information.

PATENT INFORMATION

U.S. patents pertaining to the drug progesterone: None.

U.S. patents pertaining to the composition and formulation of PROMETRIUM (progesterone, USP) Capsules: None.

U.S. patents pertaining to methods of use of PROMETRIUM (progesterone, USP) Capsules: None.

The person signing this application on behalf of the applicant declares that he is aware of no U.S. patent which claims the drug progesterone, the PROMETRIUM (progesterone, USP) Capsules, or a method of using the PROMETRIUM (progesterone, USP) Capsules, and with respect to which U.S. patents a claim of patent infringement could reasonably be asserted against a person, not licensed thereunder by the owner, who engages in the manufacture, use or sale of the PROMETRIUM (progesterone, USP) Capsules.

19. CLAIMED EXCLUSIVITY

Pursuant to the provisions of Section 505(c)(4)(D)(iii) and 505(j)(4)(D)(iii) of the Food, Drug and Cosmetic Act (FDCA) and 21 C.F.R. Section 314.108(b)(4), in the February 8, 1996 submission to NDA 19-781, the applicant has claimed three (3) years of exclusivity for its PROMETRIUM (progesterone, USP) Capsules for oral administration attaching to the dosage form and route of administration and extending to any use of micronized progesterone capsules for oral administration.

In accordance with Section 306(k) of the FD&C Act, Schering Corporation certifies that, with respect to this application, it did not and will not knowingly use services of any persons that have been debarred under the provisions of Section 306(a) or (b) of the Act.

NDA 19-781
Prometrium (Progesterone USP) Capsules 100 mg
Schering Corporation

Advisory Committee Meeting Minutes

This application was not the subject of an Advisory Committee Meeting.

NDA 19-781
Prometrium (Progesterone USP) Capsules 100 mg
Schering Corporation

Federal Register Notices

This application was not the subject of any Federal Register Notices.

NDA 19-781
Prometrium (Progesterone USP) Capsules 100 mg
Schering Corporation

Advertising Material

No advertising material has been submitted.

Memorandum

To: NDA 19-781 Division File

From: Theresa H. van der Vlugt, MD /S/
Medical Officer

Subject: Review of SCH 961: Prometrium® Capsules Four-Month Safety Update Report

Date: May 6, 1998

A review of SCH 961: Prometrium® Capsules Four-Month Safety Update Report was completed. This safety update includes information from three Phase IV

Pooling data from post-marketing experiences produced a total of 288 adverse events in 173 patients that have been reported since the introduction of oral micronized progesterone in 1980 through May 31, 1997. Twenty-seven (9%) of these were classified as serious adverse experiences, including three fetal deaths in patients treated for unapproved indications, one cancer of the pancreas, and one incidence of excessive bleeding.

Overall, the Phase IV studies have shown a low incidence of adverse events).

This report is acceptable. No further action is indicated.

Concur - MM MD 5-6-98

cc: HFD-580/DMoore/MMann/TvanderVlugt

Group Leader Memorandum

NDA:	**19-781**
Drug and Indication:	**Prometrium™ (progesterone) for the treatment of secondary amenorrhea**
Dose:	**Four 100 mg capsules daily for ten days**
Applicant:	**Schering Corporation**
Submission Received:	**September 30, 1987**
Resubmissions Received:	**March 17, 1989 and February 8, 1996**
Date of Memorandum:	**May 4, 1998**

An approvable letter was submitted to the sponsor (Schering) for this application on March 28, 1997 with the outstanding issue being extensive revisions to the proposed package insert.

Labeling revisions have included changes to the physician package insert as well as designing a new insert specifically for patients. Negotiations have been completed and the physician and patient package inserts are acceptable.

A phase IV study

This study remains a commitment on the part of the sponsor.

An approval letter will be issued since labeling is acceptable.

/S/ 5-6-98

Marianne Mann, M.D.
Deputy Director, HFD-580

cc:
NDA 19-781
HFD-580/Rarick/van der Vlugt/Mann

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 16, 1990

FROM: Director, Division of Metabolism and Endocrine Drug Products, HFD-510

SUBJECT: Division Director's Memo for NDA 19-781

TO: The File (NDA 19-781)

My views regarding this NDA are contained in the "not approvable" letter.

/S/

Solomon Sobel, M.D.

cc: NDA Arch.
HFD-510
HFD-510/EGalliers/8.16.90/ \divdir.mem

NDA 19-781
Prometrium (Progesterone USP) Capsules 100 mg
Schering Corporation

November 1, 1996 Submission

Safety Update Review

Included in Medical Officer review dated October 8, 1996.

NDA 19-781
Prometrium (Progesterone USP) Capsules 100 mg
Schering Corporation

Microbiology Review

No microbiology review is required for capsule formulation.

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dr. Daniel Boring, Chair, HFD-530, Corporate Building, Room N461

From: Division of Reproductive and Urologic D. P./ HFD-580
Attention: Dr. Amit K. Mitra Phone: (301) 827-4238

Date: 7-May-1998

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Prometrium^{R} **NDA#:** 19-781

Established name, including dosage form: Progesterone, USP Capsules

Pregn-4-ene-3,20-dione
$C_{21}H_{30}O_2$, Molecular Weight: 314.5

Other trademarks by the same firm for companion products: - None

Name and address of applicant: Schering Corporation, 2000 Galloping Hill Road, Kenilworth, NJ 07033

Indications for Use (may be a summary if proposed statement is lengthy): Prometrium^{R} is indicated for secondary amenorrhea
Dosage Form: Soft gelatin capsule **/Strengths:** 100 mg; **Route of Administration:** Oral**/Dispensed:** _(prescription)

Initial comments from the submitter (concerns, observations, etc.): This is an old NDA. The tradename may have been submitted earlier for review. However, the documentation for the tradename review is not available in the divisional document room. Therefore, the tradename is being submitted for review. An action is urgently needeed.

filename: 20682.tm

NOTE: *Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.*

Rev Oct. 1993

NDA 19-781

1999

Schering Corporation
Attention: Joseph Lamendola, Ph.D.
Vice President, U.S. Regulatory Affairs
Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Lamendola:

Please refer to your September 30, 1987, new drug application (NDA) and your resubmission dated March 17, 1989, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prometrium (Progesterone USP) Capsules, 100 mg.

Review of the two clinical trials submitted (T91-006 and C90-557) raised several questions pertaining to the selection of the appropriate dose of micronized progesterone for the intended indication, and how information about the safety and efficacy of this dose could best be communicated in the package insert. Prior to our taking a regulatory action on your resubmission, we would like to have the opportunity to discuss these issues with you in a meeting.

Our questions about selection of the appropriate dose have been raised by the following findings in the submitted clinical studies:

1. In trial T91-006, which studied doses of 200 mg and 300 mg of micronized progesterone in women with secondary amenorrhea, only the 300 mg dose produced a significantly greater rate of withdrawal bleeding than did placebo.

2. In trial C90-557, which studied doses of 100 mg, 200 mg, 300 mg and 400 mg of micronized progesterone in a post-menopausal patient population, only the 400 mg/day dosage produced a significantly greater proportion of complete secretory activity than did placebo.

   In the submitted analysis of this data, we note that you conclude that both the 300 mg/day and 400 mg/day doses produce a higher rate of total secretory activity than placebo. However, your proposed definition of secretory changes, which includes both partial and complete transformation, is unacceptable. Complete secretory conversion is the appropriate endpoint for several reasons. First, it is the common clinical definition of secretory transformation. Second, a response less than complete would imply either that an inadequate dose of micronized progesterone was used, or that micronized progesterone was an ineffective progestin. Third, an irregular pattern or distribution of secretory transformation would probably result in prolonged bleeding due to irregular endometrial shedding.

3. In trial C90-557, the 400 mg/day dose produced a significantly higher rate of withdrawal bleeding than did the 300 mg/day dose.

These observations suggest that 400 mg/day would be the most effective dose because (in a post-menopausal population) it produced the highest frequency of withdrawal bleeding after medication discontinuation and because it was the only dose with a significantly greater frequency of complete secretory conversion compared to placebo. However, this dose has not been studied in the target population for the proposed indication, i.e., women of reproductive age with secondary amenorrhea, nor compared to the 300 mg dose in this population. Therefore, there does not appear to be adequate data regarding the safety and efficacy of this dose for labeling in the package insert.

We look forward to discussing these issues at the meeting scheduled for November 1, 1996. If you have any questions, please contact:

Diane Moore
Consumer Safety Officer
(301) 827-4260.

Sincerely yours,

/S/ 10/23/96

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 19-781
HFD-580/Div. files
HFD-580/LRarick/HJolson/CCropp/MRhee/KRaheja/AJordan
HFD-510/PStewart
HFD-870/GBarnette/ADorantes

drafted: dm/October 21, 1996/n19781.gc

Concurrences:
LPauls 10.23.96/Hjolson 10.23.96

General Correspondence

NDA 19-781

AUG 17 1990

Schering Corporation
Attention: Douglass Given, M.D., Ph.D.
Vice President, Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Given:

Reference is made to your new drug application dated September 30, 1987, and resubmitted on March 17, 1988, under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for the preparation Utrogestan (progesterone capsules).

We also acknowledge receipt of your amendments dated October 23 and December 9, 1987; March 15, 1988; May 24, July 17, August 4 and 22, September 5 and 21, 1989; and January 24, 19, and 30, February 7, 16, and 23, April 3 and 9, May 11, and June 5, 1990.

We have completed our review and find that the information presented is inadequate and that the application is not approvable. The deficiencies are as follows:

1. Under section 505(d) of the Act and Title 21 of the Code of Federal Regulations (CFR) section 314.125(b), you have failed to provide substantial evidence consisting of adequate and well-controlled studies, as defined in 21 CFR 314.126, that Utrogestan will have the effect it is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.

   The application contained a single study by Dr. Simon in patients with secondary amenorrhea. Utrogestan 300 mg was found to be statistically significantly different from placebo and from Utrogestan 200 mg; Utrogestan 200 mg was not statistically significantly different from placebo.

   The single study by Dr. Vargyas regarding the effects on the endometrium indicated that micronized progesterone at a dose of 200 mg per day for 14 days each cycle is not a good progestational agent and does not satisfactorily transform proliferative endometrium into secretory endometrium.

   The submitted published articles by Lane *et al.* (*British Medical Journal*, Volume 287, October 29, 1983) and King and Whitehead (*Fertility and Sterility*, Volume 46, December 1986) do not provide substantial evidence of a good progestational response with a dose 300 mg/day micronized progesterone.

   The application does not, therefore, provide substantial evidence of the efficacy of Utrogestan as claimed in the labeling.

2. The application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b) because it fails to provide the following bioavailability and bioequivalence information:

a. Review of the calculated AUC values for the different pharmacokinetic studies indicates that different values were submitted in the original NDA submission dated September 30, 1987, as compared to the values given in the March 17, 1989, submission. For example, an $AUC_{(0-24)}$ value of 471.55 for patient in Study 1 was given in the September 30, 1987, submission (volume 3, page 713) in comparison to a value of 404.307 in the March 17, 1989, resubmission (page 143). Please explain the discrepancies in the calculated AUC values for the different studies and indicate which values are correct. If the conclusions of the different studies are based upon incorrectly calculated AUC values, then new data analyses using the correct values will be required.

b. In Studies 1 and 2, the study designs were less than ideal with respect to bioavailability/pharmacokinetic considerations. That is, on Day 5 (assuming steady state) a complete blood level profile was not characterized over the entire 24 hr dosing interval (i.e., samples were only collected up to 10 hr post-dosing). This approach limits the utility of the results for accurately assessing drug accumulation (i.e., using AUC) and the overall effect of food on progesterone's oral availability under chronic administration and analyzing the steady state dose proportionality for the package insert's proposed dosing regimen. You should address these concerns and provide justification and additional data analyses as appropriate (e.g., the degree of error that is imposed as a result of using truncated AUC values on Day 5, etc.) to help support the accuracy of the conclusions from these studies.

c. In Study 3, two consecutive doses each of oral Utrogestan (200 mg Q.D.) and a marketed intramuscular (IM) product (50 mg Q.D.) were given in which blood samples were collected from Day 1 to 72 hr post dose on Day 2. From this study, you attempt to assess the relative bioavailability of the proposed market capsule to a marketed intramuscular reference product using $AUC_{(0-72)}$ following the Day 2 dose (i.e., actually $AUC_{(24-96)}$ following the dose at time zero on Day 1). Because of the limitations of this approach, we believe that the determined results are probably less than accurate.

For example, inspection of the observed blood level results indicates (i) for neither of the two study treatments are progesterone levels back to baseline before the Day 2 dose and (ii) steady state is not achieved by Day 2 (especially for the intramuscular dose) for which Day 2 $AUC_{(0-24)}$ values could have been used if steady state had been achieved. Due to progesterone levels being carried over from the first dose on Day 1 and the continuing accumulation of progesterone on Day 2 (especially for the IM route), the net result is that the relative bioavailability calculations using only Day 2 $AUC_{(0-72)}$ values will be biased. Therefore, based upon the study design employed, it would be better to use AUC calculated from Day 1 plus Day 2 to infinity to arrive at a more accurate assessment of relative bioavailability. You should determine the elimination rate constants and half lives for progesterone for each product and then conduct the relative bioavailability data analysis accordingly.

d. The application has only used t-tests for statistical comparisons and should have used analysis of variance (ANOVA) in order to analyze different sources of variation. The use of only a t-test does not allow one to ascertain effects other than the treatment comparison. The ANOVAs should use the following statistical model: Response = Sequence, Subject(Sequence), Period, and Treatment. This should be provided for all studies wherever applicable and then the Two One Sided Test Procedure should be employed for the treatment comparisons (see *Journal of Pharmacokinetics and Biopharmaceutics*, vol 15, no.6, 1987, pp 657-680) as for the dose normalized values (e.g., AUC and C_{max}) for study 2.

e. For Studies 1 and 2, you should establish when steady state was achieved in these studies (e.g., statistical analysis using C_{min} values using the ANOVA and the Two One Sided t-test Procedure).

f. The submission (volume 3 of 5, page 384) states that, "The Utrogestan product tested in the pharmacokinetic studies submitted in the application has a formulation identical to the product proposed for marketing in the U.S." It is further indicated that, "The formulation submitted to the IND with the study protocol was not used. Prior to initiation of the pharmacokinetic studies, the formulation of the capsule shell was changed to remove the parabens." You should address the following issues:

(1) Was the capsule formulation used in each of the pivotal clinical safety and efficacy studies the exact same formulation as was used in the pharmacokinetic studies and which is to be marketed?

(2) You should provide a table that lists each pivotal clinical and pharmacokinetic study number, the formulation of the capsule tested in each study, the batch number, the size of the batch, information whether it was a pilot or production size batch and whether it was made on production size equipment plus information about the mean size and range of the drug particles per study batch.

g. Metabolism as well as protein binding data should be submitted. These data could be obtained from the literature.

h. In Study 2, the dose proportionality of progesterone was studied at 100, 200 (2 * 100 mg capsule) and 300 mg (3 * 100 mg capsules) under fasting conditions. Knowing the significant effect of enhanced oral availability of progesterone when given with food at the 200 mg dose, it is important to know the consequences of food on the dose proportionality of the 300 mg dose. You should address this point with respect to the conduct of the clinical safety and efficacy studies.

3. We remind you that the labeling must comply fully with 21 CFR 201.57. We also have the following comments regarding the labeling:

We are reserving further comment on the proposed label and labeling until the application is found adequate in other respects.

We also have the following additional comments regarding the biopharmaceutics section of the applications:

1. You should clearly indicate how you have measured drug concentrations that exceeded the highest concentration of the linear dynamic range of the assay's standard curve for the collected blood samples. (The procedure involved, such as dilution or linear interpolation, should be clarified and documented).

2. It would be helpful if you provided for each study, the plasma concentration versus time plots for each study subject (preferably comparative treatment plots on the same scale). The data points should be joined in the plots in order to get a better idea of the fluctuations or patterns in drug blood levels.

3. You should define the meaning of "s.d." or "cv"; e.g., on page 382 of vol. 1.3, the summary table lists the parameters as mean ± cv (coefficient of variation). Tables IV to VIII on pages 459 through 464 list the same parameters as mean ± s.d. (standard deviation).

4. For appropriate evaluation of the rupture test, the application should include the individual capsule rupture times. The data should be provided with the mean and coefficient of variation.

5. In Study 1 which evaluated the effect of food on Utrogestan absorption, it was shown that food increased the extent of progesterone's oral availability about two-fold based upon mean AUC values and increased peak drug concentrations about four-fold based upon mean peak concentrations. The application should indicate if, in the pivotal clinical safety and efficacy studies, patients were instructed to take Utrogestan with or without meals or whether they were uncontrolled as to when Utrogestan was given in relation to meals. Additionally, the application should

describe the dosing regimens with respect to meals in all of the pivotal clinical studies -- knowing that food appears to significantly affect the oral availability of progesterone.

Within 10 days after the date of this letter, you are required to amend the application or notify us of your intent to file an amendment or follow one of the other options under 21 CFR 314.120. In the absence of such action FDA may take action to withdraw the application. Any amendment should respond to all the deficiencies listed. A partial reply (one which does not address all remaining outstanding deficiencies) will not be processed as a major amendment, nor will the review clock be reactivated until all deficiencies have been addressed.

Should you have any questions regarding this NDA, please contact Ms. Enid Galliers at 301-443-3490.

Sincerely yours,

/S/ 8/9/90

Solomon Sobey, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research

8.1.90
eng

cc: NDA Arch.
HFD-510
HFD-500/LRipper
HFD-80
HFD-510/RBennett/KRaheja/HNunn
HFD-426/JHunt
HFD-713/DMarticello
HFD-510/EGalliers/7.16,17,18,19.90/8.1.90/ft/8.1.90/ \19781na2.nda
Concurrences:REastep/DHertig/AJordan/HNunn/7/18/YChiu/7/19/RBennet/7/20/90/
PCorfman/7/20/PSathe/JHunt/8/1/90/

NOT APPROVABLE

JAN 29 1990

NDA 19-781

LaSalle Laboratories
Attention: Mr. Michael X. Morrell
1717 N Street, N.W.
Washington, D. C. 20036

Dear Mr. Morrell:

Reference is made to your new drug application submitted September 30, 1987, pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act and resubmitted March 17, 1989, for Utrogestan (progesterone) Capsules, NDA 19-781.

We also refer to the telephone conversation of January 26, 1990, between Mr. Jay Bua, of your firm, and Ms. Rita Hassall, of our staff.

In that conversation, it was mutually agreed that there would be an extension of the review time (30 days) for this application as provided for under 21 CFR 314.100(c). The new due date is February 26, 1990.

If you have any questions, please contact Ms. Rita R. Hassall at 301-443-3510.

Sincerely yours,

/S/ 1/29/90

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research

cc: NDA Arch
HFD-80
HFD-510 RHassall 1/29/90
HFD-510/RHassall 1/26/90
Concurrences:Eastepl.26.90
Due Date Extension

UtroExt

MAY 3 1 1989

NDA 19-781

La Salle Laboratories
Attention: Michael X. Morrell
c/o Akin, Gump, Strauss, Hauer and Feld
1333 New Hampshire Ave, NW, Suite 400
Washington, D.C. 20036

Dear Mr. Morrell:

Reference is made to your pending new drug application for Utrogestan (progesterone USP) Capsules, NDA 19-791.

We have completed our initial review of the chemistry, manufacturing and controls information in this application, and we have identified deficiencies, that if not corrected, would make the application not approvable under section 505(b)(1) of the Act and 21 CFR 314.125(b).

The deficiencies are as follows:

1. An authorization letter from is necessary to allow reference to their DMF for the composition of the

2. The identity test methods for the capsules must be revised to specify the use of the USP progesterone reference standard as stated on p. 1085. Additionally, the methods should be rewritten in the style, format, and terminology used by the USP, e.g., "control" solution should be "standard" solution and "revealing" reagents should be "spray" reagents or solutions. Copies of a typical curve obtained with these methods should be submitted.

3. The proposed stability-indicating assay method should be revised to include a system suitability test. Specify the use of the USP progesterone reference standard, and define "DDS" and "1 vik of pic A reagent". In addition, validation data in support of the method's specificity, accuracy, precision, linearity and limits of detection for degradation products should be submitted.

4. In the protocol for domestic stability studies it is recommeded that testing of the room temperature samples after 6 months be included.

5. The stability data (including profiles) generated for the four lots described on p. 098 must be submitted.

6. Before the submitted European stability data can be considered as supporting data, a complete description of the sample packaging must be provided and a more complete description of the results should be included since the spectrophotometric analysis is not stability-indicating.

7. It is necessary that you submit three copies of a new Methods Validation Package which includes the following items. However, it is not necessary to include draft labeling in the package:

   a. A List of Samples that specifies the amount and lot number of each sample to be submitted.

   b. A complete composition statement for the capsules.

   c. The revised analytical methods as described above including your validation data.

   d. The rupture test method submitted in the March 3, 1989 amendment.

   e. Your analytical results obtained on the samples to be submitted including copies of tracings.

8. Regarding the submitted draft labeling, on the display panel of the carton labels and the blister label, La Salle Laboratories must be qualified by one of the phrases required by 21 CFR 201.1(h)(5).

Please submit the required information as soon as possible so as not to delay further review.

Sincerly yours,

/S/ 5/30/89

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research

cc:
HDA Arch
HFD-510
HFD-510/Nunn 5/26/89
HFD-510/RHassall 5/13/89/ft/ras/5/25/89/3215H
Concurrence:REastep/Nunn/Chiu/5/15/89
US

Utro.Chem

NDA 19-751

APR 18 1988

Besins Pharmaceuticals, Inc.
Akin, Gump, Strauss, Hauer and Feld
Attention: Michael X. Morrell
1333 New Hampshire Ave., N.W., Suite 400
Washington, D.C. 20036

Dear Mr. Morrell:

Reference is made to the new drug application submitted September 30, 1987 on behalf of Besins Pharmaceuticals, Inc. for Utrogestan (progesterone, USP) Capsules, NDA 19-751, which was subsequently found not suitable for filing by this Agency.

A full Biopharmaceutics review was not done because the NDA was not filed. However, in an abbreviated review of the submission the following deficiencies were noted:

1. The various pharmacokinetic parameters for each subject in each study should be tabulated. Only the mean values for the AUC, Tmax and Cmax for all three studies were provided.

2. Though the assay procedure was provided, proper assay validation data was not. You should provide the various standard curve values for all the different runs. You should also calculate the accuracy and precision of the assay and indicate the sensitivity of the assay as validated in your laboratory.

3. You indicate that comparative dissolution data are not necessary for this application since USP states that liquid filled soft gelatin capsules are exempt from any dissolution and disintegration requirements. However, you should consult with the Division of Biopharmaceutics to discuss the need for an in vitro quality control test.

Sincerely yours,

4/18/88

Solomon Cobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFN-810
Center for Drug Evaluation and Research

cc:NDA Arch. RHassall 4/15/88
HFN-810
HFN-810/RHassall 4/14/88/ft/jat/4/15/88
Concurrence:RBennett/Corfman/4/14/88
Letter Out

Wang 1342r

NDA 19-781

Besins Pharmaceuticals, Inc.
c/o Akin, Gump, Strauss, Hauer and Feld
Attention: Mr. Michael X. Morrell
1333 New Hampshire Avenue, Suite 400
Washington, D.C. 20036

Dear Mr. Morrell:

Reference is made to the new drug application (NDA) submitted by you on behalf of Besins Pharmaceuticals, Inc. for Utrogestan Capsules, NDA 19-781.

On the basis of our review of the NDA received on October 8, 1987 and acknowledged on October 16, 1987, we have determined that the application is not acceptable for filing under 21 CFR 314.101.

The application is not sufficiently complete to permit a substantive review. Specifically, the deficiencies are as follows:

1. The application provides no clinical studies which demonstrate the efficacy and safety of the drug for the indications sought.

2. Literature reports are provided but are not relevant to an evaluation of the safety and effectiveness of the drug for the proposed indications.

Further, the DESI notice (DESI 9238) which you referenced states that FDA concluded that progesterone injection, not oral progesterone, is effective for use in amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer. Therefore, Utrogestan, a capsule for oral administration, is not covered by this Notice.

Within 30 days of the date of this letter, you may request in writing an informal conference about FDA'S refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

Sincerely yours,

11/30/87

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFN-810
Office of Biologics Research and Review
Center for Drugs and Biologics

11/25/87

cc: Orig. NDA
HFN-810
HFN-810/RHassall 11/19/87rev per RBennett 11/25/87/ft/jaf/11-25-87
Concurrences: REastep 11/23 DHertig AJordan RBennett PCorfman 11/24/87
Refusal to file
Wang 0271r

NDA 19-781

Besins Pharmaceutical, Inc.
c/o Akin, Gump, Strauss, Hauer and Feld
Attention: Mr. Michael X. Morrell
1333 New Hampshire Avenue, Suite 400
Washington, D. C. 20036

OCT 16

Dear Mr. Morrell:

We have received the new drug application you have submitted on behalf of Besins Pharmaceutical, Inc. pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Utrogestan Capsules

Date of Application: September 30, 1987

Date of Receipt: October 8, 1987

Our Reference Number: 19-781

Unless we find the application not acceptable for filing, the filing date will be December 8, 1987.

Please begin any communication concerning this application be citing the NDA number listed above. Should you have any questions conerning this NDA, please contact Ms. Rita Hassall at (301) 443-3510.

Sincerely yours,

10/16/87

Roger D. Eastep
Supervisory Consumer Safety Officer
Division of Metabolism and
Endocrine Drug Products, HFN-810
Office of Biologics Research and Review
Center for Drugs and Biologics

cc:Orig. NDA 10/16/87
HFN-810
HFN-810/RHassall 10/14/87/ft/hgr/10/15/87
Concurrence: REastep/10/14/87

Acknowledement

Wang 7031R

NDA 19-781
Prometrium (Progesterone USP) Capsules 100 mg
Schering Corporation

November 3, 1995 cover letter

The cover letter from the submission dated November 3, 1995, for a Statistical review (temporary jacket) was not found.

JUN 19

NDA 19-781
Utrogestan (micronized progesterone)

June 8, 1995
Schering-Plough

Memorandum of Teleconference

Industry Participants:
Ms. Barbara Matolsz; Regulatory Affairs
Doreen Lechner, Ph.D.; Regulatory Affairs
Robert Alekel; Regulatory Affairs
Nicholas DeAngelis, Ph.D.; Analytical
Stephen Liebowitz, Ph.D.; Process Development

FDA Staff:
Dr. Chiu
Dr. Srinivasachar
Ms. Kish

Discussion and Conclusion:

The sponsor requested this meeting to discuss their modified stability program which they plan to submit within the next three months. The sponsor now has a dissolution test based on a biodisk (either USP test III or IV). They also wished to communicate a new piece of information regarding formulation; the proportion of small sized micronized progesterone particles appears to be critical in the manufacture of an acceptable tablet. Because of this the sponsor is refining their specifications. The sponsor was quick to point out that the specifications have not changed to the point that anything made previously is now outside specification, and therefore the tablets used in clinical trials are within the old and new specifications. The sponsor also noted that the tablets used in the clinical trials are made from micronized progesterone obtained from all new batches will be made from material obtained from

Dr. Chiu noted the division would require at least one stability batch be produced in the United States if they wish to include the US site in their amendment. The sponsor argued that they had historical data from that site already. Dr. Chiu noted that because the packaging materials have changed, and because the batch size in the historical data was less than ten percent of the proposed production batches, a stability batch from the US site will be required. Dr. Chiu also noted that in the December meeting with the sponsor, the division said that we would require a single material batch made in the U.S. The sponsor suggested amending the amendment in the fall with preliminary batch stability data from the U.S. site. Dr. Chiu said this would not be acceptable; however, it would be permissible to send, at the time of submission, three months of real time data and three months of accelerated data, and an amendment six months later with six more months of real time data (for a total of nine months) and an additional three months accelerated data. She reiterated by saying that before approval of a two year expiration date nine months of real time data and six months of accelerated data for stability would be required; she further noted that this was also agreed to in the December meeting.

The sponsor stated that a single lot had been used to make all three Canadian batches. Dr. Chiu said that as long as they were equivalent to the clinical batches that would be acceptable. The sponsor said that they will reevaluate the timing of submission of the

amendment taking into consideration the requirements for the U.S. site and that they would get back to us regarding when they expect to submit the amendment and whether the submission will include the U.S. site.

/S/

Christina Kish, CSO

6/14/95

cc:
Arch. NDA
HFD-510
HFD-510/YJohnson/EGalliers/SSobel
HFD-510/YChiu/KSrinivasachar
HFD-510/CKish/6.8.95/n19781.tc

Concurrences:KSrinivasachar 6.12.95/YChiu 6.13.95/EGalliers 6.19.95

MEETING MINUTES

NDA 19-781
Utrogestan (micrinized Progestin)

March 2, 1995
Schering

Memorandum of Meeting

Attending:

Dr. Sobel	Dr. Bennett
Dr. Corfman	Dr. Price
Dr. Bey	Ms. Kish

Industry Participants:

Ms. E. Krhour	Mr. C. Cuffie
Mr. A.S. Kaplan	Mr. R Spivey

Background:
Schering intends to respond to the deficiency letter for this NDA in July or August 1995, and wishes to discuss how the PEPI trial data for progestins in post-menopausal women might affect the labeling of their drug. Utrogestans indication is to be for secondary amenorrhea and abnormal uterine bleeding due to hormonal imbalance.

Discussion and Conclusion:
Dr. Sobel stated at the beginning of the meeting that no decisions regarding PEPI trial data had been made. Schering suggested that the PEPI trial data should change the class labeling of progestins. They also proposed that they put the PEPI trial data in the Precautions section of the labeling for Utrogestan despite the fact that the indicated population for Utrogestan is pre-menopausal, and the dose regimen short term. Their argument was that since many doctors might prescribe this off label, they should have access to the information via the precautions section. Schering suggested that the agency try to persuade the PEPI investigators to share their data with Schering. Dr. Sobel declined.

Schering asked how biopsy materials should be read; Dr. Corfman and Dr. Price told them that they will be required to have two independent readers with a third independent reader for conflict resolution. The pathologists should use Blaustein's text for their readings. With this the meeting was concluded.

/S/ 4/20/95

Christina Kish, CSO

cc:
NDA 19-781
HFD-510
Meeting Attendees
HFD-510/YJohnson
HFD-510/CKish/4.14,20.95/n19781.mm

Concurrences: SSobel 4.18.1995/PCorfman 4.18.1995/ABey 4.17.1995/RBennett 4.17.1995/PPrice 4.20.95

NDA 19-781
Prometrium
Schering Corporation

July 23, 1991

Memorandum of Meeting

Schering Representatives:

Michael Belman - Manager, Statistics
Alfred Chaikin - Director, Regulatory Affairs
Cynthia Cuffie, M.D, - Director, Clinical Research
Alex Giaquinto, Ph.D. - Vice President, World-wide Regulatory Affairs
Teddy Kosoglou, M.D. - Associate Director, Clinical Pharmacology
Rogerio Lobo, M.D. - USC School of Medicine (consultant)
Dean Moyer, M.D. - USC School of Medicine (consultant)

FDA Staff:

Dr. Sobel
Dr. Corfman
Dr. R. Bennett
Dr. Golden
Dr. Ragavan
Dr. Price
Dr. M. Bennett
Mr. Hertig
Ms. Braithwaite
Dr. Bradley (HFD-426)

Purpose:

The meeting was requested by Schering to discuss their proposed clinical program. This is in response to the Division's not approvable letter dated August 17, 1990.

Discussion and Conclusions:

Mr. Chaikin began the meeting with a brief overview of the proposed program. He indicated that there would be two studies to address the clinical pharmacology deficiencies, and one study to address the clinical deficiencies. See the submission dated July 11, 1991 for specific details.

Dr. Kosoglou continued with a presentation of the two clinical pharmacology studies. The first, to evaluate the effect of food on oral bioavailability on Prometrium, and the second, to evaluate the PK profile and dose-proportionality of progesterone after administration of Prometrium. He indicated that both studies would be performed in healthy male volunteers. Drs. Corfman and Golden asked why the study was not being performed in the proposed target population for the drug (young females). Dr. Kosoglou responded by stating that due to the type of studies being performed, the proposed study population (males) would minimize intra and inter-subject variability and should be sufficient. Dr. Bradley indicated that from his standpoint, male volunteers were acceptable. Dr. Sobel concurred.

Dr. Cuffie proceeded with a presentation of the proposed clinical program. She indicated that the objective of the study was to demonstrate the mechanism of action (progestational activity) of the product. She further indicated that the efficacy evaluation would be an overall clinical assessment of each endometrial biopsy using the following three categories: (1) Positive secretory activity, (2) No secretory activity, and (3) Marginal secretory activity. She stated that the morphological criteria used to determine this effect would be based upon the Noyes Criteria.

After the presentations by Schering, Dr. R. Bennett made the following points:

> In principle, the use of secretory changes are acceptable; however, the use of the "marginal" category will require further clarification. He continued (with consensus from other members of the Division) by stating that the overall program presented by Schering was acceptable.

At the meeting conclusion, Schering asked several questions regarding the development of their estrogen and/or progestin products for the indication of post menopausal hormone replacement therapy. The Division indicated that protocol designs should be developed based upon the specific labelled indications sought (e.g., treatment of vasomotor symptoms, prevention of osteoporosis, etc.), and encouraged additional meetings to discuss these proposals. Dr. Sobel indicated that one well-designed study demonstrating the lowest effective dose of added progestin for the prevention of endometrial hyperplasia would suffice for approval of a combined estrogen/progestin product. Dr. Hertig indicated that to fulfill the preclinical requirements for hormone replacement therapy (chronic use), a 2-year rat carcinogenicity study using the clinical form of the drug is required. The study should have three dose levels consisting of 100 females per group. The highest dose should be 50 times the human blood level of progesterone, and the lowest dose should be approximately equivalent to the human blood level. In addition, a rat dose-finding study will be necessary. To obtain blood levels, a 1-week study should be sufficient, however, if toxicity is expected or observed, a longer study may be necessary. He further indicated that the protocol should be submitted to the Division for review prior to implementation.

The representatives of Schering then expressed their gratitude to the Division for the comments and suggestions made in order to aid them in their drug development plans.

/S/

Lana L. Braithwaite, CSO

NDA 19-781
Utrogestan (micronized progesterone)

February 13, 1990
LaSalle Laboratories

MEMORANDUM OF MEETING

Representing LaSalle Laboratories:
Mr. Antoine Besins, Chairman of the Board
Mr. Michael Morrell, Pres. and CEO
Mr. Jay Bua, Managing Director
Bruno DeLignieres, M.D., Consultant
Allyn L. Golub, Ph.D., Consultant

FDA Staff:
Dr. Sobel
Dr. Corfman
Ms. Galliers
Dr. Troendle
Dr. R. Bennett

Purpose: The firm requested this meeting to discuss the firm's responses to the deficiencies identified in the January 22, 1990, meeting between LaSalle Laboratories and FDA.

Discussion and Conclusions: FDA stated that the data did not demonstrate that Utrogestan performs as a progestin in a number of respects, and therefore, the class labeling is inappropriate. LaSalle agreed and expressed its desire to change the labeling in whatever ways specified by FDA. LaSalle then reminded FDA that the only indication for which it was seeking approval was that of inducing withdrawal bleeding in premenopausal women, which LaSalle believed it had demonstrated. At the time of the initial submission, study of the withdrawal bleeding indication was suggested by FDA as the simplest study that could be done to support an NDA.

FDA stated that the 300 mg dosage did not induce the anticipated late secretory and fine structural changes in many of the subjects - leading to the doubt that the dosage was high enough. The incidence of withdrawal bleeding was approximately 80%. LaSalle said that withdrawal bleeding was achieved even with the 200 mg dose. A discussion ensued as to whether the classical definition based on secretory and fine structure changes or the more modern efficacy assessment would be used to evaluate the efficacy of this drug. The firm claimed that >80% induction of withdrawal bleeding was a very satisfactory result and that the drug should be approved for that indication.

1. Further discussion led to the agreement that LaSalle would search the literature to provide evidence or assurance that 80% induction of withdrawal bleeding was as good as or better than the efficacy of other progestins.

2. A number of suggestions and requirements were made by FDA with respect to the labeling of this drug as stated below, and the firm agreed to revise its labeling and submit it immediately.

   a. Class labeling will not be used. The only indication will be the treatment of secondary amenorrhea, and the efficacy rate for the induction of withdrawal bleeding will be stated as will be the extent of secretory change.

   b. Because of the possibility that physicians may use this micronized progesterone as part of a hormone replacement regimen, the labeling will state that there is no evidence establishing the efficacy of this product for endometrial protection in a postmenopausal population.

   c. FDA suggested that a cautionary statement be included stating that there is no (or insufficient) evidence regarding the safety of long-term use of this drug.

   d. The section of the labeling describing the mode of action will be modified accordingly.

Although FDA proposed discussion of this drug and the appropriate criteria for assessing its efficacy at the June F+MH Advisory Committee, the firm stated that it hoped for an approval well before then - although participation in such a debate would be interesting. Because the biopharmaceutics review has not been completed yet, Dr. Golub will confer independently with Mr. Hunt regarding those issues.

LaSalle requested a meeting or telephone conference with Dr. Price regarding Estrogel as soon as possible.

Post-meeting Note: Dr. Bennett recalled that the sponsor was to submit data demonstrating that biochemical end-points were better than histological secretory changes in demonstrating efficacy of progestins.

/S/

Enid Galliers, CSO

cc: NDA Arch.
HFD-510
HFD-510/Participants/REastep/RHassall/PPrice
HFD-510/EGalliers/2.16.90/ft/3/2/90/ \19781eor.mom
Concurrences:RBennett/PCorfman/GTroendle/SSobel/2/21/90/RBennett/2/28/90

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19-781

CORRESPONDENCE

DUPLICATE

SCHERING CORPORATION

GALLOPING HILL ROAD KENILWORTH, N. J. 07033

CABLES: SCHERING KENILWORTH
TELEX: 138316
138280
TELEPHONE: (908) 298-4000

ORIG AMENDMENT
BL

May 6, 1998

Lisa Rarick, M.D., Director
Division of Reproductive & Urologic Drug Products
for Drug Evaluation and Research
5600 Fishers Lane
HFD-580, Room 17B-45
Rockville, MD 20857

NDA 19-781
PROMETRIUM® Capsules
100 mg (Progesterone)

SUBJECT: GENERAL CORRESPONDENCE - REVISED DRAFT LABELING

In reference to our May 4, 1998 telephone conversation with Diane Moore, we have incorporated the requested reference (Med Sci Res 1987; 15:703-704) into the Prometrium Labeling on Page 10 (See attached revised labeling). In reference to our Phase IV commitment, please refer to the June 11, 1997 (corrected June 23, 1997) Memorandum of Telecon between Ms. Diane Moore, CSA, and Ms. Paula Rinaldi of Schering Corporation. Ms. Moore confirmed that the pharmacokinetic study (as included in the description of the Phase IV study commitment in the March 28, 1997 action letter) was not required for the Phase IV study for this application.

The Phase IV commitment

As agreed in our November 12, 1996 letter, we commit to this Phase IV study.

It is our intention to provide a draft protocol by the end of 3rd Quarter 1998.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

Tonya L. Johnson

for Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

TJ/sb

Desk Copy: Diane Moore

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Schering Corporation	5/1/98
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number *(Include Area Code)***
(908) 298-2628	(908) 298-2243

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*

2000 Galloping Hill Road
Kenilworth, New Jersey 07033

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

Joseph F. Lamendola, Ph.D.
Vice President
2000 Galloping Hill Road
Kenilworth, NJ 07033

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 19-781

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
progesterone, USP	PROMETRIUM®

CHEMICAL/BIOCHEMICAL /BLOOD PRODUCT NAME *(if any)*	CODE NAME *(if any)*
Pregna-4-ene-3, 20 dione	SCH 961

DOSAGE FORM	STRENGTHS	ROUTE OF ADMINISTRATION
Soft Gelatin Capsule	100 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Secondary Amenorrhea

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING, AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION
Final Draft Labeling

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
	1. Index
X	2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
	17. Field copy certification (21 CFR 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Paula E. Rinaldi /for Dr. Lamendola	Joseph F. Lamendola, Ph.D. Vice President, U.S. Regulatory Affairs	5/1/98

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2000 Galloping Hill Road, Kenilworth, NJ 07033	(908) 298-2628

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Washington, DC 20201

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FORM FDA 356h (7/97)

SCHERING CORPORATION

ORIGINAL

CALLOPING HILL ROAD KENILWORTH, N.J. 07033

NEW CORRESP

CABLES: SCHERING KENILWORTH NC
TELEX 138316
138280
TELEPHONE (908) 298-4000

April 7, 1997

Lisa Rarick, M.D., Acting Director
Division of Reproductive and Urologic Drug Products
HFD-580, Room 17B-45
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

NDA 19-781
PROMETRIUM®
(progesterone, USP) Capsules

SUBJECT: GENERAL CORRESPONDENCE

Dear Dr. Rarick:

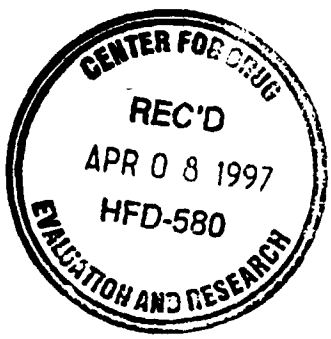
We acknowledge receipt of your March 28, 1997 NDA approvable letter and are informing you of our intention to submit an amendment to the NDA, with revised labeling and updated safety information.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

for/ Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

PER:dm



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noted 8-12-96

SCHERING CORPORATION

NEW CORRESP

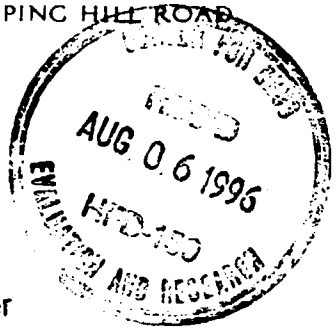
ORIGINAL

NC

CALLOPING HILL ROAD KENILWORTH, N. J. 07033

CABLES SCHERING KENILWORTH
TELEX: 138316
138280
TELEPHONE (908) 298-4000

AJ 8/13/96



August 1, 1996

Ms. Nancy B. Sager
Center for Drug Evaluation and Research
HFD-357
5600 Fishers Lane
Rockville Maryland 20857

NDA 19-781
PROMETRIUM Capsules
(Progesterone)

SUBJECT: REVISIONS TO THE ENVIRONMENTAL ASSESSMENT REPORT FOR NDA 19-781 AS DISCUSSED DURING OUR PHONE CONVERSATION OF AUGUST 1, 1996

Noted - NAI
D Davis
8/13/96

Dear Ms. Sager:

Schering Corporation authorizes FDA to modify the Environmental Assessment submitted in the 2/8/96 Amendment to NDA 19-781 for PROMETRIUM Capsules to include the name and address of the dosage form manufacturer, R.P. Scherer North America, formerly designated as Contract Manufacturer #2. The name and address should be added to the following FOI releasable portions of the EA:

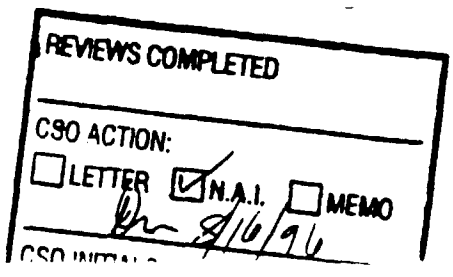
Item 4c Production Locations
Item 6 Site of Manufacture of the Drug Product

R.P. Scherer's name and address are provided below:

R.P. Scherer North America
2725 Scherer Drive
St. Petersburg, Florida 33716

All other information provided in Appendices 2 and 3 will remain confidential as originally submitted in the 2/8/96 Amendment to NDA 19-781.

The above changes will assure consistency between the labeling proposed in the 2/8/96 Amendment to NDA 19-781 and the Environmental Assessment Report.



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Sincerely,

Alexander R. Glaquinto, Ph.D.
Senior Vice President
Worldwide Regulatory Affairs

DMF:dc

Desk Copy: Ms. Patricia Stewart, HFD-510, Room 14B-04

SCHERING CORPORATION

CALLOPING HILL ROAD KENILWORTH, N. J. 07033

CABLES: SCHERING KENILWORTH
TELEX: 138316
138280
TELEPHONE: (908) 298-4000

May 13, 1998

Lisa Rarick, M.D., Director
Division of Reproductive & Urologic Drug Products
for Drug Evaluation and Research
5600 Fishers Lane
HFD-580, Room 17B-45
Rockville, MD 20857

NDA 19-781
PROMETRIUM® Capsules
100 mg (Progesterone)

SUBJECT: GENERAL CORRESPONDENCE

We have committed to conducting a Phase IV safety and efficacy study of Prometrium 300 mg and 400 mg doses in women with secondary amenorrhea. As noted in our May 6, 1998 letter, we intend to provide a draft protocol for this study by the end of third quarter 1998. We now wish to inform you that pending agreement on the protocol design, we intend to initiate this study during the first quarter 1999. Given the nature of the study, and the stringent inclusion/exclusion criteria, we estimate that it will take approximately eighteen months to enroll all subjects. We therefore plan to submit a complete study report to the NDA by early 2001.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

Paula C Riviello

for/ Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

PR/sb
Desk Copy: Diane Moore

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Schering Corporation	May 13, 1998
TELEPHONE NO. *(Include Area Code)* (908) 298-2628	**FACSIMILE (FAX) Number** *(Include Area Code)* (908) 298-2243

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:

2000 Galloping Hill Road
Kenilworth, New Jersey 07033

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

Joseph F. Lamendola, Ph.D.
Vice President
2000 Galloping Hill Road
Kenilworth, NJ 07033

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 19-781

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
progesterone, USP	PROMETRIUM®

CHEMICAL/BIOCHEMICAL /BLOOD PRODUCT NAME *(if any)*	CODE NAME *(if any)*
Pregna-4-ene-3, 20 dione	SCH 961

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Soft Gelatin Capsule	100 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Secondary Amenorrhea

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING, AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION
General Correspondence

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)