

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

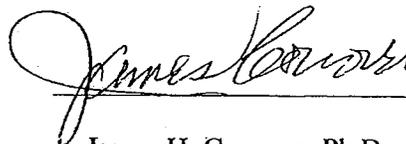
22-057

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

1.3.5.1 PATENT INFORMATION STATEMENT

Ferring knows of no patents that claim this drug or a method of using this drug to which a claim of patent infringement could reasonably be asserted.

Signature:

A handwritten signature in cursive script, reading "James H. Conover", written over a horizontal line.

Name of Responsible Person:

James H. Conover, Ph.D.
Executive Director,
Regulatory Affairs

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER
NDA#22-057
NAME OF APPLICANT / NDA HOLDER
Ferring Pharmaceuticals Inc.
400 Rella Blvd.(Suite 300)
Suffern, NY 10901

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Endometrin (progesterone) Vaginal Tablet

ACTIVE INGREDIENT(S)
progesterone

STRENGTH(S)
100 mg

DOSAGE FORM
Vaginal Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
d. Name of Patent Owner	Address (of Patent Owner)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	<input type="checkbox"/> Yes	<input type="checkbox"/> No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

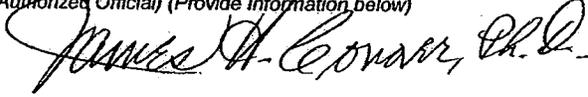
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed
8/21/2006



NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Address

City/State

ZIP Code

Telephone Number

FAX Number (if available)

E-Mail Address (if available)

(845) 770-2003

JIM.CONOVER@FGLKING.COM

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 22-057

SUPPL # 000

HFD # 580

Trade Name Endometrin® Vaginal Insert

Generic Name (progesterone)

Applicant Name Ferring Pharmaceuticals, Inc.

Approval Date, If Known 21-JUN-2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-701 Crinone®/Prochieve® (progesterone) Vaginal Gel
NDA# 19-781 Prometrium® (progesterone) Capsule
NDA# 17-362 Progesterone for injection

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

N/A

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 2004-2

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form:
John C. Kim, RPh, JD
Title: Regulatory Health Project Manager
Date: 21-JUN-2007

Name of Office/Division Director signing form:
Scott Monroe, MD
Title: Acting Director, Division of Reproductive and Urologic Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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this page is the manifestation of the electronic signature.**

/s/

Scott Monroe
6/21/2007 05:39:23 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-057 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: 21-AUG-2006 PDUFA Goal Date: 21-JUN-2007

HFD 580 Trade and generic names/dosage form: Endometrin® (progesterone) Vaginal Insert

Applicant: Ferring Pharmaceutical, Inc. Therapeutic Class: 3S

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: To support embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
 No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
 Disease/condition does not exist in children
 Too few children with disease to study
 There are safety concerns
 Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

NDA 22-057

Page 3

This page was completed by:

{See appended electronic signature page}

John C. Kim, RPh, JD
Regulatory Health Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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/s/

John C. Kim
6/21/2007 08:05:19 AM

1.3.3 Debarment Certification

Pursuant to FDA's "Guidance for Industry: Submitting Debarment Certification Statements", Section 306(K)(1) of the FD&C Act; 21 U.S.C. 335a(k)(1), Ferring Pharmaceutical Inc. submits the following Debarment Certification:

The undersigned certifies that Ferring Pharmaceuticals Inc. did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [Section 306(a) or (b), in connection with the Endometrin® (NDA 22-057).

Signature:



Name of Responsible Person:

James H. Conover, Ph.D.
Executive Director,
Regulatory Affairs



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-057

NDA ACKNOWLEDGMENT

Ferring Pharmaceuticals, Inc.
Attention: James H. Conover, Ph.D.
Executive Director, Regulatory Affairs
400 Rella Boulevard, Suite 300
Suffern, NY 10901

Dear Dr. Conover:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Endometrin [®] (progesterone) Vaginal Tablet, 100 mg
Review Priority Classification:	Standard (S)
Date of Application:	August 21, 2006
Date of Receipt:	August 21, 2006
Our Reference Number:	NDA 22-057

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 20, 2006, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 21, 2007.

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. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

NDA 22-057

Page 2

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-0932.

Sincerely,

{See appended electronic signature page}

John C. Kim, R.Ph., J.D.
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

John C. Kim
9/1/2006 11:17:58 AM

Kim, John

From: ron.hargreaves@ferring.com
Sent: Monday, June 18, 2007 8:37 AM
To: Kim, John
Subject: RE: Endometrin sales figures for Israel

John,

Here is the information on sales of Endometrin in Israel. Since we have sales information for Hong Kong I am providing this also.

Regards,

Ron Hargreaves

Endometrin Sales in Israel and Hong Kong

Israel

of tablets

/

/

b(4)

2007 (Forecast)

Hong Kong

of tablets

/

/

b(4)

(Forecast)

From: Kim, John [mailto:john.kim@fda.hhs.gov]
Sent: Friday, June 15, 2007 5:51 PM
To: Hargreaves, Ron
Subject: RE: Endometrin sales figures for Israel

Only Israel is needed, but if you want to provide Hong Kong as well, that would be fine.

From: ron.hargreaves@ferring.com [mailto:ron.hargreaves@ferring.com]
Sent: Friday, June 15, 2007 5:28 PM
To: Kim, John
Subject: Endometrin sales figures for Israel

6/21/2007

John,

I have the information on sales of Endometrin in Israel but I think there may be a typo in the numbers. Rather than send you a possibly incorrect report I have asked my colleagues in Europe to check the numbers. I expect to receive a response on Monday morning and I will then send the sales information to you. I will also provide information on sales in Hong Kong at the same time.

Regards,

Ron

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6/21/2007

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/s/

John C. Kim
6/21/2007 03:36:19 PM
CSO

Kim, John

From: ron.hargreaves@ferring.com
Sent: Friday, June 15, 2007 12:15 PM
To: Kim, John
Subject: NDA 20-057;Endometrin; Packaging materials

John,

As per your request earlier this week, we commit to modifying our packaging materials, at the next printing, such that the "brush stroke" will not cover part of the product name, Endometrin.

Best regards,

Ron Hargreaves

R. T. Hargreaves, Ph.D.
Vice President, Regulatory Affairs
Ferring Pharmaceuticals Inc.
4 Gatehall Drive, Third Floor
Parsippany, NJ 07054
Tel: 973-796-1620
Fax: 973-796-1694
Email: ron.hargreaves@ferring.com

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/s/

John C. Kim
6/21/2007 03:35:41 PM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-057 Supplement # 000 Efficacy Supplement Type SE- N/A

Proprietary Name: **Endometrin® Vaginal Tablet**
Established Name: **progesterone**
Strengths: **100 mg**

Applicant: **Ferring Pharmaceuticals, Inc.**
Agent for Applicant (if applicable): **N/A**

Date of Application: **August 21, 2006**
Date of Receipt: **August 21, 2006**
Date clock started after UN:
Date of Filing Meeting: **October 3, 2006**
Filing Date: **October 20, 2006**
Action Goal Date (optional):

User Fee Goal Date: **June 21, 2006**

Indication(s) requested: Pregnancy through progesterone supplementation as part of an (ART) treatment program for : _____ women. **b(4)**

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES

2. This application is an eNDA or combined paper + eNDA YES

This application is: All electronic Combined paper + eNDA

This application is in: NDA format CTD format

Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cdet/guidance/2353fml.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, 3 Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO
- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 68,097
- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) 30-MAR-2005 NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 20-JUN-2006 NO
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
N/A YES NO

- Risk Management Plan consulted to OSE/IO? N/A YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO

- If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 3, 2006

NDA #: 22-057

DRUG NAMES: Endometrin® (progesterone) vaginal tablet

APPLICANT: Ferring Pharmaceuticals, Inc.

BACKGROUND: Endometrin is administered vaginally and is indicated for the progesterone supplementation as part of an Assisted Reproductive Technology treatment program for infertile women.

ATTENDEES: Gassman, Slaughter, McKinney, Wang, Apparaju, Christner, Sobhan, Kober, and Kim

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Audrey Gassman, MD
Secondary Medical:	Shelley R. Slaughter, MD, PhD
Statistical:	Mahboob Sobhan, PhD
Pharmacology:	Leslie McKinney, PhD
Statistical Pharmacology:	N/A
Chemistry:	Ying Wang, PhD
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Sandhya Apparaju, PhD
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	Pending
DSI:	
OPS:	N/A
Regulatory Project Management:	John Kim
Other Consults:	

Per reviewers, are all parts in English or English translation? YES NO

If no, explain:

CLINICAL FILE REFUSE TO FILE

- Clinical site audit(s) needed? YES NO
If no, explain:

- Advisory Committee Meeting needed? YES, date if known _____ NO

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
BIOPHARMACEUTICS		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• Biopharm. study site audits(s) needed?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
PHARMACOLOGY/TOX	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• GLP audit needed?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
CHEMISTRY		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• Establishment(s) ready for inspection?	YES <input checked="" type="checkbox"/>	NO <input type="checkbox"/>
	• Sterile product?	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
	If yes, was microbiology consulted for validation of sterilization?	YES <input type="checkbox"/>	NO <input type="checkbox"/>

ELECTRONIC SUBMISSION:

Any comments: electronic NDA in CTD format

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

John C. Kim, RPh, JD
Regulatory Health Project Manager

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this page is the manifestation of the electronic signature.**

/s/

John C. Kim
6/21/2007 09:14:14 AM
CSO

Kim, John

From: Delasko, Jeanne
Sent: Thursday, June 07, 2007 9:20 AM
To: Kim, John
Cc: Burke, Laurie B
Subject: Comments NDA 22-057: Endometrin

Attachments: DelaskoBurke.FinalReview.06.07.07.doc

Hi John,

Here are SEALD's comments. Laurie Burke has concurred. Let me know if you have questions.

Jeanne



DelaskoBurke.Fi
alReview.06.07.



NDA 22-057

INFORMATION REQUEST LETTER

Ferring Pharmaceuticals, Inc.
Attention: James H. Conover, Ph.D.
Executive Director, Regulatory Affairs
400 Rella Boulevard, Suite 300
Suffern, NY 10901

Dear Dr. Conover:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Endometrin[®] (progesterone) Vaginal Insert, 100 mg.

We also refer the teleconference between representatives you and the Agency on February 22, 2007, in which discussions regarding the established name were held.

We are reviewing the container/carton labeling section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

General Comments:

1. As discussed in the February 22, 2007, teleconference, your established name, "Progesterone — Vaginal — " should be changed to "(progesterone) Vaginal Insert." Therefore, all labeling (Package Insert, Patient Package Insert, blister label, and carton label) should state "Endometrin[®] (progesterone) Vaginal Insert, 100 mg." All references to vaginal — should be stated as "vaginal insert." b(4)
2. In the DESCRIPTION section of the Package Insert, add the established name to the running text and the therapeutic class of the drug.
3. In the HOW SUPPLIED section of the Package Insert, state the shape, color, and imprint information of the vaginal insert.

Regarding the Blister Label _____ : b(4)

1. See general comment 1.
2. Add the route of administration statement "For Vaginal Use Only." We recommend using a different font color to improve the readability and increase prominence (i.e. red).

Regarding the Inner and Outer Carton Labeling:

1. See general comment 1.
2. Increase the prominence of the strength commensurate with the proprietary and established names and add a space between the numerical strength "100" and the unit of measure "mg."
3. We recommend using a different font color to improve the readability and increase prominence of the route of administration statement "For Vaginal Use Only" (i.e. red) in the main panel.

Please note that additional comments regarding the format and content of the Package Insert and Patient Package Insert may follow.

If you have any questions, call John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 796-0932.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
Center of Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
4/11/2007 11:45:29 AM
Chief, Branch III



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-057

Ferring Pharmaceuticals, Inc.
Attention: James H. Conover, Ph.D.
Executive Director, Regulatory Affairs
400 Rella Boulevard, Suite 300
Suffern, NY 10901

Dear Dr. Conover:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Endometrin® (progesterone) Vaginal Tablet, 100 mg.

We also refer to the meeting between representatives of your firm and the FDA on February 22, 2007. The purpose of the meeting was to discuss CMC issues.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Linda Athey, Regulatory Health Project Manager for Quality, at (301) 796-2096.

Sincerely,

{See appended electronic signature page}

Donna Christner, Ph.D.
Pharmaceutical Assessment Lead
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 22, 2007
TIME: 10:30 – 11:30 AM
LOCATION: FDA/CDER
APPLICATION: NDA 22-057
DRUG NAME: Endometrin® (progesterone) vaginal insert
TYPE OF MEETING: Teleconference

MEETING CHAIR: Donna Christner, Ph.D.

MEETING RECORDER: Linda Athey

FDA ATTENDEES:

ONDQA/Division of Pre-Marketing Assessment II

Dr. Donna Christner, Pharmaceutical Assessment Lead
Dr. Ying Wang, Chemist
Linda Athey, Regulatory Health Project Manager

Office of New Drugs, Division of Reproductive and Urologic Products

John Kim, R.Ph., J.D., Regulatory Health Project Manager

FERRING PHARMACEUTICAL ATTENDEES:

Dr. Jim Conover, Regulatory Affairs
Dr. Ronald Hargreaves
Dr. Larry Huang

BACKGROUND:

CMC comments were emailed to the sponsor February 13, 2007 with a request for a teleconference with Ferring.

MEETING OBJECTIVES:

Discuss the established name, addition of microbial testing, and revise microbial specifications.

DISCUSSION POINTS:

FDA Comment 1:

Your proposal concerning the established name has been reviewed by ONDQA management. We recommend that the established name read: (progesterone) vaginal insert.

Discussion 1:

┌ The
API is inside the bracket and the dosage form is outside the bracket, ex. Endometrin®
(progesterone) vaginal insert.

b(4)

FDA Comment 2:

Add microbial test to your stability protocol at each time point. Also, perform microbial tests on the 3 stability lots and provide results to the Agency.

Discussion 2:

Because the moisture limit for the dosage form is — a microbial test is needed. Ferring proposed to perform microbial tests on the 3 lots currently on stability (Lots 0804.001, 0804.005, and 0804.006) and provide results to the Agency within 4-5 weeks. The sponsor proposed that if the results are satisfactory, they may not need to add microbial tests to their stability protocol at each time point. FDA agreed that if the results of microbial testing are satisfactory upon evaluation by the FDA, the decision on the frequency of the testing during stability would be revisited and the sponsor would be advised of our decision.

b(4)

FDA Comment 3:

Total aerobic microbial count limit of NMT _____ in the specification for excipient pregelatinized starch will lead to final tablet microbial count exceeding the microbial limit for drug product (NMT _____ because pregelatinized starch is _____ of the tablet. Revise your microbial specification for pregelatinized starch to conform to the drug product specification.

b(4)

Discussion 3:

Ferring agreed to reduce the microbial limit for the excipient pregelatinized starch to NMT _____. FDA stated that this was satisfactory and that the commitment must be officially submitted to the NDA in writing.

b(4)

Additional Discussion A:

Ferring has three batches on stability. Each of the three batches has now been tested and meets specifications after storage for 2 years. Can they submit this updated stability data? FDA stated that they could submit the data but requested that it be submitted as soon as possible but prior to 21-Mar-2007. If the information was submitted within 90 days of the PDUFA goal date we may need to either extend the clock or not review the data at our discretion.

Additional Discussion B:

The first batch of bulk product has been packaged and labeled using the suggested name "progesterone vaginal ____". Ferring asked if it was possible to use this batch as commercial or physician samples, using a sticker to cover the incorrect information with the correct information. FDA stated to submit the request in writing for our consideration and we would reply after review of the request.

b(4)

DECISIONS (AGREEMENTS) REACHED:

See above

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

Ferring will send an amendment with the updated stability data and include a statement that they agree with our request.

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/s/

Linda D Mullins-Athey
3/30/2007 01:19:30 PM
PROJECT MANAGER FOR QUALITY

Donna Christner
3/30/2007 01:29:07 PM
CHEMIST
I concur

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: February 15, 2007

TO: John Kim, Regulatory Project Manager
Audrey Gassman, M.D., Dental Officer
Division of Reproductive and Urologic Drug Products

THROUGH: Constance Lewin, M.D., M.P.H.
Chief, Good Clinical Practice Branch I (GCPB1, HFD-46)
Division of Scientific Investigations (DSI)

FROM: Roy Blay, Ph.D.
Reviewer, GCPB1, DSI, HFD-46

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-057

APPLICANT: Ferring Pharmaceuticals, Inc.

DRUG: Endometrin[®]

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Pregnancy through progesterone supplementation as part of an assisted reproductive technology treatment program for infertile women

CONSULTATION REQUEST DATE: September 14, 2006

DIVISION ACTION GOAL DATE: May 31, 2007

PDUFA DATE: June 21, 2007

I. BACKGROUND

The indication for the investigational drug Endometrin[®] is pregnancy through progesterone supplementation as part of an assisted reproductive technology treatment program for infertile women. This drug is not a New Molecular Entity.

In support of this NDA, FDA inspected protocol# 2004-02, entitled, "A Multi-Center, Randomized, Open-Label, Parallel Group Study of a Vaginal Micronized Progesterone Tablet (Endometrin[®]) Compared to Crinone 8% Vaginal Gel in Female Patients Undergoing In Vitro Fertilization (IVF)). The primary objective of this phase 3 study is to assess the efficacy of two different doses of the test article against the reference product Crinone 8% in terms of ongoing pregnancy rates in women undergoing IVF.

The following sites were selected for inspection for the protocol identified above based on enrollment numbers, adverse events, and reported protocol violations.

II. RESULTS (by site):

Name	City, State	Protocol	Inspection Date	EIR Received Date	Final Classification
Kevin Doody, M.D.	Bedford, TX	2004-02	30 Oct-2 Nov, 2006	29 Nov 06	NAI
Vicki Schnell, M.D.	Webster, TX	2004-02	14-20 Nov, 2006	26 Jan 07	NAI
Mostafa Abuzeid, M.D.	Rochester Hills, MI	2004-02	16-26 Oct, 2006	27 Nov 06	VAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

Protocol # 2004-02

1. Site# 05

Kevin Doody, M.D.
1701 Park Place Avenue
Bedford, TX 76022

- a. What was inspected: 130 subjects were screened with 19 screening failures. The records for 40 subjects were reviewed in depth for the following study parameters including, but not limited to, informed consent, inclusion/exclusion criteria, bleeding logs, transvaginal ultrasound reports, adverse event reporting, concomitant medication reporting, and diagnosis of ovarian hyperstimulation syndrome.
- b. Limitations of inspection: There were no limitations to the inspection.
- c. General observations/commentary: The inspection did not reveal any regulatory violations in the conduct of this study.

d. Data acceptability/reliability: The data appear acceptable in support of the relevant indication.

2. Site #019

Vicki Schnell, M.D.

Center for Reproductive Medicine

450 Medical Center Boulevard, Suite 202

Webster, TX 77598

a. What was inspected: 125 subjects were randomized to the study. The records for 34 subjects were reviewed in depth for the following study parameters including, but not limited to, informed consent, inclusion/exclusion criteria, bleeding logs, transvaginal ultrasound reports, and adverse event reporting.

b. Limitations of inspection: There were no limitations to the inspection.

c. General observations/commentary: The inspection did not reveal any regulatory violations in the conduct of this study.

d. Data acceptability/reliability: The data appear acceptable in support of the relevant indication.

3. Site #026

Mostafa Abuzeid, M.D.

IVF-Michigan

3950 S. Rochester Road, Suite 2300

Rochester Hills, MI 48307

a. What was inspected: Records were reviewed for the following study parameters including, but not limited to, informed consent, source data, IRB correspondence, laboratory results, adverse event reporting, concomitant medication reporting, and drug accountability.

b. Limitations of inspection: There were no limitations to the inspection.

c. General observations/commentary: Adverse events experienced by two subjects were not promptly reported to the IRB and sponsor. Subject 26-058 underwent a cholecystectomy that was not reported promptly to the IRB, and, while subject 26-001 reported back and leg pain, burning upon voiding and abdominal pain, the subject's CRF noted only uterine cramping.

d. Data acceptability/reliability: The data appear acceptable in support of the relevant indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL
RECOMMENDATIONS

The inspections of Drs. Doody and Schnell did not identify any regulatory violations. The inspection of Dr. Abuzeid noted two subjects who experienced adverse events that were not promptly reported. Overall, the data appear acceptable in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Reviewer, Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

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/s/

Roy Blay
2/15/2007 03:42:05 PM
CSO

Constance Lewin
2/20/2007 11:20:06 AM
MEDICAL OFFICER



INFORMATION REQUEST LETTER

NDA 22-057

Ferring Pharmaceuticals, Inc.
Attention: James H. Conover, Ph.D.
Executive Director, Regulatory Affairs
400 Rella Boulevard, Suite 300
Suffern, NY 10901

Dear Dr. Conover:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Endometrin[®] (progesterone) Vaginal Tablet, 100 mg.

We have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- 1) What was the central laboratory used for Chemistry and Hematology values in Study 2004-02?
- 2) How was the determination made between classifying a subject with the MedDRA preferred term of "vaginal haemorrhage" as opposed to "metrorrhagia"?
- 3) In Study 2004-01, a total of 8 subjects had undissolved vaginal tablets that were noted during gynecologic examination as follows:
 - 1 of 9 subjects (11%) in the 50 mg daily
 - 2 of 11 subjects (18%) in the 100 mg daily
 - 2 of 9 subjects (22%) in the 200 mg daily
 - 3 of 10 subjects (30%) in the 200 mg twice daily
 - a) Provide information on the time between the administration of the vaginal tablet on the final day, and when the gynecologic examination was performed for each of these subjects.
 - b) Provide details as to whether vaginal examination revealed one undissolved tablet per subject or whether more than one tablet was found.
- 4) In the Adverse Event (AE) dataset for Study 2004-02 in SOC_NM under "Infections and infestations," there are 9 AEs listed as "fungal infections NEC." It was also noted that there are 9 AEs listed as "vaginal mycosis." It appears that these adverse events may all be classified as vaginal mycosis. Confirm whether all of these "fungal infections NEC" are vaginal mycosis or other (and define other by organ category). If all of these "fungal

infections NEC" are actually vaginal candidiasis or vaginal mycosis, re-categorize them and recalculate these numbers into the preferred term of "vaginal mycosis." Report the numbers for each treatment group for vaginal mycosis and other in table format. If any of the treatment groups has vaginal candidiasis rates > 2%, resubmit Table 37 in the final study report for Study 2004-02 with the added numbers.

- 5) For Study 2004-01, some of the Subject Identifications and associated serum progesterone concentrations that were tabulated in the study report (2004-01.pdf) do not match with those submitted for analysis in the associated SAS transport file (ES0_PK.xpt). Explain the discrepancies for the following:

Group 1	50 mg QD	Data from subjects 2016 and 2035 are reported in the study report but not in the SAS transport file.
		Data from subject 2001 are included in the SAS file but not in the study report.
Group 2	100 mg QD	Data from subject 2021 are reported in the study report but not in the SAS transport file.
		Data from subject 2018 are included in the SAS file but not in the study report.
Group 3	100 mg BID	Data from subjects 2018 and 2023 are included in the study report but not the SAS file.
		Data from subjects 2016 and 2021 are included in the SAS file but not in the study report.
Group 4	200 mg QD	Data from subjects 2001 and 2039 are included in the study report but in the SAS file.
		Data from subject 2035 are included in the SAS file but not in the report study.
Group 5	200 mg BID	Data from subjects 2039 and 2040 are included in the SAS file but not in the study report.

- 6) The effect of concomitant vaginal product use (e.g., antifungal cream) on the pharmacokinetics of Endometrin needs to be addressed.

If you have any questions, call John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 796-0932.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph., M.P.A.
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
1/11/2007 10:21:41 AM



INFORMATION REQUEST LETTER

NDA 22-057

Ferring Pharmaceuticals, Inc.
Attention: James H. Conover, Ph.D.
Executive Director, Regulatory Affairs
400 Rella Boulevard, Suite 300
Suffern, NY 10901

Dear Dr. Conover:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Endometrin[®] (progesterone) Vaginal Tablet, 100 mg.

We also refer to your submission dated October 4, 2006.

We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Clinical

1. Confirm that there are no outstanding regulatory actions or safety issues regarding Endometrin[®] in the countries where the drug is currently approved and marketed.
2. We note that the total number of adverse events (AEs) in Table 37 does not appear to match the AE dataset (in the SAS transport file) for study 2004-02 using the variable AETERM. Check the total numbers of adverse events as listed in Table 37 against your SAS transport file AE dataset and make all corrections for all listed adverse events. Report the new percentages, and explain any new findings.
3. Provide a summary table for all adverse events > 1% for study 2004-02.
4. Provide a summary table of the number of serious adverse events by site and treatment group for study 2004-02. In addition, provide a secondary summary table of the number of overall adverse events by site and treatment group, similar to what is outlined for subjects randomized in Section 10.1 Table 7.
5. Provide the following Tables for study 2004-02 which were referred to but not actually provided in the submission:
 - Tables 14.2.5.1 through 14.2.5.10 (Live Birth Rate)
 - Tables 14.2.6.1 through 14.2.6.10 (Spontaneous Abortion Rate)
 - Tables 14.2.7.1 through 14.2.7.10 (Elective Abortion Rates)
 - Tables 14.3.5.3.1 through 14.3.5.3.7 (Second Trimester Fetal Loss Rate)
 - Tables 14.3.5.4.1 through 14.3.5.4.7 (Third Trimester Fetal Loss Rate)
 - Tables 14.3.5.5.1 through 14.3.5.5.7 (Fetal Anomaly Rate)
 - Tables 14.3.5.6.1 through 14.3.5.6.7. (Birth Defect Rate)

6. Provide the following secondary analyses:
 - The ongoing pregnancy rate (based on the presence of an intrauterine gestational sac with fetal heart motion) and 95% confidence interval for all subjects age 35 and over in each treatment group.
 - The mean difference for the pregnancy rate and the 95% confidence interval of that difference for each Endometrin group versus Crinone® group.
7. Submit electronic copies of the financial disclosure statements for site #10 that were provided via fax on October 4, 2006.
8. Provide a copy of the Investigator's Brochure.

Clinical Pharmacology

1. Provide the pharmacokinetic parameters in individual subjects of the clinical pharmacology studies in SAS transport file format.
2. Provide the analytical methodology (and associated assay validation report) employed in the analysis of tissue progesterone concentrations.

Chemistry, Manufacturing & Controls

1. State whether the blister line is also sanitized prior to a packaging run. Provide information on the steps taken to ensure the drug product is not contaminated prior to or during packaging into blisters.
2. The Dissolution specification limit is listed as either NLT — or NLT — (Q) in 20 minutes in different parts of the NDA. Identify which limit is correct and update the specification sheet if necessary. The appropriateness of the Dissolution Specification will be a review issue.
3. The established name (progesterone (—) vaginal —) will be reviewed by the Office of New Drug Quality Assessment working group to determine if the term — is appropriate.

b(4)

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If you have any questions, call John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 796-0932.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph., M.P.A.
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
11/17/2006 02:19:10 PM
Chief, Project Management Staff



FILING COMMUNICATION

NDA 22-057

Ferring Pharmaceuticals, Inc.
Attention: James H. Conover, Ph.D.
Executive Director, Regulatory Affairs
400 Rella Boulevard, Suite 300
Suffern, NY 10901

Dear Dr. Conover:

Please refer to your August 21, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Endometrin[®] (progesterone) Vaginal Tablet, 100 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on October 20, 2006, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 796-0932.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph., M.P.A.
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
11/3/2006 11:06:03 AM
Chief, Project Management Staff



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 68,097

Ferring Pharmaceuticals, Inc.
Attention: James H. Conover, Ph.D.
Executive Director, Regulatory Affairs
400 Rella Boulevard, Suite 300
Suffern, NY 10901

Dear Dr. Conover:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Endometrin[®] (progesterone) Vaginal Tablet.

We also refer to the pre-NDA meeting between representatives of your firm and the FDA on May 31, 2006.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call John C. Kim, R.Ph., J.D., Regulatory Project Manager, at (301) 796-0932.

Sincerely,

{See appended electronic signature page}

Shelley R. Slaughter, M.D., Ph.D.
Medical Team Leader
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 31, 2006 TIME: 10:30 am – 12 noon

LOCATION: Food and Drug Administration
White Oak Building 22, Conference Room 1309
10903 New Hampshire Avenue
Silver Spring, MD 20993

APPLICATION: IND 68,097

DRUG NAME: Endometrin® (progesterone) Vaginal Tablets

INDICATION: Progesterone supplementation ——— as part of an Assisted Reproductive Technology treatment for infertile women with progesterone deficiency. ⌋

b(4)

TYPE OF MEETING: Type B, Pre-NDA

MEETING CHAIR: Shelley R. Slaughter, M.D., Ph.D

MEETING RECORDER: John Kim, R.Ph., J.D.

FDA ATTENDEES:

Scott Monroe, M.D. – Acting Director, Division of Reproductive & Urologic Products (DRUP)
Shelley R. Slaughter, M.D., Ph.D. – Medical Team Leader, DRUP
Audrey Gassman, M.D. – Medical Officer, DRUP
Doanh (Donny) Tran, R.Ph., Ph.D. – Pharmacokinetics Reviewer, Office of Clinical Pharmacology
Donna Christner, Ph.D. – Pharmaceutical Assessment Lead, Pre-Marketing Assessment Division II, Office of New Drug Quality Assessment
Lynnda Reid, Ph.D. – Pharmacology/Toxicology Supervisor, DRUP
Leslie McKinney, Ph.D. – Pharmacology/Toxicology Reviewer, DRUP
Stephen E. Wilson, Ph.D. – Director, Division of Biometrics III
Margaret Kober, R.Ph., M.P.A. – Chief, Project Management Staff, DRUP
John Kim, R.Ph., J.D. – Regulatory Health Project Manager, DRUP

FERRING ATTENDEES:

Kenneth Kashkin, M.D. – Vice President of Medical and Regulatory Affairs, Ferring Pharmaceuticals, Inc.
Vladimir Yankov, M.D. – Executive Medical Director, Ferring Pharmaceuticals, Inc.
Emily Blake, M.D. – Medical Director, Ferring Pharmaceuticals, Inc.
Ronald Hargreaves, Ph.D. – Regulatory Affairs, Ferring Pharmaceuticals, Inc.
James Conover, Ph.D. – Executive Director, Regulatory Affairs, Ferring Pharmaceuticals, Inc.
Larry Huang, Ph.D. – CMC, Larry Huang, Ferring Pharmaceuticals, Inc.

b(4)

BACKGROUND:

The Sponsor has developed Endometrin, an effervescent tablet containing micronized progesterone to be placed intravaginally with an applicator. The Sponsor has proposed that Endometrin be used for luteal supplementation for women undergoing ART and _____ . The Sponsor plans to submit the results of a PK/PD study (2004-01) and one Phase 3 clinical study (2004-02) to support the filing of the NDA. The Division previously met with the Sponsor at an End of Phase 2 meeting on February 28, 2005.

b(4)

DISCUSSION POINTS:

The Sponsor initiated the meeting with a slide presentation of the Phase 3 study results (see attachment) and a demonstration of how the proposed CTD (ICH) hybrid eNDA submission will be organized.

The discussions are generated from the Sponsor's specific questions that follow.

1. Clinical Question:

Does the FDA agree that the Endometrin® Clinical and PK data supports the proposed Indication and Dosage and Administration recommendation, and that this clinical data set will allow for acceptance of the NDA for review?

FDA response: No.

- a. *The clinical data set appears to be acceptable to submit for filing for luteal supplementation. If upon review of the actual submission portions of the NDA are inadequate, the NDA would not be filed.*
- b. *It is premature to speculate as to whether or not the data supports labeling.*

Additional DRUP clinical comments:

1)

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Ferring Response:

We (Ferring) acknowledge that in the NDA only the indication for luteal phase supplementation _____ will be sought.

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- 2) *The Division also reminds you of FDA's recommendation in both the advice letter on 22-Oct-04 and at the EOP2 meeting that the study investigators be blinded to the treatment (at least assessor-blind). The open-label study design the Sponsor has chosen will, therefore, be a review issue.*

Ferring Response:

The Phase 3 study was not conducted as an open-labeled study, but as an assessor-blinded study.

- 3) *The Division requests that you report the percentages of the difference of the lower limit of the 95% confidence intervals to the first decimal point. The first decimal point should appear in the clinical study report as well.*

Ferring Response:

The non-inferiority limit for the Phase 3 study was defined as equal to or greater than -10% and confirmed that the non-inferiority limit for twice daily (BID) dosing was at -10%.

- 4) *As recommended at the EOP2 meeting, we recommend that you provide detailed past obstetrical history including gravidity, parity, previous abortions, and ectopic pregnancy information.*
- 5) *We recommend that the age, ethnicity, type of ART procedure, and body mass index (BMI) of the subject be included in the dataset containing the primary efficacy endpoint.*
- 6) *We request that you submit the duration of use of Endometrin[®] in all subjects who achieved pregnancy.*
- 7) *We recommend that all subjects who received one dose or more of Endometrin[®] whether or not they had embryo transfer be included in the data set and primary efficacy analysis.*

Ferring Response:

The primary efficacy data set will include all subjects who have taken at least one dose of Endometrin and this would be the Intent-to-Treat (ITT) population.

- 8) *We request that you submit subgroup analyses of the primary efficacy endpoint (ongoing pregnancy) by ovarian reserve as measured by Day 3 serum FSH, age of female partner and the type of insemination occurring [i.e. conventional IVF vs. intracytoplasmic sperm in injection (ICSI)].*
- 9) *We request that you present additional analyses that examine sub-stratification of clinical data based on BMI and infertility diagnosis.*
- 10) *We request that you report the outcomes (live births, terminations, multiple gestations) of all pregnancies that occurred in study 2004-02.*

Additional DRUP clinical pharmacology comments:

- 1) *We remind you of FDA's previous recommendation to examine the effects of concurrent use of other vaginal products on Endometrin[®] pharmacokinetics.*
- 2) *We recommend that you provide in the NDA exposure-response analyses used for dose selection in Phase 3 trial.*
- 3) *We request that you perform a current literature search and include in the NDA relevant information on progesterone ADME properties, drug interactions,*

special populations, and any other intrinsic or extrinsic factors that may affect Endometrin[®] pharmacokinetics to supplement your studies. For each literature reference, provide a brief summary relating to the point being made as well as a copy of the full paper. If the literature does not provide sufficient information on progesterone metabolism (e.g., metabolic pathway) and drug-drug interactions (e.g., CYP inhibition and induction), the Division recommends in vitro studies to address these areas.

- 4) *We request that you verify that the NDA will include pharmacokinetic data files from all studies. Provide the files in SAS transport format and also include the corresponding data definition files.*
- 5) *We recommend that you confirm in the Biopharmaceutics section that there are no changes in formulation or manufacturing process between the clinical trial product and the to-be-marketed product that would require a bioequivalence study.*
- 6) *We request that you provide a table listing all clinical studies in the NDA with columns identifying the manufacturing site and lot number for all lots of drug used in each corresponding clinical study.*

2. Regulatory Question:

Will FDA accept the proposed CTD (ICH) hybrid eNDA submission from Ferring (via Octagon) for review?

FDA response: Yes, barring any unusual complications during the submission process. Also be aware that the Physician Labeling Rule will be in effect on June 30, 2006.

The integrated summary of efficacy (ISE) should include only the "proof-of-efficacy" study. The integrated summary of safety (ISS) should integrate the data of all of the clinical studies (including the PK/PD study). It would be acceptable to present the ISS in parallel format. For ease of review, the Division requests that ISS and ISE data be presented by "cut and paste" rather than hyperlink. This is especially relevant for the main tables.

Ferring Response:

We will be happy to meet with the Division to discuss navigation of the NDA after it is submitted.

3. Nonclinical Question:

Does FDA agree that since both Clinical and PK studies have been conducted without any additional safety issues that additional toxicological studies will not be needed for the NDA?

FDA response: No additional nonclinical studies are needed.

4. CMC Question

The Endometrin tablets are packaged in foil pouches which are paper-backed. Our entire stability protocol was run on this configuration. This packaging configuration is not tested for child resistance, because Endometrin® is not an oral dosage form, and because it is a naturally occurring hormone. Does FDA have any concerns or issues with our proposed packaging?

FDA response: The FDA has no concerns or issues with the proposed packaging in regard to child resistance. We remind you that the Poison Prevention Packaging Act is administered by the Consumer Product Safety Commission.

ACTION ITEMS:

- The Project Manager will provide meeting minutes within 30 days of the meeting date.

Signature: Meeting Chair

{See Appended Electronic Signature}

Shelley R. Slaughter, M.D., Ph.D.

ATTACHMENTS:

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/s/

Shelley Slaughter
6/30/2006 09:13:40 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 68,097

Ferring Pharmaceuticals, Inc.
Attention: James H. Conover, Ph.D
Executive Director, Regulatory Affairs
400 Rella Boulevard, Suite 300
Suffern, NY 10901

Dear Dr. Conover:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Endometrin[®] (progesterone) Vaginal Tablet.

We also refer to the November 18, 2005, correspondence containing your request for an End-of-Phase 2 Chemistry, Manufacturing, and Control (CMC) teleconference and a list of specific CMC questions.

We further refer to the preliminary draft responses that were faxed to you on January 4, 2006, and to the telephone conversation between you and Mr. John Kim, requesting to cancel the teleconference on January 9, 2006.

The preliminary draft comments have been fully vetted and will be the official minutes of our planned meeting.

If you have any questions, call John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 796-0932.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
Center of Drug Evaluation and Research

Enclosure

MEETING MINUTES

MEETING DATE (PLANNED): January 9, 2006 **TIME:** 1 pm – 2 pm

APPLICATIONS: IND 68,097

DRUG NAME: Endometrin® (progesterone) Vaginal Tablet

SPONSOR: Ferring Pharmaceuticals, Inc

TYPE OF MEETING: End-of-Phase 2, CMC

FDA PARTICIPANTS (PLANNED):

Moo-Jhong Rhee, Ph.D. – Branch Chief, Branch III, Pre-Marketing Assessment Division II (PMAD II), Office of New Drug Quality Assessment (ONDQA)

Donna Christner, Ph.D. – Pharmaceutical Assessment Lead, PMAD II, ONDQA

Shelley R. Slaughter, M.D., Ph.D. – Medical Team Leader, Division of Reproductive and Urologic Products (DRUP)

Audrey Gassman, M.D. – Medical Officer, DRUP

Yangmee Shin, Ph.D. – Pharmacology/Toxicology Reviewer, DRUP

Donny Doanh Tran, R.Ph., Ph.D. – Pharmacokinetics Reviewer, Office of Clinical Pharmacology (OCP) @ DRUP

John Kim, R.Ph., J.D. – Regulatory Health Project Manager, DRUP

FERRING PARTICIPANTS (PLANNED):

Larry Wong, Ph.D. – Director of Pharmaceutical Development, Ferring Pharmaceuticals, Inc.

James Conover, Ph.D. – Executive Director, Regulatory Affairs, Ferring Pharmaceuticals, Inc.

BACKGROUND:

The Sponsor has developed a progesterone tablet to be used vaginally with an applicator for treatment of infertile women with progesterone deficiency. The Sponsor had an EOP2 meeting on February 28, 2005, to discuss Sponsor's pivotal Phase 3 protocol. On November 17, 2005, the Sponsor requested a separate EOP2 CMC meeting via teleconference, which was scheduled for January 9, 2006.

DISCUSSION POINTS:

The sponsor has asked the following three CMC questions:

QUESTION #1: *We have manufactured three primary stability batches of Endometrin® using the same formulation and container closure system that will be proposed for marketing in our planned NDA. While two tablet strengths (50 mg and 100 mg) were produced from each batch, only the 100 mg strength will be proposed for market.*

Batch #1 ⌋

⌋

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Batch #2 T
Batch #3 T

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Each of these three batches will have — two-year stability for the estimated NDA submission. All of these batches should qualify as primary stability batches, according to my previous minuted teleconference with the DRUDP Chemistry Team Leader. Does FDA agree?

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FDA response: Yes, we agree. The three batches cited will qualify as primary stability batches, as outline in our teleconference held on June 28, 2004.

QUESTION #2: We have provided a two page "Master Specification for Release Testing" document, which details Endometrin® batch testing methods and parameters required for batch release. Our manufacturer is Pharmaceuticals International, Inc. (PII) located in Maryland. Does the FDA have any issues with our specifications?

FDA response: It is unclear from the specifications if the assay will be performed on only two tablets. Assay should be performed on a tablet composite (usually 20 tablets).

Provide information on the dissolution method, including media, apparatus, and apparatus speed. The appropriateness of the acceptance criteria will be determined upon review of the data submitted in the NDA.

Sponsor response (faxed January 4, 2006): The following two methods are used to perform assay and dissolution on 100 mg progesterone vaginal tablets:

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Please note these validated methods are available for your review.

FDA response: Sponsor's faxed response is acceptable. We have no further issues with the specifications. However, the validated methods will be review issues upon filing of an NDA.

QUESTION #3: *Please see the "Stability Protocol" for an outline of the stability and sampling plan, as well as information on our packaging for the marketed product. Does FDA have any questions concerning the Stability Protocol?*

FDA response: The submitted "Stability Protocol" is adequate.

Additional CMC comment: Submit Letters of Authorization to reference any Drug Master Files for the drug substance and the container closure system.

Moo-Jhong Rhee, Ph.D.
Chief, Branch III

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/s/

Moo-Jhong Rhee
1/24/2006 03:56:13 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 68,097

Ferring Pharmaceuticals, Inc.
Attention: James H. Conover, Ph.D.
Executive Director, Regulatory Affairs
400 Rella Boulevard, Suite 300
Suffern, NY 10901

Dear Dr. Conover:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Endometrin[®] (progesterone) Vaginal Tablets.

We also refer to an End of Phase 2 meeting between representatives of your firm and the FDA on February 28, 2005.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call John Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 827-3003.

Sincerely,

{See appended electronic signature page}

Shelley R. Slaughter, M.D., Ph.D.
Medical Team Leader
Division of Reproductive and Urologic Drug
Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 28, 2005 **TIME:** 12:30 pm – 2 pm

LOCATION: Food and Drug Administration
Parklawn Building, Conference Room "C"
5600 Fishers Lane
Rockville, MD 20857

APPLICATION: IND 68,097

DRUG NAME: Endometrin® (progesterone) Vaginal Tablets

SPONSOR: Ferring Pharmaceuticals, Inc.

INDICATION: Progesterone supplementation _____ as part of an Assisted Reproductive Technology treatment program for infertile women with progesterone deficiency. **b(4)**

TYPE OF MEETING: Type B, End of Phase 2

MEETING CHAIR: Shelley R. Slaughter, M.D., Ph.D

MEETING RECORDER: John Kim, R.Ph., J.D.

FDA ATTENDEES:

Daniel Shames, M.D. – Director, Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580

Shelley R. Slaughter, M.D., Ph.D. – Medical Team Leader, DRUDP (HFD-580)

Audrey Gassman, M.D. – Medical Officer, DRUDP (HFD-580)

John Kim, R.Ph., J.D. – Regulatory Project Manager, DRUDP (HFD-580)

Yangmee Shin, Ph.D. – Pharmacologist, DRUDP (HFD-580)

Dhruba J. Chatterjee, Ph.D. – Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Michael Welch, Ph.D. – Biostatistics Team Leader, Division of Biostatistics II (HFD-715)

Katherine Meaker, Ph.D. – Statistician, Division of Biostatistics II (HFD-715)

EXTERNAL CONSTITUENT ATTENDEES:

Kenneth Kashkin, M.D. – Vice President of Medical and Regulatory Affairs, Ferring Pharmaceuticals, Inc.

Vladimir Yankov, M.D. – Executive Medical Director, Ferring Pharmaceuticals, Inc.

Emily Blake, M.D. – Medical Director, Ferring Pharmaceuticals, Inc.

James Conover, Ph.D. – Executive Director, Regulatory Affairs, Ferring Pharmaceuticals, Inc. **b(4)**

b(4)

BACKGROUND:

Ferring has developed a progesterone tablet to be used vaginally with an applicator for treatment of infertile women. Ferring has submitted to this IND the results of a pK/pD Study (2004-01) and two phase 3 clinical Study protocols (2004-02 and 2004-06) for review.

Endometrin® is currently marketed in Israel and Hong Kong as an effervescent tablet containing micronized progesterone, and is usually administered as a 100 mg tablet applied twice daily.

DISCUSSION POINTS:

The discussions are generated from the Sponsor's specific questions that follow.

Nonclinical

QUESTION#1: *Based on the findings during the in-life and necropsy phases of the 90-day vaginal irritation-toxicity study in rabbits, and considering that the histopathological evaluation will be presented, does the Agency agree that there are no safety concerns for proceeding into Phase3?*

Division Response: No. We cannot concur with the adequacy and safety of the 90-day rabbit vaginal study without an independent review of the data. A Phase 3 study cannot be initiated until the Division informs that there are no issues for proceeding into Phase 3.

QUESTION#2: *Should the histopathological evaluation of the 90-day study indicate that Endometrin is safe for clinical use, Ferring is considering that the non-clinical safety assessment required for the registration and commercialization is complete. Does the FDA concur?*

Division Response: We will need to independently review the histopathological findings that are observed in the 90-day study. After review of the 90-day study, if no safety issues are identified then we concur that no further nonclinical studies will be required to file a New Drug Application.

QUESTION#3: *The pK/pD studies of Endometrin® are complete, does the FDA concur that the Clinical Pharmacology program is complete for the NDA?*

Division Response: No. Exposure-response relationship and the lowest effective dose have not been characterized. It appears that C_{max} and AUC are under-proportional. When comparing high doses of Endometrin (100 mg twice a day and 200 mg twice a day) with PK results from the package insert for Crinone® (progesterone vaginal gel) 4% and 8%, the exposures appear lower for Endometrin. Ferring needs to address the effect of other vaginally administered creams on absorption of drug from this product.

Additional comments: The Clinical team believes that the optimal dose of Endometrin® to take forward to Phase 3 trials may not have been identified. Given the Division's more

narrowly-defined lower-bound of the 95% confidence interval of the difference in pregnancy rates between Endometrin and the comparator (see discussion below), the issue of power of the study becomes more critical. More precise dose finding may allow you to perform a two-armed Phase 3 study which would reduce the number of subjects required to adequately power the trial.

However, it is Ferring's risk to proceed with the currently identified dosage strengths and regimens.

QUESTION#4: *Does the FDA agree with our pivotal Phase 3 Protocol 2004-02 with respect to the dosage regimen, proposed design, and primary outcomes and statistical plan?*

Division Response: No. We do not concur with the currently proposed protocols 2004-02 and 2004-06. Our decision is based on the following:

Dosage of Endometrin®:

- 1) We concur with the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) that based on the data from Protocol 2004-01, there are insufficient dose-finding data to begin Phase 3 studies. We recommend additional Phase 2 studies. It is, however, at your risk to proceed to Phase 3.
- 2) We question why you are proceeding into Phase 3 based on a dose-finding model that you have stated may not be the most appropriate for your Phase 3 trial. As stated above, this is at your risk.
- 3) In addition, we concur with OCPB that an additional drug-drug interaction study should be performed to look at the effects of vaginal creams and gels on the pK/pD parameters of Endometrin®. In the absence of data, this may be a labeling issue.

Design, Primary Outcome and Statistical Plan:

A. Study Protocols 2004-02

- 1) We remind you of our previous recommendations (Advice letter dated 22-Oct-04) regarding a proposed clinical trial with the primary endpoint of clinical pregnancy rate. Of these recommendations, the following were not addressed in the protocol contained in your briefing document :
 - The study investigator should be blinded to the treatment (assessor-blind). No individual who is making any decisions (investigator or ultrasonographer should be aware of treatment). We recommend using a clinical nurse and consulting safety gynecologist.
 - We recommend that you exclude subjects with a body mass index (BMI) > 38 kg/m²
 - We recommend you record detailed past obstetrical history including: gravidity, parity, previous abortions, and ectopic pregnancies.
 - We recommend that you provide a standard method (grading) of determining the severity of ovarian hyperstimulation syndrome (both in terms of what

criteria would lead to cancellation and what would be considered a serious adverse event) to allow uniformity between sites.

- 2) You have proposed 2004-02 as a non-inferiority study comparing Endometrin 100 mg BID and 200 mg BID (see previous comments on dosage) to Crinone[®] 8% gel. You have further proposed that based on an expected clinical pregnancy rate of 30% in the comparator, non-inferiority will be declared if the lower bound of the 95% confidence interval of the difference in clinical pregnancy rates between Endometrin and Crinone[®] 8% excludes a difference greater than 15% in favor of Crinone[®] 8%.

We do not concur with your non-inferiority limit.

You mention that the subject sample size to accomplish our previously recommended non-inferiority limit of 6 % would be larger than that required for approval of the comparator Crinone[®] 8% (May 13, 1997) and other (infertility) drug products presented to the FDA. We do not dispute this. However, in September 2003 we received the Reproductive Health Advisory Committee's recommendation that we should look at the endpoint of clinical pregnancy in our evaluation of gonadotropin drug products used to help infertile women to conceive. This is a departure from the previous approval requirements for gonadotropins and requires a larger sample size. Even more recently on October 29, 2004, we granted approval of your drug product Menopur[®] administered by subcutaneous injection (NDA 21-663) based upon Study MFK/IVF/0399E (protocol not presented to the FDA for review) that evaluated a total of 727 subjects (373 in the Menopur arm and 354 in the comparator arm) for the primary endpoint of clinical pregnancy rate. In this study, for which agreements were made prior to the Advisory Committee, the pre-specified non-inferiority limit (for which the lower-bound of the 95% confidence interval could not exceed) was a difference of 10%. The lower bound of the 95% confidence interval of the difference by your analysis was -3.3 thus excluding that the difference in pregnancy rate between Menopur and the comparator was greater than 10% in favor of the comparator. The Division does not wish to lower the standard for demonstration of efficacy for Endometrin relative to this recent (2004) approval of Menopur.

The Division notes that at the September 29, 2003 Advisory Committee meeting, Dr. Emerson made some calculations on the lower acceptable limit of the 95% confidence interval of clinical pregnancy rate based on data from previously approved gonadotropin or menotropins drug products. The Division's clinical team interpreted this as a recommendation by Dr. Emerson that the difference between products should be no greater than this value of 6% (or 8%). We note that it is not entirely clear to us that this recommendation was tied only to an approximately 20% expected clinical pregnancy rate. We have sought clarification from Dr. Emerson regarding his calculations and whether these would be adjusted with a background rate of 30% as opposed to 20%.

Given all of the preceding information, we continue to recommend a tighter non-inferiority limit of 6%-8% on the difference in clinical pregnancy rate. Most importantly, we do not feel that the bar for efficacy demonstration of this product should be lower than for your recently approved Menopur[®] which represents an

application that is close to our thinking on these drug products. Remember, that these are our recommendations (guidance) and represent our thoughts relative to demonstration of efficacy.

In view of the difference in interpretation of the recommendation in the Advisory Committee transcript, we would be willing to allow (i.e., before publication of a draft guidance), a pre-specified 10% difference as the lower limit of the 95% Confidence Interval such as in the Menopur Study MFK/IVF/0399E.

If after this discussion, we can not agree on a non-inferiority limit we invite you to submit your protocol as a special protocol assessment and we will seek the input of one or more SGE consultants.

- 3) We recommend that randomization and analyses be stratified and powered for subgroup analyses of ovarian reserve as measured by Day 3 serum FSH, age of the female partner and the type of insemination occurring [i.e. conventional in-vitro fertilization (IVF) vs. intracytoplasmic sperm injection (ICSI)]. We further recommend a sub-stratification of data based on body mass index (BMI) and infertility diagnosis. The analysis of data relative to sub-stratification groups can be descriptive. Studies should be powered to demonstrate differences in these (sub-stratification) groups only if specific claims regarding these groups are sought.
- 4) Additional General comments:
 - Standardize the criteria for human chorionic gonadotropin administration.
 - Standardize the criteria for down-regulation for all centers.
 - Exclude subjects that use using additional hormonal drug products (including progesterone creams, other steroid drug products including hydrocortisone) from these phase 3 protocols.
 - Provide justification for the exclusion of GnRH antagonists which are the only approved drugs for. Exclusion of these drug products may be a labeling issue.
 - Clarify whether daily or depot gonadotropin releasing hormone agonists will be used. In study MFK/IVF/0399E submitted to NDA 21-663, it appeared that there were clinical differences in pregnancy rates seen with the various preparations of these agonists.
 - We recommend that if you plan on allowing daily and depot gonadotropin releasing hormone agonists in these protocols, that these subjects be stratified.
 - Provide justification for the use of the combination of Repronex[®] and Bravelle[®] in these protocols. This may impact labeling for Endometrin[®].
 - Clarify how the IVRS system will perform the randomization in more detail.
 - Standardize your terminology of clinical and ongoing pregnancy in both protocols. We recommend that the term clinical pregnancy refer to a pregnancy defined by the presence of a gestational sac and fetal heartbeat beginning at six weeks post embryo transfer.

B. Study 2004-06 for Endometrin®

In response to our suggested alternative approach of a study to evaluate time to onset of clinical pregnancy, you have presented "Study 2004-06". We have the following comments:

- 1) The Division's current recommendation for the endpoint of time-to-onset of clinical pregnancies is based on recommendations received at the Reproductive Health Advisory Committee Meeting on September 29, 2003. The analysis of time to onset-of-clinical pregnancy is a new consideration for the Division. Time to onset analyses are not however, new to the field of Infertility. Review of the literature reveals that survival analyses have been used to evaluate fertility after ectopic pregnancy; success rates (for pregnancy) after surgery. We heard from members of the Advisory Committee that in considering the pregnancy endpoint, we should be attempting to capture all of the potential (both fresh and frozen) cycles of gonadotropin drug products. We thought the best way to do this would be a consideration of a time-to-event analyses for studies of drug products in ART where both fresh and frozen cycles are included. We have spent the last year obtaining advice internally and externally from our SGE for the guidance document, Dr. Emerson, in order refine the recommendations in our draft guidance prior to publishing of this document for general comments. The recommendations are evolving. The advice we have given you is based on interim recommendations and these recommendations will remain as interim (and subject to change) until the guidance is finalized.
- 2) A phase 3 study (such as proposed in 2004-06) using the time-to-event analysis should be conducted over a maximum of a one-year period per subject. Both fresh gonadotropin and cryopreserved treatment cycles should be considered (Ideally no more than two cryopreserved embryo transfers per every fresh gonadotropin cycle). As stated previously, the inclusion of cryopreserved cycles would allow an analysis of the maximum potential of Endometrin®.
- 3) We concur in the statistical summary of median time from randomization to occurrence. Based on our discussion of the Guidance Document and for completeness we also offer the alternatives of:
 - Proportion of subjects achieving clinical pregnancy (gestational sac with fetal heart beat) at a fixed point in time ex. 6 months, 9 months, etc.
 - Mean number of days without pregnancy that occurred during the 9 months or 12-months of a study.

QUESTION# 5: *Does FDA agree that upon completion of pivotal study 2004-02 that Ferring's NDA registration program for commercialization is complete?*

Division Response: No.

- We have concerns that dose-finding should be further assessed prior to phase 3 study(ies) commencement.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Shelley Slaughter
3/30/05 03:33:47 PM

ACTION PACKAGE CHECKLIST

Application Information

BLA # NDA # 22-057	BLA STN# NDA Supplement # 000	If NDA, Efficacy Supplement Type N/A	
Proprietary Name: Endometrin® Established Name: (progesterone) Dosage Form: Vaginal Insert		Applicant: Ferring Pharmaceuticals, Inc.	
RPM: John C. Kim, RPh, JD		Division: Reproductive and Urologic Products	Phone # 301-796-0932
<p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>N/A</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</p> <p><input checked="" type="checkbox"/> Confirmed <input type="checkbox"/> Corrected</p> <p>Date: 6-JUN-2007</p>	
❖ User Fee Goal Date		21-JUN-2007	
❖ Action Goal Date (if different)			
❖ Actions			
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR	
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None	
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed	

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 3 NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies NDAs and NDA Supplements: <input type="checkbox"/> OTC drug Other: Other comments:	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP <input checked="" type="checkbox"/> N/A
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<p>❖ Exclusivity</p>	
<ul style="list-style-type: none"> • NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity? • NDAs/BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> • NDAs: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) • NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) • NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires: <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires: <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires: <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<p>❖ Patent Information (NDAs and NDA supplements only)</p>	
<ul style="list-style-type: none"> • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> • Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. • [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified <input checked="" type="checkbox"/> N/A 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii) <input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> • [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (<i>If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews).</i>) • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner’s receipt of the applicant’s</p>	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified <input type="checkbox"/> Yes <input type="checkbox"/> No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

within the 45-day period).		
<p>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</p> <p>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</p>		
Summary Reviews		
❖ Summary Reviews	Division Director	21-JUN-2007
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)		N/A
Labeling		
❖ Package Insert		
<ul style="list-style-type: none"> Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 		20-JUN-2007
<ul style="list-style-type: none"> Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 		20-JUN-2007
<ul style="list-style-type: none"> Original applicant-proposed labeling 		21-AUG-2006
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 		23-MAR-2005 Prochieve 10-DEC-2004 Prometrium
❖ Patient Package Insert		
<ul style="list-style-type: none"> Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 		20-JUN-2007
<ul style="list-style-type: none"> Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 		20-JUN-2007
<ul style="list-style-type: none"> Original applicant-proposed labeling 		21-AUG-2006
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 		N/A
❖ Medication Guide		
<ul style="list-style-type: none"> Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 		N/A
<ul style="list-style-type: none"> Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 		N/A
<ul style="list-style-type: none"> Original applicant-proposed labeling 		N/A
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 		N/A
❖ Labels (full color carton and immediate-container labels)		
<ul style="list-style-type: none"> Most-recent division-proposed labels (only if generated after latest applicant submission) 		23-MAY-2007
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 		21-AUG-2006
❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)		<input checked="" type="checkbox"/> DMETS 16-FEB-2007 <input checked="" type="checkbox"/> DSRCS 8-FEB-2007 <input checked="" type="checkbox"/> DDMAC 17-JAN-2007 <input checked="" type="checkbox"/> SEALD 7-JUN-2007 <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs

Administrative Documents

Administrative Documents	
Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	21-JUN-07
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval 	N/A N/A
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Post-marketing Commitment Studies	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) 	N/A
<ul style="list-style-type: none"> Incoming submission documenting commitment 	N/A
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	18-JUN-2007 11-APR-2007 11-JAN-2007 17-NOV-2006 3-NOV-2006 1-SEP-2006
❖ Internal memoranda, telecons, email, etc.	18-JUN-2007 15-JUN-2007 30-MAR-2007
❖ Minutes of Meetings	
<ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) 	N/A
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date</i>) 	20-JUN-2006
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date</i>) 	30-MAR-2005
<ul style="list-style-type: none"> Other (e.g., EOP2a, CMC pilot programs) 	24-JAN-2006 CMC only
❖ Advisory Committee Meeting	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date of Meeting 	N/A
<ul style="list-style-type: none"> 48-hour alert or minutes, if available 	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
CMC/Product Quality Information	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	20-JUN-2007 15-JUN-2007 14-NOV-2006
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
❖ Environmental Assessment (check one) (original and supplemental applications)	
<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) 	15-JUN-2007 See CMC review, page 53.
<ul style="list-style-type: none"> <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) 	N/A
<ul style="list-style-type: none"> <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) 	N/A

❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (indicate date of each review)	28-FEB-2007 <input type="checkbox"/> Not a parenteral product
Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 19-JUN-2007 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (indicate date(s)) • Compliance Status Check (approvals only, both original and supplemental applications) (indicate date completed, must be within 60 days prior to AP) 	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed

Nonclinical Information

❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	14-MAY-2007 4-OCT-2006
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	N/A
❖ Nonclinical inspection review Summary (DSI)	<input checked="" type="checkbox"/> None requested

Clinical Information

❖ Clinical review(s) (indicate date for each review)	21-JUN-2007 Team Leader 20-JUN-2007 4-OCT-2006
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	See Clinical review § 4.6, page 32.
❖ Clinical consult reviews from other review disciplines/divisions/Centers (indicate date of each review)	<input checked="" type="checkbox"/> None
❖ Microbiology (efficacy) reviews(s) (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
❖ Safety Update review(s) (indicate location/date if incorporated into another review)	See Clinical review § 7.2.9, pages 104.
❖ Risk Management Plan review(s) (including those by OSE) (indicate location/date if incorporated into another review)	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input type="checkbox"/> None requested
• Clinical Studies	20-FEB-2007 9-FEB-2007 5-FEB-2007 24-JAN-2007
• Bioequivalence Studies	N/A
• Clin Pharm Studies	N/A
❖ Statistical Review(s) (indicate date for each review)	DRAFT 19-OCT-2006
❖ Clinical Pharmacology review(s) (indicate date for each review)	24-MAY-2007 2-NOV-2006

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.