

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-057

CHEMISTRY REVIEW(S)

Memorandum

Date: June 20, 2007
From: Ying Wang, Ph.D.
Through: Moo-Jhong Rhee, Ph.D.
To: CMC Review #1 of NDA 22-057
Subject: Compliance Status Update for Establishment

At the time of the CMC review was written, the site inspection of establishment was still pending. On June 19, 2007 the overall "Acceptable" recommendation was made by the Office of Compliance (EES report attached) for this NDA. This memorandum closes all pending issues for this NDA from the CMC perspective.

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On Original**

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DMF No:

AADA:

Responsibilities:

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b(4)

Profile:

CTL

OAI Status: NONE

Estab. Comment:
_____ (on

THIS SITE PERFORMS ┌

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b(4)

15-SEP-2006 by D. CHRISTNER () 301-796-1341)

Milestone Name Creator	Date	Type	Insp. Date	Decision & Reason
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SUBMITTED TO OC CHRISTNERD	15-SEP-2006			
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OC RECOMMENDATION FERGUSONS	15-SEP-2006			
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ACCEPTABLE

BASED ON PROFILE

Establishment:

CFN _____

FEI _____

b(4)

b(4)

DMF No:

AADA:

Responsibilities:

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ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Profile: CTL OAI Status: NONE

Estab. Comment: THIS SITE PERFORMS

b(4)

(on 07-SEP-2006 by D. CHRISTNER () 301-796-1341)

Milestone Name Creator	Date	Type	Insp. Date	Decision & Reason
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SUBMITTED TO OC 15-SEP-2006
CHRISTNERD

OC RECOMMENDATION 15-SEP-2006
FERGUSONS

ACCEPTABLE

BASED ON PROFILE

Establishment: CFN _____

FEI _____

b(4)

b(4)

DMF No:

AADA:

Responsibilities:

b(4)

Profile: TCM

OAI Status: NONE

Estab. Comment: THIS SITE PERFORMS

b(4)

TESTING FOR THE FINAL DOSAGE FORM (on 07-SEP-2006 by D.
CHRISTNER ())
301-796-1341)

Milestone Name Creator	Date	Type	Insp. Date	Decision & Reason
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SUBMITTED TO OC 15-SEP-2006
CHRISTNERD

SUBMITTED TO DO 15-SEP-2006 10D
FERGUSONS

ASSIGNED INSPECTION T 05-OCT-2006 PS
MGARCIAL

INSPECTION SCHEDULED 14-JUN-2007 15-JUN-2007
BSEEMAN

INSPECTION PERFORMED 18-JUN-2007 18-JUN-2007
BSEEMAN

INSPECTION NOT YET CLOSED AT TIME INFORMATION ENTERED INTO EES. INVESTIGATOR
PLANS TO

ISSUE A TWO ITEM FDA 483. WILL BE CLASSIFIED VAI.

DO RECOMMENDATION 18-JUN-2007 ACCEPTABLE
BSEEMAN

INSPECTION

INSPECTION NOT YET CLOSED AT TIME INFORMATION ENTERED INTO EES. INVESTIGATOR
PLANS TO

ISSUE A TWO ITEM FDA 483. WILL BE CLASSIFIED VAI.

OC RECOMMENDATION 19-JUN-2007 ACCEPTABLE
FERGUSONS

DISTRICT

RECOMMENDATION

Establishment:

CFN

FEI

b(4)

DMF No: _____

AADA:

Responsibilities:

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ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

DRUG SUBSTANCE STABILITY TESTER

Profile: CSN OAI Status: NONE

Estab. Comment: **Γ** **1** (on 07-SEP-2006 by **b(4)**
D.

CHRISTNER () 301-796-1341)

Milestone Name Creator	Date	Type	Insp. Date	Decision & Reason
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SUBMITTED TO OC CHRISTNERD	15-SEP-2006			
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OC RECOMMENDATION FERGUSONS	15-SEP-2006			ACCEPTABLE
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BASED ON PROFILE

Establishment: CFN FEI **b(4)**

b(4)

DMF No: AADA:

Responsibilities: **Γ** **1** **b(4)**

Profile: TCM

OAI Status: NONE

Estab. Comment: (on 07-

SEP-2006 by D. CHRISTNER () 301-796-1341)

b(4)

Milestone Name Creator	Date	Type	Insp. Date	Decision & Reason
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SUBMITTED TO OC CHRISTNERD	15-SEP-2006			
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SUBMITTED TO DO FERGUSONS	15-SEP-2006	10D		
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DO RECOMMENDATION KCAMPBEL	18-SEP-2006			ACCEPTABLE
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BASED ON FILE REVIEW

GMP EI CONDUCTED 9/6-8/2006 IS CURRENTLY UNDER REVIEW BUT WILL BE CLASSIFIED VAI (NO FDA

483 ISSUED). PROFILE CLASS TCM WILL BE UPDATED AS ACCEPTABLE. THERE ARE NO PENDING

ENFORCEMENT ACTIONS THAT WOULD IMPACT THIS RECOMMENDATION.

OC RECOMMENDATION FERGUSONS	18-SEP-2006			ACCEPTABLE
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RECOMMENDATION

DISTRICT

Establishment: CFN

FEI

b(4)

b(4)

DMF No:

AADA:

Responsibilities:

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b(4)

Profile:

CTL

OAI Status:

NONE

Estab. Comment:

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b(4)

(on 07-SEP-2006 by D. CHRISTNER () 301-796-1341)

Milestone Name Creator	Date	Type	Insp. Date	Decision & Reason
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ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

SUBMITTED TO OC 15-SEP-2006
CHRISTNERD

OC RECOMMENDATION 15-SEP-2006
FERGUSONS

ACCEPTABLE

BASED ON PROFILE

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/s/

Ying Wang
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Moo-Jhong Rhee
6/20/2007 01:14:27 PM
CHEMIST
Chief, Branch III

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/s/

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6/20/2007 01:06:37 PM
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Moo-Jhong Rhee
6/20/2007 01:14:27 PM
CHEMIST
Chief, Branch III

**NDA 22-057
CMC Review #1**

Endometrin Progesterone Vaginal Insert

Ferring Pharmaceuticals, Inc.

**OND Division of Reproductive and Urologic Products
(DRUP)**

**Ying Wang, Ph.D.
Manufacturing Science Branch,
Division of Pre-marketing Assessment III, ONDQA**

**For Branch III, Division of Pre-marketing Assessment II,
ONDQA**



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Chemistry Review Data Sheet

1. NDA 22-057
2. Review #1
3. Review Date: March 16, 2007
4. Reviewer: Ying Wang, Ph.D.
5. Previous Documents: None
6. Submissions Being Reviewed:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original NDA	21-Aug-2006
Test Report Resubmission	4-Oct-2006
Response to CDER IR Letter	22-Dec-2006
Response to CDER IR Letter	26-Jan-2007
Amendment –microbial test results during stability	23-Mar-2007
Response to e-mail sent on April 11, 2007	19-April-2007
Amendment for commitment to microbial spec. for excipient	25-April-2007
Amendment	May 24, 2007
Amendment	June 8, 2007
Amendment	June 14, 2007

7. Name & Address of Applicant:

Name: Ferring Pharmaceuticals Inc.

Address: 400 Rella Blvd., Suite 300, Suffern, NY 10901

Representative: James H. Conover

Telephone: 845-770-2668



Chemistry Review Data Sheet

8. Drug Product Name/Code/Type

- a) Proprietary Name: Endometrin
- b) Non-Proprietary Name (USAN): Progesterone Vaginal Insert
- c) Code Name: N/A
- d) Chem. Type/Submission Priority:
 - Chem Type: 3
 - Submission Priority: S

9. Legal Basis for Submission: NDA is submitted under 505 (b)(1)

10. Pharmacology Category: Progesterone supplement for ART treatment

11. Dosage Form: Vaginal Insert – Immediate Release

12. Strength/Potency: 100 mg

13. Route of Administration: Vaginal

14. Rx/OTC Dispensed: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)

SPOTS product – Form Completed

Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name: Pregn-4-ene-3,20-dione

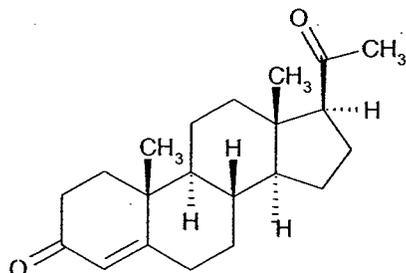
Molecular Formula: $C_{21}H_{30}O_2$

Molecular Weight: 314.47



Chemistry Review Data Sheet

Chemical Structure:



17. Related/Supporting Documents:

A. Supporting DMFs:

DMF #	T Y P E	HOLDER	ITEM REFERENCED	Code ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS ³
—	2	—	/	1	Adequate	March 5, 2007	See Chemistry Review #2 by Ying Wang
—	3	—		4	Adequate		See this review in P7 section
—	3	—		3	Adequate	23-May-2003 by B. Ho for NDA 16-324/S029	
3, Pg13	3	T		3	Adequate	11-Mar-2005 by S. Pope for NDA 21-788	Comments in NDA review

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



Chemistry Review Data Sheet

³ Include reference to location in most recent CMC review

B. Other Supporting Documents:
None

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND 68,097		Ferring Pharmaceutical	Endometrin Progesterone Vaginal Tablet

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			
EES	Site Inspection	15-Sep-2006	Pending	
Pharm/Tox	N/A			
Biopharm	N/A			
LNC	Established Name			Established name has been changed to "progesterone vaginal insert". See Labeling section comments.
Methods Validation	To be validated per ONDQA policy			
ODS/DMETS	Trademark and labeling	29-Aug-2006	Richard Abate	Trademark is acceptable. Other labeling comments see review sections
EA	Categorical Exclusion is claimed		Y. Wang	The claim is acceptable.
Microbiology	Microbial and moisture limits and test schedule	10-Oct-2006	Vinayak Pawar	Moisture limit is high and needs to be monitored rigorously. Microbial test needs to be added during stability. Moisture limit is tested during stability. Microbial test has been added during stability.

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The Chemistry Review for NDA 22-057

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval from the CMC perspective pending satisfactory cGMP recommendation from the Office of Compliance.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Endometrin is white to off-white, modified-caplet-shaped vaginal insert debossed with "FPI" on one side and "100" on the other side. It is an immediate release tablet and is available in 100 mg strength. The tablets are packaged in aluminum/aluminum peel blisters. A disposable insertion device is copackaged with the product to facilitate insertion of the tablets into the vagina. Excipients corresponding to conventional oral tablets are used for the drug product. Adipic acid and sodium bicarbonate are used to provide for _____ although the formulation is not considered to be an _____ per se. Some of the excipients such as lactose monohydrate and pregelatinized starch have a high water content which leads to a corresponding high water content in the drug product. Therefore, microbial limits and moisture need to be monitored in the drug product.

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B. Description of How the Drug Product is Intended to be Used

Endometrin is a vaginal insert containing 100 mg of micronized progesterone which has effervescent properties. It is used in women who require progesterone supplementation as part of Assisted Reproductive Technology (ART) to sustain pregnancy. It is administered vaginally 2 to 3 times daily with the assistance of a disposable insertion device. The duration of treatment usually lasts for 10 weeks.

The applicant proposed, and is granted 24 months shelf life for this drug packaged in Aluminum/Aluminum peel blisters store at — 25°C — 77°F); excursions permitted between 15°-30°C (59°-86°F).

b(4)

C. Basis for Approvability or Not-Approval Recommendation

All outstanding issues for this NDA have been resolved through information request and teleconference. Therefore this NDA is recommended for approval from CMC perspective.

NOTE: As of this writing, the PAI is not yet complete. Site inspection for the drug product manufacturer Pharmaceutical International Inc. is still pending. An overall recommendation is therefore not in EES as of this writing.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CMC Reviewer: Ying Wang, Ph.D.
Branch Chief: Moo Jhong Rhee, Ph.D.,
Project Managers: Linda Mullins-Athey, ONDQA PM, John Kim, OND PM

C. CC Block

45 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Ying Wang
6/15/2007 04:17:40 PM
CHEMIST

Moo-Jhong Rhee
6/15/2007 04:28:09 PM
CHEMIST
Chief, Branch III

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division: Division of Reproductive and Urologic Products
NDA: 22-057
Applicant: Ferring Pharmaceuticals
Stamp Date: 21-Aug-2006
PDUFA Date: 21-Jun-2007
Trademark: Endometrin
Established Name: Progesterone
Dosage Form: Effervescent vaginal tablet
Route of Administration: Vaginal
Indication: Pregnancy through progesterone supplementation as part of an ART treatment program for _____

b(4)

PAL: Donna F. Christner, Ph.D.

	YES	NO
ONDQA Fileability:	x	<input type="checkbox"/>
Comments for 74-Day Letter	x	<input type="checkbox"/>

Summary and Critical Issues:

A. Summary

Endometrin is an effervescent vaginal tablet containing 100 mg of micronized progesterone, used for progesterone supplementation as part of an Assisted Reproductive Technology (ART) treatment for infertile women with progesterone deficiency. The tablets are packaged in aluminum/aluminum peel blisters. A commercially available, disposable tablet insertion device is provided in the product package to facilitate insertion of the tablets into the vagina. It is typically administered two or three times a day (BID or TID).

Clinical trials were conducted under IND 68,097, which was opened on 19-May-2004. CMC-related regulatory guidance was provided in a number of meetings/correspondences with the company:

- preIND meeting held 23-Oct-2003
- CMC type C meeting held 28-Jun-2004
- EOP2 CMC meeting scheduled for 09-Jan-2006
- preNDA meeting held on 31-May-2006

The sponsor has licensed the product from an Israeli company and has transferred the formulation and manufacturing process to the US. The formulation is identical to the Israeli product, which has been commercially available in Israel and Hong Kong since 2003. The same formulation has been used throughout the clinical trials. There have been no changes in the manufacturing process.

An overview of the application is provided in the ASSESSMENT NOTES.

B. Critical issues for review

The drug substance DMF is currently inadequate and will require review. A test for _____
_____ has been added to the specification and validated by the drug product manufacturer and
will require review.

b(4)

The sponsor sanitizes all drug-contact parts of the manufacturing equipment with _____ . It is
unclear whether the packaging line is also sanitized. A microbiology consult was sent on 22-Sep-
2006 to determine if adequate controls are in place to assure that there is no contamination of the
dosage form and that microbial growth would not be an issue for the vaginal tablet.

b(4)

Dissolution specifications are set at _____ . This will need to be evaluated to see if the
specification is adequate in order to assure product quality.

b(4)

Packaging DMFs may require review if there is not enough information provided in the NDA.

The sponsor has listed the established name as _____ . This
will require critical evaluation.

b(4)

C. Comments for 74-Day Letter

The following comments should be conveyed to the sponsor, either in the 74-day letter or in
an Information Request letter as early as possible in the review cycle.

*Please state whether the blister line is also sanitized prior to a packaging run. Please provide
information on the steps taken to ensure the drug product is not contaminated prior to or during
packaging into blisters.*

*The Dissolution specification limit is listed as either _____ (Q) in 20 minutes in
different parts of the NDA. Please identify which limit is correct and update the specification
sheet if necessary. The appropriateness of the Dissolution Specification will be a review issue.*

b(4)

*The established name _____ will be reviewed by the ONDQA.
to determine if the term _____ is appropriate.*

b(4)

D. Recommendation:

This NDA is fileable from a CMC perspective. There are four comments to be conveyed to the
sponsor in the 74-day letter. A single reviewer, Ying Wang, has been assigned. In accordance
with the GRMP guidelines, the review will need to be completed at month 8, which would be 21-
May-2007.

Donna F. Christner, Ph.D.

Filing Checklists

A. Administrative Checklists;

YES	NO		Comments
X		On its face, is the section organized adequately?	
X		Is the section indexed and paginated adequately?	
X		On its face, is the section legible?	
X		Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	
X		Has an environmental assessment report or categorical exclusion been provided?	Categorical exclusion claimed as per 21 CFR 25.20

B. Technical Checklists;

1. Drug Substance

X		Does the section contain synthetic scheme with in-process parameters?	DMF	/
X		Does the section contain structural elucidation data?	DMF	
X		Does the section contain specifications?	DMF	
X		Does the section contain information on impurities?	DMF	
X		Does the section contain validation data for analytical methods?	DMF	
X		Does the section contain container and closure information?	DMF	
X		Does the section contain stability data?	DMF	

b(4)

2. Drug Product

X		Does the section contain manufacturing process with in-process controls?	
X		Does the section contain quality controls of excipients?	
X		Does the section contain information on composition?	
X		Does the section contain specifications?	Scanned master specification sheet
X		Does the section contain information on degradation products?	
X		Does the section contain validation data for analytical methods?	
x		Does the section contain information on container and closure systems?	
X		Does the section contain stability data with a proposed expiration date?	24 month expiry proposed (QOS)
x		Does the section contain information on labels of container and cartons?	
x		Does the section contain tradename and established name?	

C. Review Issues

x		Has all information requested during the IND phases, and at the pre-NDA meetings been included?	
	x	Is a team review recommended?	
x		Are DMFs adequately referenced?	

DMF No.	Holder	Description	LOA Included	Status
_____	_____	Progesterone USP	Yes	Inadequate on 18-June-2002 by A. Raw for _____
_____ _____	_____	/	Yes (in Container closure system section)	
_____ _____	_____	_____	Yes (in Container closure system section)	Adequate on 23-May-2003 by B. Ho for NDA 16-324/S-029
_____ Dated 5/1999, Section 3, Pg 13	_____	/	Yes	
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ASSESSMENT NOTES

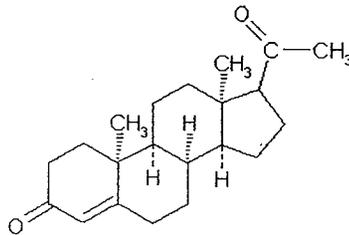
Clinical trials were conducted under IND 68,097, which was opened on 19-May-2004. The sponsor has licensed the product from an Israeli company and has transferred the formulation and manufacturing process to the US. The formulation is identical to the Israeli product, which has been commercially available in Israel and Hong Kong since 2003. The following CMC-related meetings and or correspondences took place between the sponsor and FDA:

- **preIND meeting held 23-Oct-2003:** No CMC questions were asked, but the following comments were conveyed to the sponsor.
 - Sponsor was referred to the Guidances for Phase 1 and Phase 2/3 studies
 - For drug substance, it was recommended that the sponsor include a description of the drug substance, name and address of the manufacturer, DMF reference, specifications and stability.
 - For drug product, it was recommended that a list of components, quantitative composition, name of manufacturer, brief description of manufacturing and packaging, specifications, stability, copies of labels and a claim for a categorical exclusion be provided in the IND
- **CMC type C meeting held 28-Jun-2004:** A teleconference was held to give guidance on primary stability batches. In response to questions, FDA stated that:
 - studies should be conducted on at least three primary batches of the drug product with the same formulation and container closure as proposed for marketing.
 - The process should be comparable to production batches and should meet the same specifications as intended for marketing. Two of the three batches should be at least pilot scale, and the third could be smaller if justified.
 - Where possible, different batches of drug substance should be used to manufacture the drug product batches. Stability studies should be performed on each individual strength and container size, unless bracketing or matrixing is applied.Sponsor asked if the original clinical trial material [redacted] could be used as the registration/primary stability batches for both strengths, and if [redacted] could be used as registration batches (commercial batch size). The answer was Yes to both inquiries, taking into account the second comment given. b(4)
- **EOP2 CMC meeting scheduled for 09-Jan-2006:** The sponsor submitted three CMC questions for this meeting. Responses were adequate and used as meeting minutes.
 - Three primary stability batches were manufactured using the same formulation and container closure system as proposed for marketing. Two batches were manufactured [redacted] and one was manufactured from a [redacted]. Do these qualify as primary stability batches. As per our response from the 28-Jun-2004 meeting, these batches qualify b(4)
 - Sponsor submitted specifications and asked if there were any issues with the specifications. A question was raised concerning the method for assay and dissolution. Sponsor provided the information, and the sponsor was informed that there were no further issues with the specifications, but the validation of the methods would be a review issue upon NDA filing.
 - The sponsor questioned whether the stability specifications were adequate. FDA responded Yes.
 - Sponsor was reminded to submit Letters of Authorization for the DMFs for the drug substance and container closure system.

- **preNDA meeting held on 31-May-2006:** Sponsor asked one CMC question concerning whether the container closure system (foil pouches which are paper-backed) would be a concern for child resistance (they have not been tested). We agreed with their assessment that because it is not an oral dosage form and is a naturally occurring hormone which is exempt for HRT, that FDA had no issues with child resistance for the packaging, but they were referred to the Poison Prevention Packaging Act.

DRUG SUBSTANCE

T



b(4)

Information is provided in DMF — A LOA is provided to reference the information. The DMF will require review.

b(4)

Drug substance is manufactured at the following facility:

~~_____~~

b(4)

Drug substance is released by USP compendial testing. Methods used are those in the compendia. The DMF holder performs particle size distribution by _____ particle size measurement. It is also performed _____ to permit characterization of the starting material used to make the drug product. **A test for _____ has been added to the specification and validated by the drug product manufacturer and will require review.**

b(4)

The sponsor has submitted both the COA provided by the DMF holder and the results of their own release testing for the API.

DRUG PRODUCT

Endometrin is an effervescent vaginal tablet containing 100 mg of progesterone, used for progesterone supplementation as part of an Assisted Reproductive Technology (ART) treatment for infertile women with progesterone deficiency. The tablets are packaged in aluminum/aluminum peel blisters. A commercially available, disposable tablet insertion device is provided in the product package to facilitate insertion of the tablets into the vagina. It is typically administered two or three times a day (BID or TID).

The sponsor has licensed the product from an Israeli company. Pharmaceuticals International Incorporated (PII) was contracted to transfer the formulation and manufacturing process. After some development work, it was decided that the final formulation would be identical to the original Israeli formula and was used for scale up and clinical supplies. The clinical trials were conducted with 50 mg and 100 mg tablets which are identical in formulation to the Israeli commercial product and the test article used in the animal toxicology studies (test article was not compressed). The formulation for the 100 mg tablets used in the Phase 1/2 and Phase 3 are identical to the commercial formulation, which is as follows:

Ingredient	Function	Supplier	%	Mg/tablet
Progesterone, USP (Micronized)	API		8.00	100.0
Colloidal Silicone Dioxide, NF				
Lactose Monohydrate, NF				
Pregelatinized Starch, NF				
Polyvinylpyrrolidone, USP				
Adipic Acid, FCC				
Sodium Bicarbonate, USP				
Sodium Lauryl Sulfate, NF				
Magnesium Stearate, NF				
Total			100.0%	1250.0

b(4)

All excipients meet compendial standards. Adipic acid, food grade (FCC) was used and additionally tested against EP specifications and qualified for use in the formulation. The sponsor states the batches intended for marketing will contain adipic acid meeting the requirements of the recently published NF (2005) monograph. Magnesium stearate is from _____ A _____ statement is included, although, as per policy, magnesium stearate derivatives are not tracked in SPOTS.

b(4)

Comment: The NF(2005) monograph for adipic acid is identical to the EP monograph. Therefore, the change from adipic acid FCC to adipic acid NF is acceptable.

The following facilities have manufacturing responsibilities:

Manufacture, release testing, packaging, stability testing

b(4)

Laser light scattering particle size analysis

b(4)

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

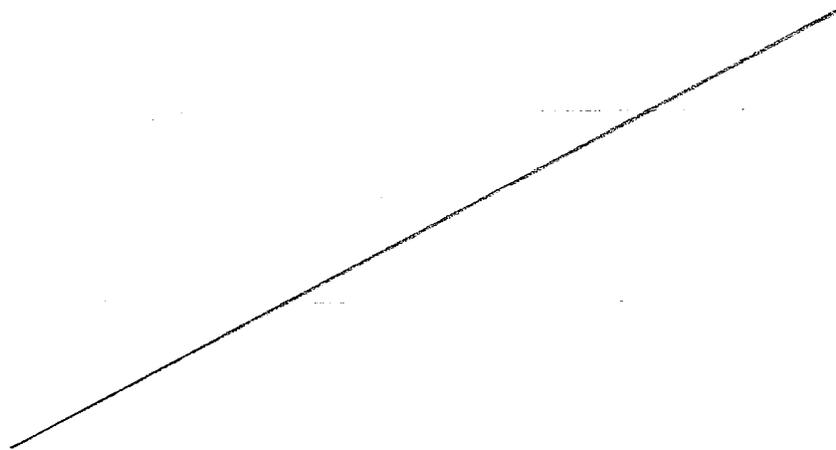
Draft Labeling (b5)

Deliberative Process (b5)

b(4)

The sponsor has established the following acceptance criteria for the drug product. Batch analysis for the three clinical/stability batches is also provided in the table. Dissolution testing is performed with Appartus II (paddles) at 50 RPM in 900 ml 0.25% SDS in DI H₂O, with a draw time of 20 minutes. A development report is included to justify the Dissolution conditions.

Table A Batch Analysis for Three Clinical/Stability Batches of Progesterone Vaginal Tablets, 100 mg



b(4)

Stability studies consist of the same tests, except for Content Uniformity and Microbial Limits. In a conversation with James McVey, Ph.D., Microbiology Team Leader, concerning the lack of a Microbial Limits test on stability, he was more concerned with the moisture limit of — because this could allow microbial growth. Other approved vaginal tablets contain a specification for microbial growth on stability, —. An official consult was sent to Microbiology on 22-Sep-2006 concerning these two issues and a comment included to the sponsor in the 74-day letter.

b(4)

—, it is important to control the moisture content in this type of dosage form. At first glance, the limit for water — (by Karl Fischer) for this drug product may be high. Other effervescent tablets have a much lower moisture limit (measured by Loss on Drying). For this formulation, Karl Fischer is the appropriate test because the major excipient (lactose monohydrate, —) is a hydrate. Analysis of the tablet formulation, taking into account the amount of excipients used in the tablet and the limits for — allowed by USP/NF, indicate that the moisture could be as high as 5.8-6.4% solely as a function of the excipients used. It would be difficult to significantly lower the water content in the dosage form below what is inherently contained in the excipients. This theoretical range is in line with what was measured in the clinical supplies at release and stability, which

b(4)

indicates that water content at this level in this tablet formulation is a property of the formulation and does not adversely affect the performance of the tablet, assuming that clinical determines that the product is safe and efficacious.

Comment: A consult will be sent to Microbiology to determine if a specification for Microbial Limits should be included on stability, and if the Moisture Limit is appropriate for this dosage form from a microbiological standpoint.

In the package, the sponsor identifies the Dissolution specification limit as either NLT — or NLT — (Q) in 20 minutes. The sponsor should identify which limit is correct and update the specification sheet if necessary. The appropriateness of the Dissolution Specification and Acceptance Criteria will be a review issue.

b(4)

Tablets are packaged in Aluminum/Aluminum peel blisters, one tablet per blister. LOAs to reference the components of the blister are provided. The DMFs may require review unless there is enough information provided in the NDA (See DMF table in this document). The sponsor originally used [redacted] which was discontinued by [redacted]. [redacted] has provided documentation (included in the NDA) that addresses the interchangeability of the [redacted] which is the replacement stock. An over wrapped, commercially-available, disposable vaginal applicator is co-packaged with the tablets. A LOA is provided to reference the applicator material, but product contact with the applicator is minimal (only immediately prior to insertion of the dosage form in the vagina), so compatibility should not be an issue. Labeling for the cartons and the Physician insert is provided in Module 1 of the NDA. Labeling for the blister cards (and cartons) are provided in the Section 3.2.P.7 Container closure system of Module 3. Instructions for loading of the tablet into the applicator is provided in the Patient Package Insert. It is a review issue on whether this is sufficient or if the information should be included either on the carton or on the overwrap. There is no text provided for the vaginal applicator overwrap. Samples of the tablets and applicators were requested on 22-Sep-2006 and received on 28-Sep-2006. The overwrap is clear. It was confirmed by the sponsor on 29-Sep-2006 that the overwrap on the samples is the same as that to be used on the commercial applicator.

b(4)

The sponsor is requesting a 24 month expiry. Stability data is provided for three lots of drug product. One lot (batch size [redacted] has 24 months of long term stability date, while the other two lots (batch size [redacted], which is the commercial batch size) have 12 months of long term stability. It was agreed prior to NDA submission that these lots would be acceptable for use as the primary stability batches.

b(4)

Establishment inspections were requested on 15-Sep-2006. As of 18-Sep-2006, all facilities except the drug product manufacturing site (PII) are acceptable. The PII site has been submitted to the District Office for a decision on whether an inspection would be assigned.

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ESTABLISHED NAME

The sponsor has proposed the established name to be: **progesterone** ——— **vaginal tablet**. Although ——— is normally indicative of a dosage form that must be dissolved or dispersed in water before (oral) administration, and which is not to be swallowed directly, this modifier accurately describes this tablet which contains a mixture of adipic acid and sodium bicarbonate, as per definition. It would be prudent to include this description or another modifier in the established name in order to minimize confusion with future generic products. **Tablet** (instead of insert) would also correspond to other approved vaginal tablets on the market.

b(4)

Justification

Sponsor has provided the manufacturing patent which contains the following statement:

b(4)

The following paragraph has been taken from the application, comparing the blood levels of progesterone from the tablet, an IM injection, and a vaginal gel:

The pharmacokinetic profile of Endometrin was compared to both progesterone in sesame oil IM (Study 2004-01) and Crinone vaginal gel (Studies 2005-08 and 2004-02). The pharmacokinetic profile of Endometrin fell between these 2 products currently in clinical use. Circulating progesterone concentrations from both Endometrin BID and Endometrin TID were higher than with Crinone but lower than with progesterone IM, and well within the range considered clinically efficacious. Endometrin would be expected to have fewer adverse effects than progesterone IM and to be at least as effective as Crinone.

Therefore, the effervescence aids in delivery of the drug substance and is an important quality of the drug product.

Recommendation:

If the effervescent action of the tablet is deemed important for the efficacy of the drug product, then it should be captured in the established name to distinguish it from other tablets that do not contain an effervescent, either with the modifier "effervescent" or with an alternate modifier. This will have a direct impact on future generics. There are approved vaginal tablets that are extended release (over 10 hours), labeled as vaginal tablets, so effervescent will distinguish these tablets, resulting in less prescribing errors.

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

/s/

Donna Christner
11/14/2006 05:10:50 PM
CHEMIST

changes made .

Moo-Jhong Rhee
11/14/2006 05:19:31 PM
CHEMIST
Chief, Branch III