

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022501Orig1s000

CHEMISTRY REVIEW(S)

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application:	NDA 22501/000	Action Goal:	
Stamp Date:	26-MAR-2009	District Goal:	22-AUG-2010
Regulatory:	21-OCT-2010		
Applicant:	WARNER CHILCOTT CO 100 ENTERPRISE DR STE 280 ROCKAWAY, NJ 07866	Brand Name:	(b) (4)
		Estab. Name:	norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets,
		Generic Name:	
Priority:	3S	Product Number; Dosage Form; Ingredient; Strengths	
Org. Code:	580		001; TABLET; NORETHINDRONE ACETATE; 1MG 001; TABLET; ETHINYL ESTRADIOL; 10UGM 003; TABLET; FERROUS FUMARATE; POTENCY NOT GIVEN 002; TABLET; ETHINYL ESTRADIOL; 10UGM
Application Comment:	THIS NDA IS FOR A LOW DOSE ORAL CONTRACEPTIVE, CONSISTING OF 10 MCG OF ETHINYL ESTRADIOL USP (EE) AND 1 MG OF NORETHINDRONE ACETATE USP (NA) DAILY FOR 24 DAYS, FOLLOWED BY A DAILY DOSE OF 10 MCG OF ETHINYL ESTRADIOL USP FOR 2 DAYS, THEN FERROUS FUMARATE FOR 2 DAYS. (on 29-APR-2009 by J. DAVID () 301-796-4247)		
	THIS IS AN NDA RESUBMISSION (CLASS 2, 6 MONTH REVIEW CLOCK). THE NDA PDUFA GOAL DATE IS: 21-OCT-2010. (on 03-MAY-2010 by J. DAVID () 301-796-4247)		
FDA Contacts:	C. TRAN-ZWANETZ	Project Manager	(HFD-800) 301-796-3877
	Y. TANG	Review Chemist	301-796-2457
	D. CHRISTNER	Team Leader	301-796-1341
Overall Recommendation:	ACCEPTABLE	on 26-MAY-2010	by A. INYARD ()
	WITHHOLD	on 19-JAN-2010	by E. JOHNSON (HFD-320) 301-796-3334

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

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

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE OTHER TESTER

Estab. Comment: THIS SITE IS FOR CONTRACT ANALYTICAL TESTING OF DRUG SUBSTANCES AND INACTIVE COMPONENTS. (on 29-APR-2009 by J. DAVID () 301-796-4247)
THE ADDRESS GIVEN FOR THIS SITE IN THE NDA IS: (b) (4)
THIS ADDRESS IS CONFIRMED ON THE FIRM'S WEBSITE FOR ANALYTICAL TESTING. (THE ADDRESS (b) (4)
(b) (4) ADDRESS.) THE FULL EMAIL FOR THE CONTACT AT THIS SITE GIVEN IN THE NDA IS:
(b) (4) (on 03-MAY-2010 by J. DAVID () 301-796-4247)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	29-APR-2009				DAVIDJE
OC RECOMMENDATION	01-MAY-2009			ACCEPTABLE BASED ON PROFILE	FERGUSONS
SUBMITTED TO OC	03-MAY-2010				DAVIDJE
OC RECOMMENDATION	03-MAY-2010			ACCEPTABLE BASED ON PROFILE	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
 (b) (4)
DMF No: (b) (4) **AADA:**
 (b) (4)
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Estab. Comment: THIS SITE IS FOR DRUG SUBSTANCE MANUFACTURE FOR ETHINYL ESTRADIOL USP AND NORETHINDRONE ACETATE USP. (on 24-APR-2009 by J. DAVID () 301-796-4247).
 THE FEI NUMBER PROVIDED IN THE NDA IS (b) (4) (NOT FOUND IN EES DATABASE). THE FULL ADDRESS GIVEN IN THE NDA IS: (b) (4) (b) (4)
 (b) (4). (on 03-MAY-2010 by J. DAVID () 301-796-4247)
Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	29-APR-2009				DAVIDJE
SUBMITTED TO DO	01-MAY-2009	10-Day Letter			STOCKM
ASSIGNED INSPECTION TO IB	04-MAY-2009	GMP Inspection			JOHNSONE
DO RECOMMENDATION	19-JAN-2010			WITHHOLD PEND REG ACTION - WARNING LTR	JOHNSONE
OC RECOMMENDATION	19-JAN-2010			WITHHOLD DISTRICT RECOMMENDATION	JOHNSONE
INSPECTION PERFORMED See EIR in Turbo.	12-FEB-2010		12-FEB-2010		MCASALE
DO RECOMMENDATION	09-APR-2010			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	12-APR-2010			ACCEPTABLE DISTRICT RECOMMENDATION	JOHNSONE
SUBMITTED TO OC	03-MAY-2010				DAVIDJE
OC RECOMMENDATION	03-MAY-2010			ACCEPTABLE BASED ON PROFILE	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

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

DMF No: (b) (4) **AADA:**
 (b) (4)

Responsibilities: DRUG SUBSTANCE (b) (4)

Estab. Comment: THIS SITE IS FOR DRUG SUBSTANCE (b) (4) FOR ETHINYL ESTRADIOL USP AND NORETHINDRONE ACETATE USP. (on 24-APR-2009 by J. DAVID () 301-796-4247)
 THE FULL ADDRESS GIVEN IN THE NDA IS (b) (4) (b) (4)
 (b) (4) (on 03-MAY-2010 by J. DAVID () 301-796-4247)

Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	29-APR-2009				DAVIDJE
OC RECOMMENDATION INSPECTION CONDUCTED	01-MAY-2009	(b) (4)	COVERED THE CSN PROFILE; CLASSIFIED NAI.	ACCEPTABLE BASED ON PROFILE	STOCKM
SUBMITTED TO OC	03-MAY-2010				DAVIDJE
OC RECOMMENDATION	03-MAY-2010			ACCEPTABLE BASED ON PROFILE	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4)

[Redacted]

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE OTHER TESTER

Estab. Comment: THE FULL ADDRESS GIVEN IN THE NDA IS: (b) (4)
(b) (4) (on 03-MAY-2010 by J. DAVID () 301-796-4247)
THIS SITE IS FOR CONTRACT ANALYTICAL TESTING OF DRUG SUBSTANCES AND INACTIVE COMPONENTS. THIS SITE IS ALSO FOR (b) (4); (on 24-APR-2009 by J. DAVID () 301-796-4247)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	29-APR-2009				DAVIDJE
OC RECOMMENDATION	01-MAY-2009			ACCEPTABLE BASED ON PROFILE	FERGUSONS
SUBMITTED TO OC	03-MAY-2010				DAVIDJE
OC RECOMMENDATION	03-MAY-2010			ACCEPTABLE BASED ON PROFILE	STOCKM

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

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

DMF No: (b) (4) **AADA:**
 (b) (4)

Responsibilities: DRUG SUBSTANCE MANUFACTURER
 DRUG SUBSTANCE (b) (4)

Estab. Comment: THE FULL ADDRESS PROVIDED IN THE NDA IS: (b) (4)
 (b) (4) (on 03-MAY-2010 by J. DAVID () 301-796-4247)
 THIS SITE IS FOR DRUG SUBSTANCE MANUFACTURE AND (b) (4) FOR ETHINYL ESTRADIOL USP AND
 NORETHINDRONE ACETATE USP. (on 24-APR-2009 by J. DAVID () 301-796-4247)

Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	29-APR-2009				DAVIDJE
OC RECOMMENDATION	01-MAY-2009			ACCEPTABLE	STOCKM
INSPECTION CONDUCTED (b) (4) CLASSIFIED VAI AND COVERED THE CSN PROFILE. FIRM'S RESPONSE TO RAI LETTER REVIEWED BY HM AND DEEMED ACCEPTABLE.				BASED ON PROFILE	
SUBMITTED TO OC	03-MAY-2010				DAVIDJE
OC RECOMMENDATION	03-MAY-2010			ACCEPTABLE	STOCKM
				BASED ON PROFILE	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

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

(b) (4)

(b) (4)

DMF No: (b) (4) **AADA:**

(b) (4)

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE (b) (4)

Estab. Comment: THE FULL ADDRESS PROVIDED IN THE NDA IS: (b) (4)
(b) (4) (on 03-MAY-2010 by J. DAVID () 301-796-4247)

THIS SITE IS FOR DRUG SUBSTANCE MANUFACTURE AND (b) (4) FOR ETHINYL ESTRADIOL USP AND
NORETHINDRONE ACETATE USP. (on 24-APR-2009 by J. DAVID () 301-796-4247)

Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	29-APR-2009				DAVIDJE
OC RECOMMENDATION	01-MAY-2009			ACCEPTABLE	STOCKM
INSPECTION CONDUCTED (b) (4) CLASSIFIED VAI AND COVERED THE CSN PROFILE. FIRM'S RESPONSE TO RAI LETTER ADEQUATELY ADDRESSED ISSUES. COMPLIANCE REVIEW DONE BY HM.				BASED ON PROFILE	
SUBMITTED TO OC	03-MAY-2010				DAVIDJE
OC RECOMMENDATION	03-MAY-2010			ACCEPTABLE	STOCKM
				BASED ON PROFILE	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: 2619635 FEI: 2619635
 WARNER CHILCOTT COMPANY, INC.
 RD 195 KM 1.1
 FAJARDO, PR 00738

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER
 FINISHED DOSAGE MANUFACTURER
 FINISHED DOSAGE OTHER TESTER
 FINISHED DOSAGE PACKAGER

Estab. Comment: THIS SITE IS FOR ANALYTICAL TESTING AND RELEASE OF THE DRUG SUBSTANCE AND INACTIVE COMPONENTS. THIS SITE IS ALSO FOR MANUFACTURING, IN-PROCESS TESTING, AND PACKAGING OF THE DRUG PRODUCT. (on 24-APR-2009 by J. DAVID () 301-796-4247)
 THE FULL ADDRESS GIVEN FOR THIS SITE IN THE NDA IS: WARNER CHILCOT COMPANY, LLC, ROAD 195 (UNION STREET) KM 1.1, ARJARDO, PR 00738-1005. (on 03-MAY-2010 by J. DAVID () 301-796-4247)

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	29-APR-2009				DAVIDJE
SUBMITTED TO DO	01-MAY-2009	10-Day Letter			FERGUSONS
DO RECOMMENDATION	18-MAY-2009			ACCEPTABLE	RHERNAND
ACCEPTABLE RECOMMENDATION BASED ON PREVIOUS INSPECTION RESULTS (NAI INSPECTION DATES: 08/1809 TO 09/15/08)				BASED ON FILE REVIEW	
RECOMMENDATION	19-MAY-2009			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	03-MAY-2010				DAVIDJE
SUBMITTED TO DO	03-MAY-2010	10-Day Letter			STOCKM
DO RECOMMENDATION	26-MAY-2010			ACCEPTABLE	RHERNAND
ACCEPTABLE RECOMMENDATION BASED ON FIRM PREVIOUS INSPECTION CLASSIFICATION, VAI DATED 12/29/2009. PROFILE CLASS TCM IS CLASSIFIED AS ACCEPTABLE IN FACTS				BASED ON FILE REVIEW	
OC RECOMMENDATION	26-MAY-2010			ACCEPTABLE	INYARDA
				DISTRICT RECOMMENDATION	

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: **CFN:** **FEI:** 3007097388

WARNER CHILCOTT UK LTD

OLD BELFAST ROAD
LARNE, , UNITED KINGDOM BT40 2SH

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Estab. Comment: THE FULL ADDRESS GIVEN FOR THIS SITE IN THE NDA IS: WARNER CHILCOTT UK LIMITED, OLD BELFAST ROAD, MILLBROOK, LARNE, NORTHERN IRELAND BT40 2SH. (on 03-MAY-2010 by J. DAVID () 301-796-4247)
THIS SITE IS FOR IN-PROCESS CHEMICAL TESTING (NO MANUFACTURING FUNCTION), RELEASE AND STABILITY TESTING OF THE DRUG PRODUCT. (on 03-MAY-2010 by J. DAVID () 301-796-4247)
THIS SITE IS FOR BACK-UP IN-PROCESS, RELEASE AND STABILITY TESTING OF THE DRUG PRODUCT. (on 16-JUN-2009 by J. DAVID () 301-796-4247)

Profile: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	16-JUN-2009				DAVIDJE
OC RECOMMENDATION	16-JUN-2009			ACCEPTABLE BASED ON PROFILE	JOHNSONE
SUBMITTED TO OC	03-MAY-2010				DAVIDJE
SUBMITTED TO DO	03-MAY-2010	GMP Inspection			STOCKM
RECOMMENDATION	06-MAY-2010			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	11-MAY-2010			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

NDA 22-501**Lo Loestrin[®] Fe^{*}**
(norethindrone acetate and ethinyl estradiol
tablets, ethinyl estradiol tablets
and ferrous fumarate tablets)

* The previous proprietary name stated in Review #1 was (b)

Warner Chilcott Company, Inc.**Yubing Tang, Ph.D.****Branch VI, Division of New Drug Quality Assessment II**
Office of New Drug Quality Assessment**CMC Review of NDA 22-501**
For Division of Reproductive and Urologic Products

Chemistry Review Data Sheet

1. NDA: 22-501
2. REVIEW: #2
3. REVIEW DATE : September 14, 2010
4. REVIEWER: Yubing Tang, Ph.D.
5. PREVIOUS DOCUMENTS:
NDA 22-501, CMC Review #1, January 07, 2010
Addendum to NDA 22-501 CMC Review #1, January 22, 2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
Resubmission

Document Date
April 20, 2010

7. NAME & ADDRESS OF APPLICANT:

Name: Warner Chilcott Co., Inc.
Address: Union Street, Rd. 195 Km 1.1
Fajardo, PR 00738-1005
Representative: 100 Enterprise Drive
Rockaway, NJ 07866
Telephone: 973-442-3200

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: *Lo Loestrin® Fe*
(Note: *Lo Loestrin® Fe* is the proprietary name in the resubmission. Formerly, the proprietary name was (b) (4) and was not accepted by DMEPA.)
- b) Non-Proprietary Name (USAN): norethindrone acetate/ethinyl estradiol
- c) Code Name/# (ONDQA only): none

Chemistry Review Data Sheet

d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL CATEGORY: Prevention of Pregnancy

11. DOSAGE FORM: tablets

12. STRENGTH/POTENCY: 1mg norethindrone acetate /10mcg ethinyl estradiol, 10mcg ethinyl estradiol

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC

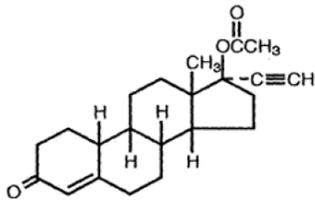
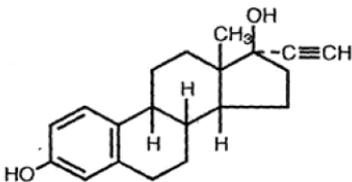
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

 SPOTS product – Form Completed Not a SPOTS product

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

Chemical Name:	Norethindrone acetate: (17 α)-17-(acetyloxy)-19-norpregn-4-en-20-yn-3-one Ethinyl Estradiol: (17 α)-19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol
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Chemistry Review Data Sheet

Structure Formula:	 <p style="text-align: center;">Norethindrone Acetate</p>  <p style="text-align: center;">Ethinyl Estradiol</p>
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Molecular Formula:	<ul style="list-style-type: none"> Norethindrone Acetate: $C_{22}H_{28}O_3$ Ethinyl Estradiol: $C_{20}H_{24}O_2$
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Molecular Weight:	<ul style="list-style-type: none"> Norethindrone acetate: 340.46 Ethinyl Estradiol: 296.40
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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Drug Substance (ethinyl estradiol)	3	adequate	July 07, 2010	Reviewed by Dr. J. Ping
	II		Drug Substance (norethindrone acetate)	3	adequate	August 01, 2008	Reviewed by Dr. J. Chang
	II		Drug Substance (ethinyl estradiol)	3	adequate	March 10, 2010	Reviewed by Dr. J. Chang
	II		Drug Substance (norethindrone acetate)	3	adequate	June 27, 2010	Reviewed by Dr. Z. Bahar
	III		(b) (4)	1	adequate	November 30, 2009	Reviewed by Dr. Y. Tang
	III			3	adequate	August 04, 2008	Reviewed by Dr. J. Chang

¹ Action codes for DMF Table:

Chemistry Review Data Sheet

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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
CMC Review #1, Feb. 16, 2006	NDA 21-871	<i>Loestrin</i> [®] 24 Fe was approved under NDA 21-871, which uses the same drug substances for the same indication, and is sponsored by the same applicant. NDA 22-501 is cross-referenced to NDA 21-871.

18. CONSULTS/CMC-RELATED REVIEWS:

Not applicable.

The Chemistry Review for NDA 22-501

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The previous Review #1 noted that this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product with adequate information on labels and labeling, except for an overall “Withhold” recommendation from the Office of Compliance.

Now, the Office of Compliance has made the overall “Acceptable” recommendation.

Therefore, from the CMC perspective, this NDA is recommended for approval.

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

Not applicable.

II. Summary of Chemistry Assessments

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

1) Drug Product

The proposed drug product, *Lo Loestrin® Fe* (norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets and ferrous fumarate tables), is a low dose oral contraceptive consisting of new dose and new regimen of the combination of norethindrone acetate (NA) and ethinyl estradiol (EE). *Lo Loestrin® Fe* is packaged in a unit-dose blister card (dispensers) containing 24 blue active tablets, 2 white active tablets and 2 brown placebo tablets.

- Each blue, round tablet contains 1 mg of norethindrone acetate, USP and 10 mcg of ethinyl estradiol, USP and is imprinted with WC on one side and 421 on the other.
- Each white, hexagonal tablet contains 10 mcg of ethinyl estradiol, USP and is imprinted with WC on one side and 422 on the other.
- Each brown, round placebo tablet contains 75 mg ferrous fumarate, USP and is imprinted with WC on one side and 624 on the other. The ferrous fumarate tablets are non-hormonal and non-therapeutic, present to facilitate ease of drug administration via a 28-day regimen.

Executive Summary Section

The following compendial excipients are contained in *Lo Loestrin® Fe*: mannitol, USP, microcrystalline cellulose, NF, FD&C Blue No. 1 Aluminum Lake (FD&C certified), sodium starch glycolate, NF, magnesium stearate, NF, povidone, USP, vitamin E, USP, lactose monohydrate, NF and sucralose, NF. The spearmint flavor in ferrous fumarate tablets is the only non-compendial excipient; however contains GRAS ingredients and has been used in other FDA approved drug products.

Lo Loestrin® Fe active tablets are manufactured using a (b) (4) process. Ethinyl estradiol, USP is (b) (4)

Container closure system for *Lo Loestrin® Fe* tablet regimen is a unit-dose blister consisting of a (b) (4) blister lidding and aluminum foil/ (b) (4) (b) (4) backing. Non-functional secondary packaging components consist of a rigid (b) (4) card (b) (4) to the unit-dose blister, a (b) (4) pouch, a (b) (4) overwrap film, prescriber and patient package inserts and (b) (4) cartons.

Based on the provided stability study data, the proposed 24 months expiration dating period is granted for *Lo Loestrin® Fe* tablets under the labeled storage conditions (stored at 25°C (77°F); excursion permitted to 15 - 30°C (59 - 86°F)).

2) Drug Substance

There are two drug substances in *Lo Loestrin® Fe*, Norethindrone acetate, USP and ethinyl estradiol, USP. The drug substances are synthetic hormones widely used as components of combination oral contraceptives. The NA and EE used in *Lo Loestrin® Fe* tablets are sourced from (b) (4). Information about the manufacture, characterization, quality control, container closure system and stability for each drug substance from each manufacturer is contained in drug master files (b) (4). LOAs (Letter of Authorization) from the holders of DMFs are provided. All DMFs have been recently reviewed and found to be adequate.

B. Description of How the Drug Product Is Intended to Be Used

Lo Loestrin® Fe is indicated for the prevention of pregnancy in women (b) (4). The dosage of *Lo Loestrin® Fe* is one blue tablet containing norethindrone acetate and ethinyl estradiol daily for 24 consecutive days, followed by one white tablet containing ethinyl estradiol daily for 2 consecutive days, followed by one brown non-hormonal (placebo) tablet containing ferrous fumarate daily for 2 consecutive days. The ferrous fumarate tablets do not serve any therapeutic purpose.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

This NDA provided adequate information on the raw material controls, manufacturing process, specifications, and container/closure system. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during the expiration dating period. Labels have required information. The Office of Compliance has issued the overall "Acceptable" recommendation for all manufacturing and testing facilities.

III. Administrative

A. Reviewer's Signature: In DARRTS

Yubing Tang, Ph.D.
Chemist, Branch VI/DNDQAII/ONDQA

B. Endorsement Block: In DARRTS

Moo-Jhong Rhee, Ph.D.
Branch Chief, Branch IV/DNDQAII/ONDQA

C. CC Block: In DARRTS

8 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22501

ORIG-1

WARNER
CHILCOTT CO INC

 (b) (4)

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

/s/

YUBING TANG
09/16/2010
Thanks.

MOO JHONG RHEE
09/16/2010
Chief, Branch IV

MEMORANDUM

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

DATE: January 22, 2010

TO: NDA 22-501, CMC Review #1

FROM: Yubing Tang, Ph.D., Chemist
(ONDQA Division of Pre-Marketing assessment II)

THROUGH: Moo-Jhong Rhee, Ph.D., Chief, Branch III
(ONDQA Division of Pre-Marketing assessment II)

CC: Donna Christner, Ph.D., Pharmaceutical Assessment Lead
(ONDQA Division of Pre-Marketing assessment II)

SUBJECT: **CMC Recommendation for NDA 22-501 due to
Recent Notification of Unacceptable cGMP
Compliance**

CMC Review #1 was completed on 08-JAN-2010 with all CMC issues resolved except for the absence of an overall “Acceptable” recommendation from the Office of Compliance.

Now the Office of Compliance has issued an overall rating of “Withhold” on 19-JAN-2010 (see attached EES summary report).

Therefore, from a CMC perspective, this NDA is recommended not to approve in its present form until all the facilities involved are fully in compliance with cGMP requirements to assure the identity, strength, purity, and quality of the drug product.

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 22501/000	Sponsor:	WARNER CHILCOTT CO
Org. Code:	580		100 ENTERPRISE DR STE 280
Priority:	3S		ROCKAWAY, NJ 07866
Stamp Date:	26-MAR-2009	Brand Name:	(b) (4)
PDUFA Date:	26-JAN-2010	Estab. Name:	norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets,
Action Goal:		Generic Name:	
District Goal:	27-NOV-2009	Product Number; Dosage Form; Ingredient; Strengths	
			001; TABLET; NORETHINDRONE ACETATE; 1MG 001; TABLET; ETHINYL ESTRADIOL; 10UGM 002; TABLET; ETHINYL ESTRADIOL; 10UGM 003; TABLET; FERROUS FUMARATE; POTENCY NOT GIVEN
FDA Contacts:	J. DAVID	Project Manager	301-796-4247
	Y. TANG	Review Chemist	301-796-2457
	D. CHRISTNER	Team Leader	301-796-1341

Overall Recommendation: WITHHOLD on 19-JAN-2010 by E. JOHNSON (HFD-320) 301-796-3334

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

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-MAY-2009

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

DMF No: (b) (4) AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS **OAI Status:** OAI ALERT

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-JAN-2010

Decision: WITHHOLD

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

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

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-MAY-2009

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE (b) (4)

Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-MAY-2009

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE (b) (4)

Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-MAY-2009

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

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

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-SEP-2009

Decision: WITHHOLD

Reason: DISTRICT RECOMMENDATION
FIRM NOT READY

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

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE (b) (4)

Profile: NON-STERILE BULK BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-MAY-2009

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: 2619635 FEI: 2619635
WARNER CHILCOTT COMPANY, INC.
RD 195 KM 1.1
FAJARDO, PR 00738

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-MAY-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22501

ORIG-1

WARNER
CHILCOTT CO INC

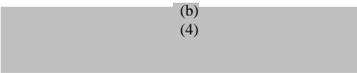
 (b) (4)

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

/s/

YUBING TANG
01/25/2010

MOO JHONG RHEE
01/25/2010
Chief, Branch III

NDA 22-501
(b)
(4)

**(norethindrone acetate and ethinyl estradiol
tablets, ethinyl estradiol tablets
and ferrous fumarate tablets)**

Warner Chilcott Company, Inc.

Yubing Tang, Ph.D.

**Branch III, Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment**

**CMC Review of NDA 22-501
For Division of Reproductive and Urologic Products**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s).....	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation	9
III. Administrative.....	9
A. Reviewer's Signature:	9
B. Endorsement Block:	9
C. CC Block:	9
Chemistry Assessment	10
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	10
S DRUG SUBSTANCE [Norethindrone acetate, USP and ethinyl estradiol, USP, Warner Chilcott Company, Inc]	10
P DRUG PRODUCT [REDACTED] (b) (4) Tablets].....	10
A APPENDICES	65
R REGIONAL INFORMATION	65
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	66
A. Labeling & Package Insert	66
B. Environmental Assessment Or Claim Of Categorical Exclusion	71
III. List Of Deficiencies To Be Communicated.....	71
V. Establishment Inspection Report	71

Chemistry Review Data Sheet

1. NDA: 22-501
2. REVIEW: #1
3. REVIEW DATE : January 07, 2010
4. REVIEWER: Yubing Tang, Ph.D.
5. PREVIOUS DOCUMENTS:
Not applicable

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	March 26, 2009
Amendment ¹	April 22, 2009
Amendment ²	October 16, 2009
Amendment ³	December 17, 2009
Amendment ⁴	December 23, 2009

1. In response to the Agency's communication dated March 26, 2009.
2. In response to the Agency's communication dated September 03, 2009.
3. In response to tele-conference between the Agency and *Warner Chilcott* dated December 14, 2009.
4. In response to the Agency's communication dated December 15, 2009.

7. NAME & ADDRESS OF APPLICANT:

Name: Warner Chilcott Co., Inc.
Address: Union Street, Rd. 195 Km 1.1
Fajardo, PR 00738-1005
Representative: 100 Enterprise Drive
Rockaway, NJ 07866
Telephone: 973-442-3200

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: (b) (4)
(note that this proprietary name is not acceptable by DMEPA. However, as the acceptable proprietary name has not been finalized at the time of filing this review, (b) (4) (b) (4) is remained throughout this CMC review.)
- b) Non-Proprietary Name (USAN): norethindrone acetate/ethinyl estradiol
- c) Code Name/# (ONDQA only): none
- d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 5
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL CATEGORY: Prevention of Pregnancy

11. DOSAGE FORM: tablets

12. STRENGTH/POTENCY: 1mg norethindrone acetate /10mcg ethinyl estradiol, 10mcg ethinyl estradiol

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC

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

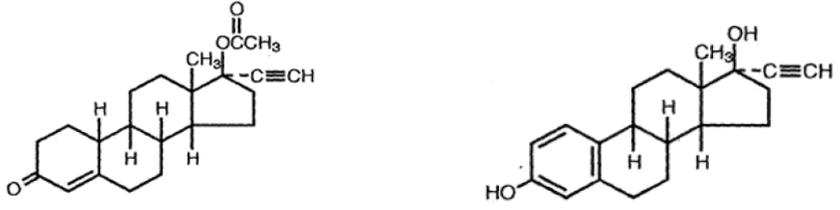
 SPOTS product – Form Completed Not a SPOTS product

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

Chemical Name:	Norethindrone acetate: (17 α)-17-(acetyloxy)-19-norpregn-4-en-20-yn-3-one
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Chemistry Review Data Sheet

	Ethinyl Estradiol: (17 α)-19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol
--	---

Structure Formula:	 <p style="text-align: center;">Norethindrone Acetate Ethinyl Estradiol</p>
--------------------	--

Molecular Formula:	<ul style="list-style-type: none"> • Norethindrone Acetate: C₂₂H₂₈O₃ • Ethinyl Estradiol: C₂₀H₂₄O₂
--------------------	--

Molecular Weight:	<ul style="list-style-type: none"> • Norethindrone acetate: 340.46 • Ethinyl Estradiol: 296.40
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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Drug Substance	3	adequate	April 15, 2009	Reviewed by Dr. G. Sun
	II		Drug Substance	3	adequate	August 01, 2008	Reviewed by Dr. J. Chang
	II		Drug Substance	3	adequate	August 04, 2008	Reviewed by Dr. J. Chang
	II		Drug Substance	3	adequate	February 02, 2009	Reviewed by Dr. U. Atwal
	III		(b) (4)	1	adequate	November 30, 2009	Reviewed by Dr. Y. Tang
	III			3	adequate	August 04, 2008	Reviewed by Dr. J. Chang

Chemistry Review Data Sheet

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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
CMC Review #1, Feb. 16, 2006	NDA 21-871	<i>Loestrin</i> [®] 24 Fe was approved under NDA 21-871, which uses the same drug substances for the same indication, and is sponsored by the same applicant. NDA 22-501 is cross-referenced to NDA 21-871.

18. CONSULTS/CMC-RELATED REVIEWS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending	as of 07-JAN-2010	
Pharm/Tox	N/A		
Biopharm	N/A		
Division of Non-prescription products	N/A		
Methods Validation	Per ONDQA’s Policy		
Labeling	Acceptable		
EA	Acceptable	26-AUG-2009	Tang, Yubing
Microbiology	Acceptable	23-DEC-2009	Pawar, Vinayak

The Chemistry Review for NDA 22-501

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Labels have adequate information as required. However, the overall “Acceptable” recommendation has not been made by the Office of Compliance as of this review.

Therefore, from a CMC perspective, this NDA is *not* recommended for “Approval” until the final “Acceptable” recommendation is made by the Office of Compliance.

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

Not applicable.

II. Summary of Chemistry Assessments

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

1) Drug Product

The proposed drug product, (b) (4) (norethindrone acetate and ethinyl estradiol tables, ethinyl estradiol tablets and ferrous fumarate tables), is a low dose oral contraceptive consisting of new dose and new regimen of the combination of norethindrone acetate (NA) and ethinyl estradiol (EE). (b) (4) is packaged in a unit-dose blister card (dispensers) containing 24 blue active tablets, 2 white active tablets and 2 brown placebo tablets.

- Each blue, round tablet contains 1 mg of norethindrone acetate, USP and 10 mcg of ethinyl estradiol, USP and is imprinted with WC on one side and 421 on the other.
- Each white, hexagonal tablet contains 10 mcg of ethinyl estradiol, USP and is imprinted with WC on one side and 422 on the other.
- Each brown, round placebo tablet contains 75 mg ferrous fumarate, USP and is imprinted with WC on one side and 624 on the other. The ferrous fumarate tablets are non-hormonal and non-therapeutic, present to facilitate ease of drug administration via a 28-day regimen.

Executive Summary Section

The following compendial excipients are contained in (b) (4): mannitol, USP, microcrystalline cellulose, NF, FD&C Blue No. 1 Aluminum Lake (FD&C certified), sodium starch glycolate, NF, magnesium stearate, NF, povidone, USP, vitamin E, USP, lactose monohydrate, NF and sucralose, NF. The spearmint flavor in ferrous fumarate tablets is the only non-compendial excipient; however contains GRAS ingredients and has been used in other FDA approved drug products.

(b) (4) active tablets are manufactured using a (b) (4) process. Ethinyl estradiol, USP is (b) (4)

Container closure system for (b) (4) tablet regimen is a unit-dose blister consisting of a (b) (4) blister lidding and aluminum foil/ (b) (4) (b) (4) backing. There is a non-functional secondary packaging components including a rigid (b) (4) card (b) (4) to the unit-dose blister, a (b) (4) pouch, a (b) (4) overwrap film, prescriber and patient package inserts and (b) (4) cartons.

Based on the provided stability study data, the proposed 24 months expiration dating period is granted for (b) (4) tablets under the labeled storage conditions (stored at 25°C (77°F); excursion permitted to 15 - 30°C (59 - 86°F)).

2) Drug Substance

There are two drug substances in (b) (4), Norethindrone acetate, USP and ethinyl estradiol, USP. The drug substances are synthetic hormones widely used as components of combination oral contraceptives. The NA and EE used in (b) (4) tablets are sourced from (b) (4). Information about the manufacture, characterization, quality control, container closure system and stability for each drug substance from each manufacturer is contained in drug master files (b) (4). LOAs (Letter of Authorization) from the holders of DMFs are provided. All DMFs have been recently reviewed and found to be adequate.

B. Description of How the Drug Product Is Intended to Be Used

(b) (4) is indicated for the prevention of pregnancy in women (b) (4). The dosage of (b) (4) is one blue tablet containing norethindrone acetate and ethinyl estradiol daily for 24 consecutive days, followed by one white tablet containing ethinyl estradiol daily for 2 consecutive days, followed by one brown non-hormonal (placebo) tablet containing ferrous fumarate daily for 2 consecutive days. The ferrous fumarate tablets do not serve any therapeutic purpose.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

This NDA provided adequate information on the raw material controls, manufacturing process, specifications, and container/closure system. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during the expiration dating period. Labels have required information.

However, the Office of Compliance has *not* made the overall “Acceptable” recommendation as of this review.

III. Administrative

A. Reviewer’s Signature: In DARRTS

Yubing Tang, Ph.D.
Chemist, Branch III/DPAIL/ONDQA

B. Endorsement Block: In DARRTS

Moo-Jhong Rhee, Ph.D.
Branch Chief, Branch III/DPAIL/ONDQA

C. CC Block: In DARRTS

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Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22501

ORIG-1

WARNER
CHILCOTT CO INC

 (b) (4)

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

/s/

YUBING TANG
01/08/2010

MOO JHONG RHEE
01/08/2010
Chief, Branch III

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division: Division of Reproductive and Urologic Products
NDA: 22-501
Applicant: Warner-Chilcott
Stamp Date: 26-Mar-2009
PDUFA Date: 26-Jan-2010
Trademark: (b) (4)
Established Name: Norethindrone acetate/ethinyl estradiol
Dosage Form: Tablet
Route of Administration: Oral
Indication: Prevention of pregnancy

PAL: Donna F. Christner, Ph.D.

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

Summary and Critical Issues:

A. Summary

The drug product, (b) (4) (norethindrone acetate and ethinyl estradiol tables, ethinyl estradiol tablets and ferrous fumarate tables) is a low dose oral contraceptive consisting of a new dose and new regimen of the combination of norethindrone acetate (NA) and ethinyl estradiol (EE). Each package contains 24 blue tablets containing 1 mg NA and 10 mcg EE, followed by 2 white tablets containing 10 mcg of EE, followed by 2 brown ferrous fumarate tablets. The ferrous fumarate tablets are present to facilitate ease of drug administration via a 28-day regimen; these tablets are non-hormonal and do not serve a therapeutic purpose. The tablets are packaged in a blister card.

B. Critical issues for review

From the initial overview of the application, it appears that the primary review should be fairly straightforward. However, a careful, in-depth review must be performed.

Special attention should be paid to the stability data to set the expiration dating period.

C. Comments for 74-Day Letter

There are no CMC comments at this time.

D. Recommendation:

This NDA is fileable from a CMC perspective. Yubing Tang, Ph.D. has been assigned.

Donna F. Christner, Ph.D.

NDA Number: 22-501

Applicant: Warner-Chilcott

Stamp Date: 26-Mar-2009

Drug Name: (b) (4)

NDA Type: 3S

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?	X		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	X		
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	X		
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	X		Categorical exclusion as per 21 CFR 25.31(b)
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	X		DMF (b) (4) DMF DMF DMF
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	X		
7	If applicable, has all information requested during the IND phases, and at the pre-NDA meetings been included?	X		
8	Have draft container labels and package insert been provided?	X		
9	Have all DMF References been identified?	X		
10	Is information on the investigational formulations included?	X		
11	Is information on the Methods Validation included?	X		
12	If applicable, is documentation on the sterilization process validation included?		X	N/A

IS THE CMC SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Donna F. Christner, Ph.D.

23-Apr-2009

Pharmaceutical Assessment Lead

Date

Moo-Jhong Rhee, Ph.D.

Branch Chief

Date

DMF	Holder	Description	LOA	Status
	(b) (4)	Ethinyl estradiol	Yes	ADEQUATE on 04-Aug-2008 by J. Chang for NDA 22-365
		Ethinyl estradiol	Yes	ADEQUATE on 01-Feb-2008 by U. Atwal for ANDA 76-393
		Norethindrone acetate	Yes	ADEQUATE on 01-Aug-2008 by J. Chang for NDA 22-365
		Norethindrone acetate	Yes	ADEQUATE on 02-Feb-2009 by U. Atwal for ANDA 76-629
		(b) (4)	Yes	See ONDC Policies on Bottles and Blisters*
			Yes	ADEQUATE on 04-Aug-2008 by J. Chang for NDA 22-365 See ONDC Policies on Bottles and Blisters*

**Policy on the Review of Container Closure Systems for Solid Oral Drug Products (Bottles), 26-Apr-2001
Policy on the Review of Blister Container Closure Systems for Oral Tablets and Hard Gelatin Capsules, 29-May-2002*

DRUG SUBSTANCES

Full information on the drug substances are provided in the referenced DMFs. More detailed information is provided in the DMF table on page 3 of this IQA.

DMF (b) (4) Norethindrone acetate
DMF (b) (4) Norethindrone acetate

DMF (b) (4) Ethinyl Estradiol
DMF (b) (4) Ethinyl Estradiol

The reviewer should check the DMFs to see if significant changes have occurred since the last reviews (see Table on page 3 of this IQA). The last reviews were both ADEQUATE for use in solid oral dosage forms.

The following facilities have responsibility for manufacturing and/or control of the drug substances:



Facility	Responsibility	Establishment Registration Number	Contact Person	Ready for Inspection
Warner Chilcott Co., Inc. Road 195 (Union Street) Km 1.1 Fajardo, PR 00738-1005	Analytical testing and release of the drug substance and inactive components Manufacturing, in-process testing, and packaging of the drug product	2619635	Lisbeth Olmeda Director, Quality Operations Phone: 787 655-8307 Fax: 787 863-5355 Email: lisbeth.olmeda@wcrx.com	yes
Warner Chilcott UK Limited Old Belfast Road, Millbrook Lame, Northern Ireland BT40 2SH	In-process, release and stability testing of the drug product	3005206014	Gillian Megaw Director, Quality Operations Phone: (028) 282 6722 ext 221 Email: gillian.megaw@wcrx.com	yes
(b) (4)				

Comment: The sponsor was contacted on 01-Apr-2009 to provide updated contact information on the drug substance manufacturer. Information was provided on 16-Apr-2009, and inspection requests submitted to EES on 24-Apr-2009 by Jeannie David.

Sponsor states that both APIs are tested according to the methods and specifications in their respective compendial monographs.

Comment: It appears that the sponsor performs USP testing on the incoming APIs. Sponsor has provided their own COAs and the COAs from the API manufactures which shows more complete testing which would better conform to ICH standards. Since these are the same APIs already used in the approved drug product under NDA 21-871 (See Form 356h for cross-reference), sourced from the same supplier, and these APIs are used in numerous oral contraceptives, the provided information should be adequate unless there are significant changes in the DMF.

DRUG PRODUCT

The drug product, (b) (4) (norethindrone acetate and ethinyl estradiol tables, ethinyl estradiol tablets and ferrous fumarate tables) is a low dose oral contraceptive consisting of a new dose and new regimen of the combination of norethindrone acetate (NA) and ethinyl estradiol (EE). Each package contains 24 blue tablets containing 1 mg NA and 10 mcg EE, followed by 2 white tablets containing 10 mcg of EE, followed by 2 brown ferrous fumarate tablets. The ferrous fumarate tablets are present to facilitate ease of drug administration via a 28-day regimen; these tablets are non-hormonal and do not serve a therapeutic purpose. The tablets are packaged in a blister card.

Composition information for each tablet is outlined below. The sponsor has used the code WC3016 for the tablets throughout the application instead of the proposed tradename.

WC3016 1/10 (norethindrone acetate and ethinyl estradiol) tablets

WC3016 1/10 tablets are blue, round, flat-faced, bevel-edged tablets debossed with “WC” on one side and “421” on the other side. The composition of WC3016 1/10 Tablets is shown in Table 1 while the composition of the EE (b) (4) is shown in Table 2.

Table 1. Batch Composition for WC3016 1/10 Tablets, Formulation #WC3016 (b) (4)

Component	Function	Mg/tablet	% w/w	Kg/batch ¹
Ethinyl Estradiol (b) (4)	Active	(b) (4)	(b) (4)	(b) (4)
Norethindrone Acetate USP	Active			
Mannitol USP (b) (4)	(b) (4)			(b) (4)
Mannitol USP				
Microcrystalline Cellulose, NF (b) (4)				
FD&C Blue # 1 Aluminum Lake				
Sodium Starch Glycolate NF				
Magnesium Stearate NF				
Total		-		

¹ Nominal batch size = (b) (4)

² Composition of Ethinyl Estradiol (b) (4) is listed in Table 2.

Table 2. Batch Formula for 250-kg Scale Batch of WC3016 Ethinyl Estradiol (b) (4) Formulation # WC3016 (b) (4)

Component	Function	% w/w	Amount/batch (kg)
Ethinyl Estradiol USP ¹	Active	(b) (4)	(b) (4)
Povidone USP (b) (4)	(b) (4)		(b) (4)
Vitamin E USP			
Lactose Monohydrate NF (b) (4)			
Total Solids		-	
(b) (4)			(b) (4)

¹ Batch quantity of ethinyl estradiol includes (b) (4)

WC3016 EE10 (ethinyl estradiol) tablets

WC3016 EE10 tablets are white, hexagonal, flat-faced, bevel-edged tablets debossed with “WC” on one side and “422” on the other side. The composition of WC3016 EE10 Tablets is shown in Table 1 while the composition of the EE (b)(4) is shown in Table 2.

Table 1. Batch Composition for WC3016 1/10 Tablets, Formulation #WC3016- (b)(4)

Component	Function	Mg/tablet	% w/w	Kg/batch ¹
Ethinyl Estradiol (b)(4)	Active	(b)(4)	(b)(4)	(b)(4)
Mannitol USP (b)(4)				(b)(4)
Mannitol USP (b)(4)				
Microcrystalline Cellulose NF (b)(4)				
Sodium Starch Glycolate NF				
Magnesium Stearate NF				
Total				

¹ Nominal batch size = (b)(4)

² Composition of Ethinyl Estradiol (b)(4) is listed in Table 2 .

Comment: The EE (b)(4) for both active-containing tablets is the same

Ferrous Fumarate tablets

Ferrous Fumarate Tablets are brown, round flat-faced, bevel-edged tablets debossed with “WC” on one side and “624” on the other side. The batch composition for Ferrous Fumarate tablets is shown in Table 1.

Table 1. Tablet Formulation for Ferrous Fumarate Chewable Tablets, Formulation # WC3026- (b)(4)

Component	Function	Mg/tablet	%w/w	kg/batch ¹
Ferrous Fumarate, USP	Main Inactive Component	75.0	(b)(4)	(b)(4)
Mannitol, USP (b)(4)				(b)(4)
Povidone, USP (b)(4)				
Microcrystalline Cellulose, NF (b)(4)				
Sodium Starch Glycolate, NF				
Magnesium Stearate, NF				
Sucralose, NF				
Spearmint Flavor (b)(4)				
Total				

¹ Nominal batch size = (b)(4)

Compendial excipients are controlled with compendial methods. Specifications and test methods are provided for non-compendial compounds.

Comment: Information is adequate to allow review.

MANUFACTURERS

The following sites have responsibility for the manufacture of the drug products.

Activity	Responsible Site
Analytical testing and release of the drug substances and inactive components	Warner Chilcott Co., Inc. Road 195 (Union Street) Km 1.1 Fajardo, PR 00738-1005
Contract analytical testing of drug substances and inactive components	(b) (4)
Manufacturing, in-process testing, and packaging of the drug product	Warner Chilcott Co., Inc. Road 195 (Union Street) Km 1.1 Fajardo, PR 00738-1005
In-process, release and stability testing of the drug product	Warner Chilcott UK Limited Old Belfast Road, Millbrook Larne, Northern Ireland BT40 2SH
Microbiological testing of drug substances and inactive materials	(b) (4)

Comment: The manufacturing sites are common to all three tablets. The sponsor was contacted on 01-Apr-2009 to provide updated contact information on the manufacturing sites. Information was provided on 16-Apr-2009, and inspection requests submitted to EES on 24-Apr-2009 by Jeannie David.

Manufacturing information is provided in the application, both as narratives and flow charts.

Comment: Information is adequate to allow review.

SPECIFICATIONS

The quality of the drug product is controlled by the following specifications:

Table 1: Quality Control Specifications for {WC3016 1/10 Tablet}

Test	Limit	Method Reference	Specification Reference	Section
Description*	Blue, round, flat-faced, beveled-edged tablets, debossed with "WC" on one side and "421" on the other	Drug Product - 42	Drug Product - 10766	3.2.P.5.1.1
Identification	HPLC – The retention time of the main peaks obtained in the chromatogram for the Assay preparation correspond to those obtained for the Standard preparation	Drug Product - 42		
Uniformity of Dosage Units	Meet the requirements of USP <905>	Drug Product - 43		
Assay – NA and EE*	NA: 90.0% to 110.0% of label claim EE: 88.0% to 112.0% of label claim	Drug Product - 42		
Related Substances – NA*	(b) (4)	Drug Product - 45		
Related Substances – EE*		Drug Product - 45		
Dissolution – NA and EE*	Meet the requirements of USP <711> Not less than (b) (4) (Q) of the labeled amount of each active is dissolved in 30 minutes	Drug Product - 44		

Table 2: Quality Control Specifications for {WC3016 1/10 Tablet} (Continued)

Test	Limit	Method Reference	Specification Reference	Section
Assay – α - (b) (4)	90.0% to 110.0% of label claim	Drug Product - 46		
*Tests performed on stability				

Table 1: Quality Control Specifications for {WC3016 EE10 Tablet}

Test	Limit	Method Reference	Specification Reference	Section
Description*	White, hexagonal, flat-faced, beveled-edged tablets debossed with "WC" on one side and "422" on the other	Drug Product - 42	Drug Product - 10767	<u>3.2.P.5.1.1</u>
Identification	HPLC – The retention time of the main peaks obtained in the chromatogram for the Assay preparation correspond to those obtained for the Standard preparation	Drug Product - 42		
Uniformity of Dosage Units	Meet the requirements of USP <905>	Drug Product - 43		
Assay – EE*	EE: 88.0% to 112.0% of label claim	Drug Product - 42		
Related Substances – EE*	(b) (4)	Drug Product - 45		
Dissolution – EE*		Drug Product - 44		
Assay – (b) (4)	90.0% to 110.0% of label claim	Drug Product - 46		

*Tests performed on stability

Table 1: Quality Control Specifications for {Ferrous Fumarate Tablet}

Test	Limit	Method Reference	Specification Reference	Section
Description	Round, flat-faced, beveled-edged, brown tablets debossed with 'W/C' on one side and '624' on the other side	Drug Product - 80	Drug Product - 10133	<u>3.2.P.5.1.1</u>
Identification	Test is positive for iron			
Uniformity of Dosage Units	Meet the requirements of USP <905>			
Assay	90.0% to 110.0% of label claim			
Dissolution	Not less than (b) (4) of label claim (Q) of ferrous fumarate is dissolved in 45 minutes. Follow the requirements of USP <711>			
Hardness	Report data from 5 tablets			
Loss on Drying	Report data			

Justification for specifications, analytical procedures and validation are provided.

Comment: Information is adequate to allow review.

The following impurities have been identified in the drug product.

Table 6: Related Substances of Norethindrone Acetate and Ethinyl Estradiol

Parent Compound	Impurity and Specification	Reaction Mechanism
Norethindrone acetate		(b) (4)
Ethinyl estradiol		

Comment: Information is adequate to allow review.

CONTAINER CLOSURE SYSTEM

The drug product is packaged in unit-dose blisters consisting of a (b) (4) blister lidding and aluminum foil (b) (4) backing. Secondary (non-functional) packaging component include (but are not limited to) a rigid (b) (4) card (b) (4) to the unit-dose blister, a (b) (4) pouch, a (b) (4) overwrap film, prescriber and patient package inserts and (b) (4) cartons.

Comment: Information is adequate to allow review.

STABILITY

The sponsor has requested 24 months of expiration based on the following stability package:

Table 1: Summary Information of WC3016 Tablets Stability Batches

Formulation	Bulk Tablet Batch #	Date of Manufacture	Drug Substance Source		Drug Substance Lot #	
			EE	NA	EE	NA
WC3016- (b) (4)	80127T	5 Mar 07	(b) (4)		84303560	85200390
WC3016-	80137T	5 Mar 07			84303560	85200390
WC3016-	80896T	18 Jan 07			84303560	85200390
WC3016-	80396T	16 Aug 06			83400690	85200370
WC3016-	80068T	15 Feb 08			L00028908	L00028459
WC3016-	80138T	27 Mar 08			87302240	87403810
(b) (4)						

For the primary stability batches, Lot 80896F has 18 months of long term stability, while Lots 80127F and 80137F have 15 months of long term stability. Supportive Lot 80396F has 24 months of stability data while lots 80068F and 80138F have 3 months of data.

Table 1: Summary Information of WC3016 EE10 Tablets Stability Batches

Formulation	Bulk Tablet Batch #	Date of Manufacture	Batch Size	Drug Substance Source	Drug Substance Lot #
WC3016-	(b) (4) 80097T	23 Mar 07	12 kg	(b) (4)	84303560
WC3016-	80107T	23 Mar 07	12 kg		84303560
WC3016-	80886T	17 Jan 06	12 kg		F0271290
WC3016-	80386T	17 Aug 06	12 kg		83400690
WC3016-	80058T	15 Feb 08	36 kg		L00028908

(b) (4)

Primary stability lot 80886T has 18 months of long term data while lots 80107T and 80097T have 15 months of data. Supportive stability data is provided on two additional lots.

Table 1: Summary Information of Ferrous Fumarate Tablets Stability Batches

Formulation	Bulk Tablet Batch #	Date of Manufacture	Packaged Lot #	Ferrous Fumarate Source	Ferrous Fumarate Lot #
WC3026	(b) (4) 80507T	24 Aug 07	80507F	(b) (4)	135868
WC3026	80577T	17 Sep 07	80577F		135868
WC3026	80587T	15 Oct 07	80587F		135868
WC3026	80018T	30 Jan 08	80018F		136045
WC3026	80038T	31 Jan 08	80038F		136045

Twelve months of long term stability data is provided on the primary stability lots 80507F, 80577F and 80587F.

Comment: Information is adequate to allow review.

LABELING

Colored copies of the carton and container labels and the PI are provided electronically.

Comment: Information is adequate to allow review

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

/s/

Donna Christner
5/7/2009 02:49:36 PM
CHEMIST

Hard copy signed off by you on 23-Apr-2009

Moo-Jhong Rhee
5/7/2009 03:12:34 PM
CHEMIST
Chief, Branch III