

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204426Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

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

Date: April 19, 2013

From: Yichun Sun, Ph.D.
Review Chemist, ONDQA
Division of New Drug Quality Assessment II
ONDQA

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Quality Assessment II
ONDQA

To: CMC Review #1 of NDA 204426

Subject: Final Recommendation

At the time when the CMC review #1 was written, there were two pending issues listed as follows:

- 1) The overall acceptable recommendation of **Establishment Evaluation** was still pending.
- 2) There were issues on the **Label/Labeling** that needed to be resolved.

Establishment Evaluation

On April 19, 2013, the Office of Compliance gave an overall **“Acceptable”** recommendation for all the facilities involved in the manufacture and test of the drug substance and drug product (**Attachment - 1**).

Evaluation of Label/Labeling

On April 5, 2013, the NDA applicant submitted an amendment providing the finalized mock up container and carton labels. Additionally, the applicant also agreed to all the CMC changes made to the package insert. All the labels/labeling issues are now **satisfactorily resolved**. The CMC sections of the final package insert, and mock up container and carton labels are attached (**Attachment - 2**).

Recommendation:

All the previous pending issues are now satisfactorily resolved, and therefore, from the ONDQA’s perspective, this NDA is recommended for **APPROVAL** with an expiration dating period of 18 months.

Attachment - 1 (Summary Report of Establishment Evaluation)

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 204426/000	Sponsor:	WARNER CHILCOTT LLC
Org. Code:	580		UNION ST RD 195 KM 1 1
Priority:	3		FAJARDO, PR 00738
Stamp Date:	21-JUN-2012	Brand Name:	norethindrone acetate and ethinyl estrad
PDUFA Date:	21-APR-2013	Estab. Name:	
Action Goal:		Generic Name:	norethindrone acetate and ethinyl estrad
District Goal:	20-FEB-2013	Product Number; Dosage Form; Ingredient; Strengths	
			001; CAPSULE, SOFT GELATIN; NORETHINDRONE ACETATE; 1.03MG
			001; CAPSULE, SOFT GELATIN; ETHINYL ESTRADIOL; .0206MG
			002; CAPSULE, SOFT GELATIN; FERROUS FUMARATE; 75MG
FDA Contacts:	Y. SUN	Prod Qual Reviewer	3017961388
	K. JENNINGS	Product Quality PM	3017962919
	P. LUCARELLI	Regulatory Project Mgr	(HFD-580) 3017963961
	D. CHRISTNER	Team Leader	3017961341

Overall Recommendation:	ACCEPTABLE	on 19-APR-2013	by T. SHARP	()	3017963208
	PENDING	on 19-APR-2013	by EES_PROD		
	PENDING	on 11-JUL-2012	by EES_PROD		
	PENDING	on 11-JUL-2012	by EES_PROD		
	PENDING	on 11-JUL-2012	by EES_PROD		
	PENDING	on 11-JUL-2012	by EES_PROD		

Establishment:	CFN: (b) (4)	FEI: (b) (4)	
	(b) (4)		
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE RELEASE TESTER		
Profile:	CAPSULES, SOFT GELATIN	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	19-APR-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

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

Establishment:	CFN: (b) (4)	FEI: (b) (4)	
	(b) (4)		
DMF No:			AADA:
Responsibilities:	FINISHED DOSAGE RELEASE TESTER FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	11-JUL-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		
<hr/>			
Establishment:	CFN: (b) (4)	FEI: (b) (4)	
	(b) (4)		
DMF No:			AADA:
Responsibilities:	DRUG SUBSTANCE MANUFACTURER DRUG SUBSTANCE (b) (4)		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	16-AUG-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		
<hr/>			
Establishment:	CFN: (b) (4)	FEI: (b) (4)	
	(b) (4)		
DMF No:			AADA:
Responsibilities:	FINISHED DOSAGE PACKAGER		
Profile:	CAPSULES, SOFT GELATIN	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	11-JUL-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

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

/s/

YICHUN SUN
04/19/2013

MOO JHONG RHEE
04/19/2013
Chief, Branch IV

NDA 204426

Minastrin™ 24 Fe (Norethindrone Acetate and Ethinyl Estradiol Capsules, and Ferrous Fumarate Capsules)

Warner Chilcott Company, LLC

Yichun Sun, Ph.D.

Review Chemist

**Branch IV, Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment**

**CMC REVIEW OF NDA 204426
For the Division of Reproductive and Urologic Products
(HFD-580)**

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Chemistry Review Data Sheet

1. NDA: #204426
2. REVIEW #: 1
3. REVIEW DATE: 07-March-2013
4. REVIEWER: Yichun Sun, Ph.D.
5. PREVIOUS DOCUMENTS:
NA
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	June 20, 2012
Amendment	February 11, 2013
Amendment	February 13, 2013
Amendment	February 26, 2013

7. NAME & ADDRESS OF APPLICANT:

Name: Warner Chilcott Company, LLC
Address: 100 Enterprise Drive
Rockaway, New Jersey 07866
Representative: Alvin Howard,
Senior Vice President Regulatory Affairs
Telephone: (973) 442-3233

8. DRUG PRODUCT NAME/CODE/TYPE:

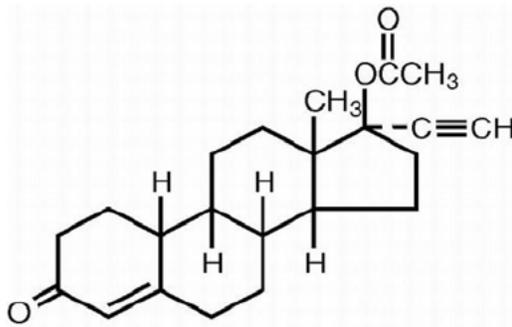
- a) Proprietary Name: Minastrin™ 24 Fe
- b) Non-Proprietary Name (USAN): norethindrone acetate and ethinyl estradiol capsules, and ferrous fumarate capsules
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3
 - Submission Priority: Standard Review

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)

10. PHARMACOL. CATEGORY: Contraceptive containing a progestin (norethindrone) and an estrogen (ethinyl estradiol).
11. DOSAGE FORM: Capsules (soft gelatin capsules), immediate release
12. STRENGTH/POTENCY: Each capsule contains 1 mg norethindrone acetate and 20 µg ethinyl estradiol. Each non-hormonal placebo capsule contains 75 mg ferrous fumarate.
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:

Norethindrone acetate

19-Norpregn-4-en-20-yn-3-one, 17-(acetyloxy)-, (17 α). Or 17-Hydroxy-19-nor-17 α -pregn-4-en-20-yn-3-one acetate



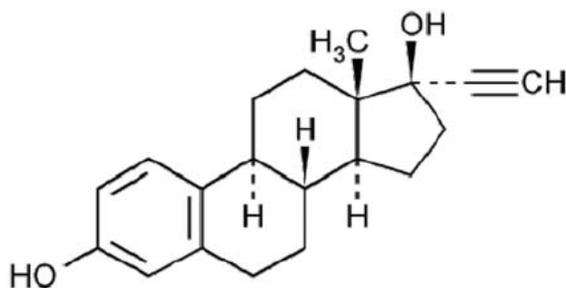
Empirical formula: C₂₂H₂₈O₃

Molecular weight: 340.46

Ethinyl estradiol

19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17 α)-. Or 19-Nor-17 α -pregna-1,3,5(10)-trien-20-yne-3,17-diol

Chemistry Review Data Sheet



Empirical formula: $C_{20}H_{24}O_2$

Molecular weight: 296.40

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE	STATUS2	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Norethindrone Acetate	3	Adequate	05/09/2012	NA
	II		Ethinyl Estradiol	3	Adequate	06/04/2012	NA
	II		(b) (4)	1	Adequate	03/06/2013	NA
	II			1	Adequate	03/06/2013	NA
	III			4	NA	NA	NA
	III			4	NA	NA	NA

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
NDA	21-871	Loestrin [®] 24 Fe (norethindrone acetate and ethinyl estradiol tablets, USP and ferrous fumarate tablets)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	----	----
EES	Pending	----	----
Pharm/Tox	N/A	----	----
Biopharm	The dissolution method and acceptance criteria are Acceptable	06-March-2013	Dr. Elsbeth Chikhale
LNC	N/A	----	----
Methods Validation	N/A	----	----
DMET/DDMAC	N/A	----	----
EA	Categorical Exclusion Acceptable (See p. 153)	See Review Date Above	Y. Sun
Microbiology	NA	----	----

The Chemistry Review for NDA 22-460**The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

However, the Office of Compliance has *not* issued an overall “Acceptable” recommendation for the facilities involved in this application.

Also, the label/labeling issues are *not* satisfactorily resolved yet.

Therefore, from the ONDQA perspective, this NDA is *not* ready for approval in its present form per 21 CFR 314.125(b) (13) and(6).

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)****Drug Substance**

Two drug substances, norethindrone acetate (NA) and ethinyl estradiol (EE), are used in the drug product, (MinastrinTM 24 Fe (norethindrone acetate and ethinyl estradiol capsules, and ferrous fumarate capsules)) of this NDA. Norethindrone acetate is a chemically synthesized compound (a progestin). It is chemically known as 19-Norpregn-4-en-20-yn-3-one,17-(acetyloxy)-,(17 α)-. Norethindrone acetate is a white to creamy white powder. Detailed CMC information of norethindrone acetate is referred to DMF # (b) (4). A letter of authorization is provided. The DMF has been reviewed and found adequate according to Dr. Roslyn Powers’s review dated May 9, 2012.

Ethinyl estradiol (EE) is also a chemically synthesized compound (an estrogen). It is chemically known as 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17 α)-. Ethinyl estradiol is a white to creamy white powder. Detailed CMC information of ethinyl estradiol is referred to DMF # (b) (4). A letter of authorization is provided. The DMF has been reviewed and found adequate according to Dr. Subhash C Dhanesar’s review dated June 14, 2012.

Drug Product

The drug product in this NDA is Minastrin™ 24 Fe (norethindrone acetate and ethinyl estradiol capsules, and ferrous fumarate capsules). Minastrin 24 Fe provides an oral contraceptive regimen consisting of 24 yellow active (soft gelatin) capsules containing 1 mg norethindrone acetate and 20 mcg ethinyl estradiol, and 4 maroon non-hormonal placebo (soft gelatin) capsules containing 75 mg ferrous fumarate. The active and placebo capsules are manufactured by (b) (4)

Both the DMFs have been reviewed and found adequate to support the use of the active and placebo capsules in the NDA. The proposed specification for the active capsules is adequate to ensure the identity, strength, purity and quality of the active capsules. The proposed specification for placebo capsules is adequate to ensure the identity and quality of the placebo capsules. The drug product is packaged in blister cards, which consist of 28 soft gelatin capsules (24 yellow (soft gelatin) capsules (active), and 4 maroon (soft gelatin) capsules (non-hormonal placebo)). The proposed expiration dating period of 18 months for the drug product is supported by the stability data provided.

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

The drug product, Minastrin™ 24 Fe (norethindrone acetate and ethinyl estradiol capsules, and ferrous fumarate capsules), is a progestin/estrogen combination oral contraceptive (COC) indicated for use by women to prevent pregnancy. The drug product is packaged in blister cards, which consist of 28 capsules (24 yellow soft gelatin capsules (active), each containing 1 mg norethindrone acetate and 20 mcg ethinyl estradiol, and 4 maroon soft gelatin capsules (non-hormonal placebo), each containing 75 mg ferrous fumarate). The ferrous fumarate (soft gelatin) capsules do not serve any therapeutic purpose. One (soft gelatin) capsule is taken by mouth at the same time every day for 28 days in the order directed on the blister pack.

C. Basis for Not-Approval Recommendation

21 CFR 314.125(b)(13)

The review on Establishment Evaluation for the manufacturing and testing facilities are still pending. The Office of Compliance has *not* given an overall acceptable recommendation for all the facilities involved in the manufacture and tests of the drug substances and drug product. (see the **Attachment** on p.153)

21CFR 314.125 (b)(6)

Issues of labels have not been satisfactorily resolved. (see the **List of Deficiencies** on p. 153)

III. Administrative**A. Reviewer's Signature**

/s/ Y. Sun, Ph.D.

B. Endorsement BlockYichun Sun, Ph.D.
Reviewer_____
DateDonna Christner, Ph.D.
CMC lead_____
DateMoo-Jhong Rhee, Ph.D.
Branch Chief_____
DateLT Kerri-Anne E. Jennings, M.S.
Project Manager_____
Date**C. CC Block**

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/s/

YICHUN SUN
03/07/2013

MOO JHONG RHEE
03/07/2013
Chief, Branch IV

Initial Quality Assessment
Branch IV
Division of New Drug Quality Assessment II

OND Division: Division of Reproductive and Urologic Products
NDA: 204426
Applicant: Warner Chilcott
Stamp Date: 21-Jun-2012
PDUFA Date: 21-Apr-2013
Trademark: TBD
Established Name: Norethindrone acetate and ethinyl estradiol soft gelatin capsules and Ferrous fumarate soft gelatin capsules
Dosage Form: Capsule
Route of Administration: Oral
Indication: Prevention of Pregnancy

CMC Lead: 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 is a new dosage form for oral contraception consisting of one soft gelatin capsule containing 1 mg of norethindrone acetate (NA) and 0.020 mg ethinyl estradiol (EE) taken daily for 24 days followed by one ferrous fumarate (placebo) soft gelatin capsule taken for 4 days. The active NA/EE capsules are oval, transparent, pale yellow with "WC" printed on the outer shell in white, while the placebo capsules are oval, opaque maroon with "WC" printed on the outer shell in white. The drug product is packaged in blister packs consisting of [REDACTED] (b) (4) aluminum [REDACTED] (b) (4) coated lidding. Each blister pack contains 24 active capsules followed by 4 placebo capsules.

The applicant cross-references their NDA 21-871 for LoEstrin 24 Fe on which this capsule dosage form is based. The applicant provides comparative bioavailability data to demonstrate that the capsule dosage form is bioequivalent to Loestrin 24 Fe tablets. It should be noted that no studies were done under a US IND [REDACTED] (b) (4)

B. Critical issues for review

The drug product DMFs may require review if there is not sufficient information provided in the NDA.

C. Comments for 74-Day Letter

There are no comments to convey at this time.

D. Recommendation:

This NDA is fileable from a CMC perspective. Yichun Sun, Ph.D. has been assigned as the primary CMC reviewer. Elsbeth Chikhale, PhD. has been assigned as the ONDQA BioPharm reviewer.

REGULATORY BRIEFING RECOMMENDATION: Branch level

Donna F. Christner, Ph.D.

ND204426A Number: Type: 3

Established/Proper Name:
Norethindrone acetate and
ethinyl estradiol capsules and
ferrous fumarate capsules

Applicant: Warner
Chilcott

Letter Date: 21-Jun-2013

Stamp Date: 21-Jun-2013

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.		X	N/A

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Request for categorical exclusion as per 21 CFR 25.31(a)

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		DMF (b) (4) for Ethinyl Estradiol DMF (b) (4) for Norethirndrone acetate
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		DMF (b) (4) for Ethinyl Estradiol DMF (b) (4) for Norethirndrone acetate
14.	Does the section contain information regarding the characterization of the DS?	X		DMF (b) (4) for Ethinyl Estradiol DMF (b) (4) for Norethirndrone acetate
15.	Does the section contain controls for the DS?	X		DMF (b) (4) for Ethinyl Estradiol DMF (b) (4) for Norethirndrone acetate
16.	Has stability data and analysis been provided for the drug substance?	X		DMF (b) (4) for Ethinyl Estradiol DMF (b) (4) for Norethirndrone acetate
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	Not a filing issue
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	Not a filing issue

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	Clinical data include bioequivalence study against approved tablet formulation. Applicant states they are bioequivalent. In vitro comparison did not meet f2 equivalence.
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		18 month expiry requested based on 9 months of room temperature data, 6 months of accelerated and intermediate data on 3 lots of drug product
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	X		Risk assessment performed for excipient determination in formulation development. However, no regulatory relief requested
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	Not a filing issue

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	N/A

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II		(b) (4)	15-Jun-2012	New DMF. No review.
	II		15-Jun-2012	New DMF. No review.	
	II		07-Jun-2012	ADEQUATE on 08-Jun-2012.	
	II		07-Jun-2012	ADEQUATE on 02-May-2012.	
	III		24-May-2012	ADEQUATE on 06-Mar-2008.	
	III		14-May-2012	No review found.	

**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*

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			N/A
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	

{See appended electronic signature page}

Donna F. Christner, Ph.D.
 CMC Lead
 Division of New Drug Quality Assessment II
 Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
 Chief, Branch IV
 Division of New Drug Quality Assessment II
 Office of New Drug Quality Assessment

Date

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

/s/

DONNA F CHRISTNER
08/15/2012

MOO JHONG RHEE
08/15/2012
Chief, Branch IV