CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204061Orig1s000

CHEMISTRY REVIEW(S)

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

Date: **March 21, 2013**

From: Rajiv Agarwal, Ph.D; Ph.D
Review Chemist, Branch IV
New Drug Quality Assessment Division II
ONDQA

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

To: CMC review # 1 dated 31-JAN-2013 (NDA 204061)

Subject: **Final Recommendation**

The last CMC Review # 1 (31-JAN-2013) has noted the following two pending issues:

- The finalized mock ups of the container/closures were not provided with the requested changes.
- PI labeling issues were not resolved.

Now the finalized mock up labels are submitted (via amendment dated 18-MAR-2013), and the labeling issues are also satisfactorily resolved (See the **Attachment-1**).

The final recommendation from the Office of Compliance has not been changed from the previous "Acceptable" (see the **Attachment-2**).

Recommendation:

This NDA is now recommended for approval from the ONDQA perspective with expiration dating period of 18 months.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Attachment-2: EES Report

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 204061/000	**Sponsor:**	TEVA BRANDED PHARM
Org. Code:	580		41 MOORES RD
Priority:	5		FRAZER, PA 19355
Stamp Date:	31-MAY-2012	**Brand Name:**	Quartette (levonorgestrel and ethinyl es
PDUFA Date:	31-MAR-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	LEVONORGESTREL/ETHINYL ESTRADIOL
District Goal:	01-OCT-2012	**Product Number; Dosage Form; Ingredient; Strengths**	

001; TABLET; LEVONORGESTREL; .15MG
001; TABLET; ETHINYL ESTRADIOL; .02MG
002; TABLET; LEVONORGESTREL; .15MG
002; TABLET; ETHINYL ESTRADIOL; .025MG
003; TABLET; LEVONORGESTREL; .15MG
003; TABLET; ETHINYL ESTRADIOL; .03MG
004; TABLET; ETHINYL ESTRADIOL; .01MG

FDA Contacts:	R. MCKNIGHT	Project Manager	3017961765
	R. AGARWAL	Review Chemist	3017961322
	D. CHRISTNER	Team Leader	3017961341

Overall Recommendation:	ACCEPTABLE	(b) (4)	by R. SAFAAI-JAZI	()	3017964463
	PENDING		by EES_PROD		

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE RELEASE TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	18-JUN-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

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:	25-JUN-2012		
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 LABORATORIES "ALSO" (DRUGS)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	18-JUN-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	21-JUN-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	18-JUN-2012		
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 MANUFACTURER		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	18-JUN-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** 1526814	**FEI:** 1526814	
	TEVA WOMEN'S HEALTH (FORMERLY BARR/DURAMED)		
	CINCINNATI, , UNITED STATES 452132520		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
	(b) (4)		
Profile:	TABLETS, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	01-NOV-2012		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

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

/s/

RAJIV AGARWAL
03/21/2013

MOO JHONG RHEE
03/21/2013
Chief, Branch IV

NDA 204061

Quartette

levonorgestrel/ethinyl estradiol
0.15 mg/ 0.025 mg,0.15 mg/ 0.02 mg, 0.15 mg/ 0.03 mg Tablets

ethinyl estradiol
0.01 mg Tablets

Levonorgestrel/Ethinyl Estradiol Tablets, 0.15 mg/ 0.025 mg:	**Pink tablets**
Levonorgestrel/Ethinyl Estradiol Tablets, 0.15 mg/ 0.02 mg:	**Light Pink tablets**
Levonorgestrel/Ethinyl Estradiol Tablets, 0.15 mg/ 0.03 mg:	**Purple tablets**
Ethinyl Estradiol Tablets, 0.01 mg:	**Yellow tablets**

Teva Pharmaceuticals

Rajiv Agarwal, Ph.D.

Review Chemist

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

CMC REVIEW OF NDA 204061
For the Division of Reproductive and Urologic Products (HFD-580)

Table of Contents

CMC Review Data Sheet

1. NDA 204061

2. REVIEW #: 1

3. REVIEW DATE: 29-JAN-2013

4. REVIEWER: Rajiv Agarwal

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	31-MAY-2012
Amendment	21-AUG-2012
Amendment	11-JAN-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Teva Branded Pharmaceuticals Product R&D, Inc.
Address:	41 Moores Road PO Box 4011 Frazer, PA 19355
Representative:	Ms. Amy C. Hummel
Telephone:	610-727-6322

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Quartette
b) Non-Proprietary Name: Levonorgestrel/Ethinyl estradiol
c) Code Name/# (ONDQA only): DR-103
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5
- Submission Priority: Standard

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

CMC Review Data Sheet

10. PHARMACOL. CATEGORY: Progestin and estrogen

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: Levonorgestrel/ Ethinyl Estradiol:
0.15 mg/0.020 mg
0.15 mg/0.025 mg
0.15 mg/0.030 mg

Ethinyl Estradiol
0.01mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __√__Rx ___OTC

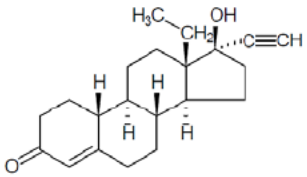
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__√__Not a SPOTS product

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

Levonorgestrel:

Structural formula:



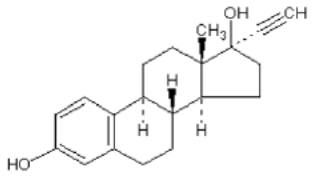
Molecular weight: 312.5
Molecular formula: $C_{21}H_{28}O_2$
Chemical Name (IUPAC):

1. 13 ß-ethyl-17ß–hydroxy-18-19-dinor-17α-pregn-4-en-20-yn-3-one
2. 18,19-Dinorpregn-4-en-20-yn-3-one,13-ethyl-17-hydroxy-(17α)-(-)-

CMC Review Data Sheet

Ethinyl Estradiol:

Structural formula:



Molecular weight: 296.41
Molecular formula: $C_{20}H_{24}O_2$
Chemical Name (IUPAC):

1. 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17β-diol
2. 17 α -Ethynylestra-1,3,5(10)-triene-3,17 β -diol
3. 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol,(17 α)-

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Ethinyl Estradiol	3	Adequate	13-JUN-2012	Dr. Subhash Dhanesar
	II		Levonorgestrel	3	Adequate	02-JUN-2009	Dr. Donna F Christner
	III		(b) (4)	7	Adequate	26-APR-2001	Per ONDC Policies on Bottles and Blisters*
	III			3	Adequate	7-MAR-2008	Dr. Bogdan Kurtyka
	III			3	Adequate	20-APR-2012	Dr. George Lunn
	IV			1	Adequate	29-JAN-2013	Dr. Rajiv Agarwal
	IV			1	Adequate	29-JAN-2013	Dr. Rajiv Agarwal
	IV			1	Adequate	29-JAN-2013	Dr. Rajiv Agarwal
	IV			1	Adequate	29-JAN-2013	Dr. Rajiv Agarwal

* ***Policy on the Review of Container Closure Systems for Solid Oral Drug Products (Bottles), 26-APR-2001***

[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
IND	72,290	Active
NDA	21544, 21840, 22262	Approved

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	01-NOV-2012	OC
Methods Validation	N/A, according to the current ONDQA policy	29-JAN-2013	Dr. Rajiv Agarwal
EA	Categorical exclusion (see review) is granted	29-JAN-2013	Dr. Rajiv Agarwal

The CMC Review for NDA 204061

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.

The Office of Compliance has made an "Acceptable" recommendation for the facilities involved in this application.

However, the issues on the label/labeling of the drug product have ***not*** been resolved.

Therefore, from the ONDQA perspective, this NDA is ***not*** recommended for approval per 21 CFR 314.125(b) (6) in its present form until label/labeling issues are satisfactorily resolved.

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

None

II. Summary of CMC Assessments

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

(1) Drug Substance

Two drug substances are levonorgestrel and ethinyl estradiol. The applicant references DMF (b) (4) for details on the description, characterization, manufacture, packaging, quality control testing, and stability of levonorgestrel. A Letter of Authorization is provided in the application. DMF (b) (4) has been reviewed and found adequate to support this application. In addition to the USP monograph requirements, Teva developed specifications for residual solvents, impurities and particle size. The acceptance criteria for particle size analysis differ due to differences in analytical methods used by Teva and (b) (4). Teva determines particle size using a (b) (4), whereas (b) (4) determines particle size using a (b) (4). This information is presented in the open part of the DMF to the NDA and is reviewed for other approved drug products and also reviewed here. It is adequate.

The applicant cross references DMF [redacted] for details on the description, characterization, manufacture, packaging, quality control testing, and stability of ethinyl estradiol. A Letter of Authorization is provided in the application. DMF [redacted] has been reviewed and is adequate. Teva's and [redacted] acceptance criteria for particle size analysis differ due to differences in analytical methods used by Teva and [redacted]. Teva performs particle size analysis using a [redacted] whereas [redacted] uses [redacted] Additionally, as part of the routine release for ethinyl estradiol, Teva tests for impurities that are not listed in [redacted] specification. The information is reviewed here and in other approved drug products and is adequate.

The final recommendation from the Office of Compliance on the compliance to the cGMP involving all facilities pertaining to the drug substance manufacturing and testing operations is Acceptable (Attachment-1).

(2) Drug Product

DR-103 is an oral contraceptive consisting of 84 tablets, each containing 0.15 mg of levonorgestrel in combination with 0.02 mg (42 tablets), 0.025 mg (21 tablets), or 0.030 mg (21 tablets) of ethinyl estradiol, followed by 7 tablets containing 0.01 mg of ethinyl estradiol alone.

The blister film used for packaging DR-103 i [redacted] The push through blister lidding foil is [redacted] aluminum foil that is printed on both sides.

Each 91-day regimen contains 3 blister cards which are placed into a single [redacted] compact.

- The first 28 count blister card contains 28 light pink levonorgestrel and ethinyl estradiol tablets, 0.15mg / 0.02mg.
- The second 28 count blister card contains 14 light pink levonorgestrel and ethinyl estradiol tablets, 0.15mg / 0.020 mg, followed by14 pink levonorgestrel and ethinyl estradiol tablets, 0.15mg / 0.025 mg.
- The third blister card is a 35 count blister card containing 7 pink levonorgestrel and ethinyl estradiol Tablets, 0.15mg / 0.025 mg followed by 21 purple levonorgestrel and ethinyl estradiol tablets,0.15mg / 0.03 mg and then 7 yellow ethinyl estradiol tablets, 0.01mg.

Filled compacts are sealed in a foil pouch containing a 2g [redacted] desiccant and a patient leaflet. Sealed pouches are then placed in a cardboard carton.

The proposed tablets are nearly identical in formulation and manufacture to those of the currently approved tablets. The tablets are different only in debossing code. There is no placebo tablet.

The drug product is manufactured by Teva Laboratories. The dissolution acceptance criteria for the two drug substances for all the previously approved combination drug product (NDAs 21544, 21840, and 22262),) were NLT (b)(4)% (Q), at 45 minutes. The release and stability data on the current combination tablets show that the dissolution criteria should be Q = (b)(4)%, 45 minutes for both drug substances. This request was conveyed to the applicant. The applicant amended (11-JAN-2013) the acceptance criteria of dissolution at release and at stability. The dissolution acceptance criteria are now adequate.

It should be noted that the acceptance criterion of (b)(4) ethinyl estradiol in this product is lower (NMT (b)(4)%) as compared to other approved products (NMT (b)(4)%).

Based on the stability data, an 18-month expiration dating period, as requested by the applicant, has been granted for storage at 25^{0}C/60% RH (controlled room temperature).

The final recommendation from the Office of Compliance on the compliance to the cGMP involving all facilities pertaining to the drug product manufacturing and testing operations is Acceptable (See Attachment-1).

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

Take one tablet by mouth at the same time every day. The dosage of Quartette is one light pink tablet containing 0.15 mg of levonorgestrel and 0.02 mg ethinyl estradiol daily for 42 consecutive days, followed by 21 pink tablets containing 0.15 mg of levonorgestrel and 0.025 mg ethinyl estradiol, followed by 21 purple tablets containing 0.15 mg of levonorgestrel and 0.03 mg ethinyl estradiol, followed by 7 yellow period stabilizing tablets containing 0.01 mg of ethinyl estradiol taken for 7 days. To achieve maximum contraceptive effectiveness, Quartette must be taken exactly as directed and at intervals not exceeding 24 hours. Instruct the patient to begin taking Quartette on the first Sunday after the onset of menstruation. If menstruation begins on a Sunday, the first light pink tablet is taken that day. One light pink tablet should be taken daily for 42 consecutive days, followed by pink tablets for 21 days, followed by purple tablets for 21 days, followed by yellow tablets taken for 7 days. A non-hormonal back-up method of contraception (such as condoms or spermicide) should be used until a light pink tablet has been taken daily for 7 consecutive days. A scheduled period, generally short and light, should occur during the 7 days that the yellow tablets are taken. Begin the next and all subsequent 91-day cycles without interruption on the same day of the week (Sunday) on which the patient began her first dose of Quartette, following the same

schedule: 42 days taking a light pink tablet, followed by 21 days taking a pink tablet, followed by 21 days of a purple tablet, followed by 7 days of taking a yellow tablet. If the patient does not immediately start her next pill pack, she should protect herself from pregnancy by using a non hormonal back-up method of contraception until she has taken a light pink tablet daily for 7 consecutive days.

C. Basis for Not-Approval Recommendation

21CFR 314.125(b)(6)

- Label/labeling issues are not satisfactorily resolved.

(See the **List of Deficiencies** on p. 64)

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Rajiv Agarwal, Ph.D.

B. Endorsement Block:

(See appended electronic signature page)

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

C. CC Block: entered electronically in DARRTS

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/s/

DONNA F CHRISTNER
01/31/2013
submitted in DARRTS for Rajiv Agarwal

RAJIV AGARWAL
01/31/2013

MOO JHONG RHEE
01/31/2013
Chief, Branch IV

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

OND Division:	Division of Reproductive and Urologic Products
NDA:	204061
Applicant:	Teva
Stamp Date:	31-May-2012
PDUFA Date:	31-Mar-2013
Trademark:	Quartette
Established Name:	Levonorgestrel and ethinyl estradiol
Dosage Form:	Tablet
Route of Administration:	Oral
Indication:	Prevention of Pregnancy
CMC Lead:	Donna F. Christner, Ph.D.

	YES	NO
ONDQA Fileability:	X	☐
Comments for 74-Day Letter	☐	X

Summary and Critical Issues:

A. Summary

The drug product is an extended-regimen oral contraceptive consisting of 84 tablets packaged in the following sequence:

- 42 light pink tablets containing 0.15 mg levonorgestrel and 0.02 mg ethinyl estradiol
- 21 pink tablets containing 0.15 mg levonorgestrel and 0.025 mg ethinyl estradiol
- 21 purple tablets containing 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol
- 7 yellow tablets containing 0.01 mg ethinyl estradiol alone

The drug product is packaged in the same components used for Seasonale, Seasonique and LoSeasonique. The blister is [redacted] (b) (4) The push through blister lidding foil is [redacted] (b) (4) aluminum foil printed on both sides. The manufacturer tested the product contact material according to USP<661> and confirmed that extractables are not present in the inks or base foil materials.

Each 91 day regimen contains 3 blister cards which are placed into a single [redacted] (b) (4) compact designed to hold two 28-count blister cards and one 35-count blister card. The compact is a nonfunctional secondary packaging component. Filled compacts are sealed in a foil pouch containing a 2g desiccant and a patient leaflet. Pouches are then placed in a cardboard carton.

B. Critical issues for review

The DMFs may require review if updates have been submitted since the last review.

Dissolution method and specification are based on the approved Seasonique drug product. Assignment of a BioPharm reviewer may not be warranted for this NDA, but this can be evaluated by the primary CMC reviewer.

C. Comments for 74-Day Letter

No comments to be conveyed at this time.

D. Recommendation:

This NDA is fileable from a CMC perspective. Rajiv Agarwal, Ph.D., Ph.D. is assigned as the primary CMC reviewer.

REGULATORY BRIEFING RECOMMENDATION: Branch-level.

_____
Donna F. Christner, Ph.D.

NDA Number: 204061 **Type: 5**

Established/Proper Name: levonorgestrel and ethinyl estradiol

Applicant: TEVA **Letter Date: 31-May-2012** **Stamp Date:31-May-2012**

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.**			N/A

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • 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.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • 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.	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: • 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) and (b)

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 Levonorgestrel DMF (b) (4) for Ethinyl Estradiol
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		DMF (b) (4) for Levonorgestrel DMF (b) (4) for Ethinyl Estradiol
14.	Does the section contain information regarding the characterization of the DS?	X		DMF (b) (4) for Levonorgestrel DMF (b) (4) for Ethinyl Estradiol
15.	Does the section contain controls for the DS?	X		DMF (b) (4) for Levonorgestrel DMF (b) (4) for Ethinyl Estradiol
16.	Has stability data and analysis been provided for the drug substance?	X		DMF (b) (4) for Levonorgestrel DMF (b) (4) for Ethinyl Estradiol
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	
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
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	Not a filing issue
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)	Ethinyl Estradiol	19-Mar-2012	ADEQUATE on 08-Jun-2012. No updates since that time.
	II		Levonorgestrel	20-Mar-2012	ADEQUATE on 02-Jun-2009. Updates submitted.
	III		(b) (4)	13-Apr-2012	No review found. See ONDC Policies on Bottles and Blisters*
	III			10-Apr-2012	ADEQUATE on 06-Mar-2008.
	III			12-Apr-2012	ADEQUATE on 20-Apr-2012
				13-Feb-2012	No review found
				13-Feb-2012	No review found
				13-Feb-2012	No review found
				13-Feb-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. Date
CMC Lead
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

{See appended electronic signature page}

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

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/s/

DONNA F CHRISTNER
07/26/2012

MOO JHONG RHEE
07/26/2012
Chief, Branch IV