

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204061Orig1s000

OTHER REVIEW(S)

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	QUARTETTE (levonorgestrel/ethinyl estradiol and ethinyl estradiol) tablets, for oral use
Applicant	Teva Pharmaceuticals Inc., USA
Application/Supplement Number	NDA 204061
Type of Application	Original NDA
Indication(s)	For use by women to prevent pregnancy
Established Pharmacologic Class ¹	Estrogen/Progestin
Office/Division	ODE III/DRUP
Division Project Manager	Pamela Lucarelli
Date FDA Received Application	May 31, 2012
Goal Date	March 28, 2013
Date PI Received by SEALD	March 25, 2013
SEALD Review Date	March 26, 2013
SEALD Labeling Reviewer	Abimbola Adebowale
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *The cross-reference to the FPI (i.e. the numerical identifier in parenthesis) at the end of the first bullet under the “Drug Interactions” heading in HL is missing.*

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI

Selected Requirements of Prescribing Information

• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

- YES** 10. Product title in HL must be **bolded**.

Comment: *Insert a space between the word “Quartette” and the first part of the parentheses in the Product Title.*

Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

- YES** 12. All text must be **bolded**.

Comment:

- YES** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Selected Requirements of Prescribing Information

Comment:

- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment:

- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

Selected Requirements of Prescribing Information

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *Recommend removing the extra space between the colon and the word “March” in the Revision Date.*

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

Selected Requirements of Prescribing Information

- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment: *No periods should be included after the numbers for the section headings in the TOC.*
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE

Selected Requirements of Prescribing Information

11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- NO** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[*see Warnings and Precautions (5.2)*]”.

Comment: For the cross reference “[See Contraindications (4).]” in the boxed warning in the FPI, a period should not be included after the parentheses. Delete the period.

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- YES** 42. All text is **bolded**.

Comment:

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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/s/

ABIMBOLA O ADEBOWALE
03/26/2013

LAURIE B BURKE
03/26/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Consumer Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: March 8, 2013

To: Pam Lucarelli
Regulatory Project Manager
Division of Reproductive and Urologic Products (DRUP)

From: Carrie Newcomer, PharmD
Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)
Office of Prescription Drug Promotion (OPDP)

Subject: NDA: 204061
QUARTETTE™ (levonorgestrel/ethinyl estradiol and ethinyl estradiol)

Background

On June 22, 2012, DRUP consulted OPDP to review the proposed package insert (PI), patient package insert (PPI), and carton/container labeling for the original NDA submission for QUARTETTE™ (levonorgestrel/ethinyl estradiol and ethinyl estradiol) (Quartette).

Please note that DCDP has reviewed the proposed PPI and our comments are based on the substantially complete version of the draft label dated March 1, 2013, and retrieved from the eRoom on March 8, 2013. Our comments are provided in the attachment.

The Division of Professional Drug Promotion (DPDP) provided comments on the PI and carton/container labeling under separate cover on March 6, 2013.

Thank you for your consult. If you have any questions on the PPI, please contact Carrie Newcomer at 6-1233, or carrie.newcomer@fda.hhs.gov.

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/s/

CARRIE A NEWCOMER
03/08/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: March 6, 2013

To: Pam Lucarelli
Regulatory Project Manager
Division of Reproductive and Urologic Products (DRUP)

From: Melinda McLawhorn, PharmD, BCPS
Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, PharmD, Acting Group Leader (DPDP)

CC: Carrie Newcomer, PharmD
Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP), OPDP

Subject: **NDA 204061**
QUARTETTE™ (levonorgestrel/ethinyl estradiol and ethinyl estradiol)

Background

On June 22, 2012, DRUP consulted OPDP to review the proposed package insert (PI), patient package insert (PPI), and carton/container labeling for the original NDA submission for QUARTETTE™ (levonorgestrel/ethinyl estradiol and ethinyl estradiol) (Quartette).

DPDP reviewed the PI from the proposed substantially complete version retrieved from the eRoom on March 1, 2013 and our comments are provided below. DPDP also reviewed the carton/container labeling submitted to the electronic document room on January 30, 2013. Our comments are provided in the attachment.

The Division of Consumer Drug Promotion (DCDP) will provide comments on the PPI under a separate cover.

Thank you for your consult. If you have any questions on the PI or carton/container labeling, please contact Melinda McLawhorn at 6-7559 or at Melinda.McLawhorn@fda.hhs.gov.

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/s/

MELINDA W MCLAWHORN
03/06/2013

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: February 22, 2013

TO: Pam Lucarelli, Regulatory Project Manager
Vaishali Popat, M.D., Medical Officer
Division of Reproductive and Urologic Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 204061

APPLICANT: Teva

DRUG: Quartette[®] (levonorgestrel and ethinyl estradiol)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Contraception

CONSULTATION REQUEST DATE: August 14, 2012
CLINICAL INSPECTION SUMMARY DATE: February 28, 2013
DIVISION ACTION GOAL DATE: March 29, 2013
PDUFA DATE: March 31, 2013

I. BACKGROUND:

The Applicant submitted this NDA to support the use of Quartette® (levonorgestrel and ethinyl estradiol) for contraception.

The pivotal study Protocol DR-103-301, entitled “A Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of a Combination Oral Contraceptive Regimen (DR-103) for the Prevention of Pregnancy in Women” was submitted and inspected in support of the indication. The primary objective of this study was to demonstrate the efficacy and safety of a 91-day combination oral contraceptive (OC) regimen (DR-103), utilizing ascending EE doses (20, 25, 30 mcg) during each 84-day cycle of EE/LNG followed by 7 days of 10 mcg EE taken for 1 year in women desiring pregnancy prevention. The primary efficacy parameter was the evaluation of pregnancy rates reported using the Pearl Index.

Site #079 was selected for inspection because of relatively large enrollment and questions regarding the enrollment/discontinuation status of Subjects #029 and #061. Site #034 was selected because it was the largest enrolling site, and Site #071 appeared to have a financial conflict of interest.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects	Inspection Dates	Final Classification
William Seger, M.D. Benchmark Research 4504 Boat Club Road, Suite 400A Fort Worth, TX 76135	DR-103-301/ Site #079/ 28 (enrolled)	14-20 Nov 2012	NAI
Janet Gersten, M.D. New Age Medical Research Corporation 8900 Southwest 117th Avenue, Suite 207-B Miami, FL 33186	DR-103-301/ Site #034/ 184 (enrolled)	16-24 Oct 2012	NAI
David Portman, M.D. Columbus Center for Women’s Health Research 99 N. Brice Road, Suite 120 Columbus, OH 43213	DR-103-301/ Site #071 78 (enrolled)	15-26 Oct 2012	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

1. William Seger, M.D.

Benchmark Research
4504 Boat Club Road, Suite 400A
Fort Worth, TX 76135

- a. **What was inspected:** At this site, for Protocol DR-103-301, 62 subjects were screened, 28 subjects were enrolled, and nine subjects completed the study. An audit of the study records of the 28 enrolled subjects was conducted. Records reviewed included, but were not necessarily limited to, informed consent forms, source documents and electronic Case Report Forms (eCRFs), protocol training documentation, IRB and monitor communications, financial disclosure, and test article disposition.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. As requested in the consult, the study records for Subjects 029 and 061 were reviewed in their entirety. Subject 029 was not compliant with the intake of the test article and subsequently became pregnant. The site learned of the pregnancy on November 8, 2010, and informed the sponsor of the pregnancy on the same day. Despite repeated attempts at written communication with the subject by the site, the subject was ultimately lost to follow up. Subject 061 withdrew consent on the advice of her primary care physician who informed her that the test article was raising her blood pressure. Review by the FDA investigator of relevant records from Visits 1 through 5 did not indicate blood pressure elevations greater than 140/90, the protocol-specified criterion for high blood pressure.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data submitted by this site may be used in support of the respective indication.

2. Janet Gersten, M.D.

New Age Medical Research Corporation
8900 Southwest 117th Avenue, Suite 207-B
Miami, FL 33186

- a. **What was inspected:** At this site, for Protocol DR-103-301, 245 subjects were screened, 190 subjects were enrolled. Of the 190 enrolled subjects, 184 subjects comprised the safety database and 119 subjects completed the study. An audit of the study records of 32 of the subjects was conducted. Signed informed consent forms were present for all screened subjects. Other records reviewed included, but were not limited to, source documents, inclusion/exclusion criteria, primary efficacy data, adverse event reports, test article disposition, IRB, sponsor, and monitor communications, and financial disclosure.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.

c. Assessment of data integrity: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. David Portman, M.D.
Columbus Center for Women's Health Research
99 N. Brice Road, Suite 120
Columbus, OH 43213

a. What was inspected: At this site, for Protocol DR-103-301, 108 subjects were screened, 78 subjects were enrolled and received investigational product (an additional two subjects were enrolled but never received the investigational product), and 53 subjects completed the study. An in-depth audit of the study records of 20 of the subjects in the study was conducted. The records of 15 additional subjects were audited for adverse event and primary efficacy data reporting. Signed informed consent forms were present for all screened subjects. Records reviewed included, but were not limited to, source documents, case report forms (CRFs), inclusion/exclusion criteria, adverse event reports, laboratory reports, IRB, sponsor, and monitor communications, test article disposition, and financial disclosure documents.

b. General observations/commentary: A Form FDA 483 was issued at the conclusion of the inspection noting that Subject 028's complaints of intermittent abdominal pain/diarrhea were not documented on the electronic CRF. Dr. Portman, in his written response dated November 6, 2012, stated the subject's complaints were evaluated at the time and deemed unrelated to the use of the investigational drug, and that it was human error that this observation was not transcribed from the source document to the CRF. Dr. Portman stated that a new data transcription process has been implemented to further reduce the incidence of such errors.

c. Assessment of data integrity: Other than the lack of documentation of a single adverse event as described above, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Seger, Gersten, and Portman's clinical investigator sites were inspected in support of this NDA. Drs. Seger and Gersten were not issued Form FDA 483s; the final classification of the inspections was NAI (No Action Indicated). Dr. Portman was issued a Form FDA 483 for not having documented the occurrence of an adverse event as described above; the final classification of the inspection was VAI (Voluntary Action Indicated). Overall, the data generated by the clinical sites and submitted by the sponsor appear adequate in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
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CONCURRENCE:

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Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

ROY A BLAY
02/26/2013

JANICE K POHLMAN
02/26/2013

SUSAN D THOMPSON
02/26/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: January 31, 2013

Reviewer: Manizheh Siahpoushan, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Zachary Oleszczuk, PharmD
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Quartette
(Levonorgestrel/Ethinyl Estradiol Tablets 0.15 mg/0.02 mg,
Levonorgestrel/Ethinyl Estradiol Tablets 0.15 mg/0.25 mg
Levonorgestrel/Ethinyl Estradiol Tablets 0.15 mg/0.03 mg
and Ethinyl Estradiol 0.01 mg Tablets)

Application Type/Number: NDA 204061

Applicant/sponsor: Teva Branded Pharmaceuticals Products, Inc.

OSE RCM #: 2012-1425

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed trade and professional product design, sample blister pack labels, foil pouch, carton, and insert labeling for Quartette (Levonorgestrel/Ethinyl Estradiol and Ethinyl Estradiol) Tablets, NDA 204061, for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

In their May 31, 2012 cover letter, the Applicant states that the content and the format of the proposed labeling for Quartette has been prepared according to the approved labeling for Teva's other combination oral contraceptives, Seasonique (NDA 021840 approved May 25, 2006) and LoSeasonique (NDA 022262 approved October 24, 2008).

According to the Applicant, this product is developed to systematically increase the estrogen dose at strategic points in the extended cycle when breakthrough bleeding is likely to occur, in order to reduce the incidence of overall breakthrough bleeding, while lowering the total estrogen exposure per 91-day extended cycle.

Additionally, the Applicant submitted a request for proprietary name review of Quartette which is currently under review under a separate cover in OSE Review #2012-1420. The proposed name was previously found acceptable in OSE Review #2010-401, dated July 26, 2010 for IND 072290.

1.2 PRODUCT INFORMATION

The following product information is provided in the June 18, 2012 proprietary name submission.

- Active Ingredient: Levonorgestrel and Ethinyl Estradiol
- Indication of Use: Prevention of pregnancy
- Route of Administration: Oral
- Dosage Form: Tablets
- Strength: 0.15 mg/0.02 mg, 0.15 mg/0.025 mg, 0.15 mg/0.03 mg and 0.01 mg
- Dose and Frequency: One tablet orally at the same time every day.
- How Supplied: Each cycle pack will be packaged in a tri-fold, perforated, white blister card where each of the first two parts has 28 combination pills and the third part has 28 combination pills and 7 Ethinyl Estradiol pills (35 pills total) for each 91 day cycle. Each tri-fold blister pack will be sealed in a foil pouch. Physician samples will be provided with the same configuration.
- Storage: 20°C to 25°C (68°F to 77°F)
- Container and Closure Systems: The primary packaging components that come in contact with the tablets are the (b) (4) blister film and the push-through aluminum foil. The blister film is (b) (4) moisture protection. The push through blister lidding

foil is (b) (4) aluminum foil that is printed on both sides. Each 91-day regimen contains 3 blister cards which are placed into a single (b) (4) compact and sealed in a foil pouch containing a 2g (b) (4) desiccant and patient leaflet. Sealed pouches are then placed in a cardboard carton.

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS database for Seasonique and LoSeasonique medication error reports which would be relevant to this review because the Applicant states that the format of the Quartette proposed labels and labeling have been prepared according to these two products. We also reviewed the Quartette labels and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) database using the strategy listed in Table 1.

Table 1: AERS Search Strategy	
Date: 7/9/12	7/7/08 (date of last search in OSE Review #208-297, dated September 16, 2008) to 7/9/12 (Seasonique) and no date listed for LoSeasonique
Drug Names: Seasonique and LoSeasonique	Trade names: Seasonique and LoSeasonique Verbatim terms: Seasonique% and LoSeasonique%
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The July 9, 2012 AERS search for Seasonique retrieved only one case which was excluded from further evaluation because it was a case of adverse events not relevant to this review. No cases were retrieved from the LoSeasonique AERS search.

2.2 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Trade and professional sample blister pack labels submitted May 31, 2012 (Appendix A)

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Trade and professional pouch foil labeling submitted May 31, 2012 (Appendix B)
- Trade and professional sample carton labeling submitted May 31, 2012 (Appendix C)
- Insert Labeling submitted May 31, 2012

3 MEDICATION ERROR RISK ASSESSMENT

The following section describes our risk assessment of the Quartette product design, labels and labeling.

3.1 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

The proposed product design for Quartette is consistent with the other 91-day regimen combination oral contraceptives that are currently in the market (i.e. Seasonique, LoSeasonique, and Seasonale). However, DMEPA identified deficiencies in the blister pack (trade and professional) labels, carton (trade and professional), foil pouch (trade and professional), and insert labeling. These deficiencies include:

- Use of intervening graphics above and below the proprietary name
- Lack of prominence of the important HIV statement on the side panel of the carton labeling
- Inadequate prominence of the established name
- Lack of a place holder for the lot number and the expiration date statements in accordance with 21 CFR 201.17 on all labels and labeling
- Presence of numbers on blister pack labeling that may be confused with the lot and expiration dates
- Lack of a ‘Start’ (or ‘start here’) statement as well as the week numbers (i.e. week 1 to week 13) on the blister pack labeling to properly communicate to patients how to take Quartette
- Unclear information in ‘Before you start taking Quartette’ section of the Patient Labeling

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. General Comments

The use of the terminology ‘(b)(4) Extended-Cycle’ may imply that these oral contraceptive tablets or dosing schedule provide an additional benefit over other oral contraceptive tablets or dosing schedule. The term ‘Extended’ as used to describe the ‘Extended-release’ formulations, allow for a reduction in frequency of administration of a drug in comparison with the frequency required by a conventional dosage form. Additionally, a patient using this product may mistakenly believe that each tablet has a longer effect than another oral contraceptive product. We note that DMEPA expressed a similar concern (i.e. ‘Extended-Regimen’ and ‘Extended-Cycle’) in previous label and labeling reviews for two other products, LoSeasonique and Seasonale in OSE Review #'s 2008-297 and 01-0240, dated September 16, 2008 and August 15, 2003, respectively. However, the approved products continue to display the terminology ‘Extended-Cycle’. Therefore, we defer to the Division to determine if the term ‘(b)(4) Extended-Cycle’ for the proposed product is appropriate.

B. Blister Pack Labels, Foil Pouch, and Carton Labeling (trade and sample)

1. Delete the (b)(4) that appears above the proprietary name (i.e. above the ‘ette’ portion of the name) and below the proprietary name (i.e. through the letter ‘Q’ and extending out). This will ensure that the proprietary name is not negatively affected by any graphic, text, or other intervening matter. For example, the beginning letter ‘Q’ in the proposed name, Quartette, may be misinterpreted as the letter ‘O’ due to the presence of the (b)(4) below the name.
2. In accordance with 21 CFR 201.17, ensure the blister pack labels, foil pouch, and carton labeling incorporate the expiration date and lot number.
3. The printed texts ‘Iss. 2/2012’ and ‘799-30-xxxxxx’ on the blister pack labels, foil pouch, and carton labeling may be confused as the expiration date and the lot number. We recommend removing these numbers.

C. Blister Pack Labels (trade and professional sample)

1. The blister pack labels do not indicate what pill should be taken first to initiate therapy. An arrow that designates which pill should be taken first, accompanied with the word ‘start’ or the phrase ‘start here’, can properly communicate to patients important information regarding how to take Quartette.
2. Include the respective week statements (e.g. week 1, week 2, etc.) for each row of the three blister pack labels for clarity.

D. Foil Pouch Labeling (trade and professional sample)

Delete the ‘(b)(4)’ statement that appears on the orange background of the lower right hand side of the foil pouch labeling. This information is repetitive because it already appears (b)(4) of the labeling.

E. Carton Labeling

1. Ensure the size and prominence of the established name is at least ½ the size of the proprietary name to be in accordance with CFR 201.10(g)(2). Additionally, to improve contrast and readability, darken the font color of the established name to provide better contrast against the white background which is currently difficult to read.
2. Increase the prominence of the important statement, ‘This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.’ on the side panel of the carton labeling, by increasing the font size and moving it further up on the label. Alternatively, this information may be relocated to the principal display panel.

F. Insert Labeling

Ensure that any changes to the presentation on the blister labels are incorporated into diagrams of the blister cards included in the Patient Package Insert. As currently presented, the blister label diagrams do not display the ‘start’ (or ‘start here’) statement or the week numbers next to each row. However, under ‘ Before you start taking Quartette’ in the Patient Package Insert, patients are instructed to refer to the ‘start arrow’ to find out where on the first tray in the pack to start taking pills. This inconsistency of information can lead to confusion in patients.

If you have further questions or need clarifications, please contact Marcus Cato, project manager, at 301-796-3903.

5 REFERENCES

OSE Review #2008-297, LoSeasonique Proprietary Name, Label, and Labeling, Lee, J.J. September 16, 2008.

OSE Review #01-0240-3, Seasonale Proprietary Name, Label, and Labeling, Dallas, S, August 15, 2003

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

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

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

/s/

MANIZHEH SIAHPOUSHAN
01/31/2013

ZACHARY A OLESZCZUK
01/31/2013

CAROL A HOLQUIST
02/03/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 204061

Application Type: Original

Name of Drug: levonorgestrel/ethinyl estradiol

Applicant: Teva Branded Pharmaceutical Products R&D, Inc

Submission Date: May 30, 2012

Receipt Date: May 31, 2012

Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by August 27, 2012. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

- YES** 4. White space must be present before each major heading in HL.

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional

• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **“HIGHLIGHTS OF PRESCRIBING INFORMATION”**.

Highlights Limitation Statement

- NO** 9. The bolded HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).”

Comment: name of drug product is not in upper case.

Product Title

- YES** 10. Product title in HL must be **bolded**.

Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement **“Initial U.S. Approval:”** followed by the **4-digit year**.

YES

Boxed Warning

12. All text must be **bolded**.

YES

13. Must have a centered heading in UPPER-CASE, containing the word **“WARNING”** (even if more than one Warning, the term, **“WARNING”** and not **“WARNINGS”** should be used) and other words to identify the subject of the Warning (e.g., **“WARNING: SERIOUS INFECTIONS”**).

YES

14. Must always have the verbatim statement **“See full prescribing information for complete boxed warning.”** centered immediately beneath the heading.

YES

15. Must be limited in length to 20 lines (this does not include the heading and statement **“See full prescribing information for complete boxed warning.”**)

YES

16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Indications and Usage

- YES** 17. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Dosage Forms and Strengths

- YES** 18. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Contraindications

- YES** 19. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

- YES** 20. Each contraindication is bulleted when there is more than one contraindication.

Adverse Reactions

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Patient Counseling Information Statement

- YES** 22. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Revision Date

- YES** 23. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 24. A horizontal line must separate TOC from the FPI.
- YES** 25. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.
- YES** 26. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
- YES** 27. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
- YES** 28. All section headings must be **bolded** and in UPPER CASE.
- YES** 29. All subsection headings must be indented, not bolded, and in title case.
- YES** 30. When a section or subsection is omitted, the numbering does not change.
- YES** 31. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)**GENERAL FORMAT**

- YES** 32. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
- YES** 33. All section and subsection headings and numbers must be **bolded**.
- YES** 34. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

- YES** 35. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.
- YES** 36. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].
- N/A** 37. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- YES** 38. All text is **bolded**.
- YES** 39. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).
- YES** 40. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Contraindications

- N/A** 41. If no Contraindications are known, this section must state “None”.

Adverse Reactions

- YES** 42. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

- N/A** 43. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Patient Counseling Information

- YES** 44. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”
-

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/s/

PAMELA LUCARELLI
08/10/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 204061 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Quartette Established/Proper Name: levonorgestrel/ethinyl estradiol and ethinyl estradiol Dosage Form: Tablets Strengths: levonorgestrel 0.15 mg/ethinyl estradiol 0.020 mg, 0.025 mg, 0.030 mg and ethinyl estradiol 0.010 mg		
Applicant: Teva Branded Pharmaceutical Products R&D Agent for Applicant (if applicable):		
Date of Application: May 30, 2012 Date of Receipt: May 31, 2012 Date clock started after UN:		
PDUFA Goal Date: March 31, 2013	Action Goal Date (if different): March 29, 2013	
Filing Date: July 30, 2012	Date of Filing Meeting: July 25, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication(s)/Proposed change(s): prevention of pregnancy		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 072290				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th data-bbox="203 1451 495 1486">Application No.</th> <th data-bbox="495 1451 773 1486">Drug Name</th> <th data-bbox="773 1451 1060 1486">Exclusivity Code</th> <th data-bbox="1060 1451 1349 1486">Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the <i>Orphan Drug Designations and Approvals</i> list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 3</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			X	
<ul style="list-style-type: none"> If yes, were all of them submitted on time? 			X	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			X	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			X	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			

<p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	X			
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	
Pediatrics	YES	NO	NA	Comment

<u>PREA</u>				
Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		X		
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s):		X		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): December 28, 2011 a request for a Pre-NDA meeting was made, but then withdrawn. The Division provided a written response to the questions the Sponsor wanted to discuss.	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				
Other Meeting(s) Dates(s): August 7, 2006 Pre-IND Meeting	X			

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 25, 2012

BLA/NDA/Supp #: NDA 204061

PROPRIETARY NAME: Quartette

ESTABLISHED/PROPER NAME: levonorgestrel/ethinyl estradiol

DOSAGE FORM/STRENGTH: levonorgestrel 0.15 mg/ethinyl estradiol 0.020 mg, 0.025 mg, 0.030 mg and ethinyl estradiol 0.010 mg

APPLICANT: Teva Branded Pharmaceutical Products R&D, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): prevention of pregnancy

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Pam Lucarelli	Y
	CPMS/TL:	Jennifer Mercier	N
Cross-Discipline Team Leader (CDTL)	Lisa Soule		Y
Clinical	Reviewer:	Vaishali Popat	Y
	TL:	Lisa Soule	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Sayed Al Habet	Y
	TL:	Myong-Jin Kim	N
Biostatistics	Reviewer:	Jia Guo	Y
	TL:	Mahboob Sobhan	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Krishan Raheja	Y
	TL:	Alex Jordan	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Rajiv Agarwal	Y
	PAL:	Donna Christner	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Roy Blay	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Chongwoo Yu		Y
	Hylton Joffe		Y
	Audrey Gassman		Y
Other attendees	Chongwoo Yu		Y
Other attendees	Marcus Cato		Y
	Zach Oleszczuk		Y
	Manizheh Siahpoushan		Y
	Kate Oswell		Y
	Melinda McLawhorn		Y
Other attendees	Yaning Wang		Y
	Jeffrey Florian		Y

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? 	<input type="checkbox"/> YES

<p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<p>Date if known:</p> <p><input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> To be determined</p> <p>Reason:</p>
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p>BIOSTATISTICS</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p>NONCLINICAL</p>	<p><input type="checkbox"/> Not Applicable</p>

<p>(PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
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<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Audrey Gassman	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day

	<p>filing letter; For NDAs/NDA supplements: see CST for choices)</p> <ul style="list-style-type: none"> • notify OMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

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

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

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

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

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

for approval on published literature based on data to which the applicant does not have a right of reference).

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

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

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

PAMELA LUCARELLI
08/09/2012