CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022247Orig1s000

<u>OTHER REVIEW(S)</u>

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA #/Product Name: 22247/Duavee (conjugated estrogens/bazedoxifene) tablets

PMR/PMC Description: Pharmacokinetic trial evaluating the effect of a strong CYP3A4 inhibitor and body weight on the exposure of conjugated estrogens and bazedoxifene titled "A Phase 1, Open-Label, Two-Period, Fixed-Sequence Study to Estimate the Effects of Steady State Administration of a Strong CYP3A4 Inhibitor on the Single-Dose Pharmacokinetics of Conjugated Estrogens/Bazedoxifene in Non-obese (Body Mass Index <30 kg/m2) and Obese (Body Mass Index ≥ 30 kg/m2) Postmenopausal Women."

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	04/01/2014
	Study/Trial Completion:	12/01/2014
	Final Report Submission:	04/01/2015
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - [ ] Unmet need
   - [ ] Life-threatening condition
   - [ ] Long-term data needed
   - [ ] Only feasible to conduct post-approval
   - [ ] Prior clinical experience indicates safety
   - [ ] Small subpopulation affected
   - [x] Theoretical concern
   - [ ] Other

Currently all conjugated estrogen (CE) products contain a class warning statement regarding the potential for increased concentrations of CE in the presence of 3A4 inhibitors. The approval of Premarin predated drug-drug interactions (DDI); therefore, we don't have a good estimation of CE increase in the presence of CYP3A4 inhibitors. Furthermore, pharmacometrics modeling using four Phase I studies showed a direct correlation between body weight and risk of endomterial hyperplasia. For Duavee, CYP3A4 inhibitors and increased body weight may increase the exposure of CE and bazedoxifene (BZA) and change the CE to BZA ratio. This alternation in CE to BZA ratio may increase the risk of endometrial hyperplasia, which can lead to endometrial cancer.

Currently, there is no obvious clinical evidence of harm from this potential DDI in Duavee's safety database that requires a pre-approval study. However, the PMR study is needed to define the potential effect of CYP inhibitors on the CE to BZA ratio that could lead to the safety risk of endometrial hyperplasia.

Reference ID: 3379577

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Based upon dose ranging studies, changes in the ratio of CE to BZA can increase the risk of endometrial hyperplasia. CYP3A4 inhibitors and body weight can affect the exposure of CE and change the CE to BZA ratio. A DDI study with Duavee and a strong CYP3A4 inhibitor and a study evaluating the effect of body weight will provide quantitative data for CE changes and possible estimation of endometrial hyperplasia risk.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Reference ID: 3379577

The sponsor agreed to conduct the study entitled: "A Phase 1, Open-Label, Two-Period, Fixed-Sequence Study to Estimate the Effects of Steady State Administration of a Strong CYP3A4 Inhibitor on the Single-Dose Pharmacokinetics of Conjugated Estrogens/Bazedoxifene in Non-obese (BMI <30) and Obese (BMI ≥30) Postmenopausal Women."

This will be a pharmacokinetic study assessing drug-drug interaction between strong CYP3A4 inhibitor and Duavee and stratified by body mass index. The primary measure of interest will be the effect on concentrations of CE and BZA.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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PMR/PMC Development Coordinator:

X *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Reference ID: 3379577

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

/s/

MEREDITH ALPERT
09/26/2013

CHRISTINE P NGUYEN
09/26/2013

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

Product Title	**DUAVEE® (conjugated estrogens/bazedoxifene) tablets for oral use**
Applicant	Pfizer Inc.
Application/Supplement Number	NDA 22247
Type of Application	Original
Indication(s)	• Treatment of moderate to severe vasomotor symptoms associated with menopause • Prevention of postmenopausal osteoporosis
Established Pharmacologic Class[1]	Estrogens with an Estrogen Agonist/Antagonist
Office/Division	ODE III/DBRUP
Division Project Manager	Samantha Bell
Date FDA Received Application	October 3, 2012
Goal Date	October 3, 2013
Date PI Received by SEALD	September 25, 2013
SEALD Review Date	September 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.

Reference ID: 3379231

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 is 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:

NO 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: *The following headings in HL are not presented in the center of the horizontal line: Indications and Usage, Dosage and Administration, Dosage Forms and Strengths, Contraindications, Warnings and Precautions, Adverse Reactions, Drug Interactions and Use in Specific Populations. Center them.*

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

Comment: *There is extra white space before the Dosage Forms and Strengths heading. Recommend decreasing the white space.*

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 reference of the Full Prescribing Information (FPI) that contains more detailed information is missing from the end of the first bullet in the Boxed Warning in HL.*

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

Section	Required/Optional
• **Highlights Heading**	Required

Reference ID: 3379231

Selected Requirements of Prescribing Information

• **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.

Comment:

NO 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment: *The horizontal line separating HL and TOC only extends across the top of the left column of the TOC (i.e. half a horizontal line). Insert a full horizontal line that extends across both columns of the 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"**.

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: *Recommend inserting a comma between "tablets" and "for oral use" in product title as follows: DUAVEE® (conjugated estrogens/bazedoxifene) tablets, for oral use*

Initial U.S. Approval

NO 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: *The 4-digit year (i.e. (2013)) that follows the verbatim statement "Initial Approval" should read as "2013" bolded, in regular font with no parentheses instead of "(2013)", bolded, italicized with parentheses.*

Reference ID: 3379231

Selected Requirements of Prescribing Information

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**").

Comment:

NO 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." in *italics* and centered immediately beneath the heading.

Comment: *The verbatim statement "See full prescribing information for complete boxed warning" is not immediately beneath the heading. There is a white space between the two. Delete the white space.*

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:

Reference ID: 3379231

Selected Requirements of Prescribing Information

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

N/A 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:

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:

Contents: Table of Contents (TOC)

Reference ID: 3379231

Selected Requirements of Prescribing Information

GENERAL FORMAT

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

Comment:

NO 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment: *The bolded heading at the beginning of TOC should read as "FULL PRESCRIBING INFORMATION: CONTENTS*"instead of "FULL PRESCRIBING INFORMATION: CONTENTS [*]."*

NO 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: *The subheading 6.1 "Clinical Studies Experience "in the TOC does not match the subheading 6.1 "Clinical Trials Experience" in the FPI. Match the TOC and FPI subheadings.*

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:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

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

Reference ID: 3379231

Selected Requirements of Prescribing Information

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

Comment:

NO 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: *FDA-Approved Patient Labeling is included as subsection 17.7 in the FPI and TOC. The FDA-approved patient labeling should not be a numbered subsection under section 17 (Patient Counseling Information) in the FPI or listed in the TOC, but appended or reprinted after the last section of labeling.*

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: *Under subsection 8.5, 8.6 and 8.7, the cross-references currently written as "[see … Pharmacokinetics (12.3)]" should read as "[see… Clinical Pharmacology (12.3)]."*

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

Selected Requirements of Prescribing Information

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:

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:

N/A 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:

Reference ID: 3379231

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/s/

ABIMBOLA O ADEBOWALE
09/26/2013

LAURIE B BURKE
09/26/2013

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

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: September 20, 2013

To: Samantha Bell
Regulatory Project Manager
Division of Bone, Reproductive, and Urologic Products (DBRUP)

From: Lynn Panholzer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 022247
Conjugated estrogens/bazedoxifene Tablets

Background

This consult review is in response to DBRUP's November 19, 2012, request for OPDP's review of the draft package insert (PI), patient package insert (PPI), and carton/container labeling for conjugated estrogens/bazedoxifene tablets. OPDP reviewed the substantially complete version of the draft PI provided by the Division of Medical Policy Programs (DMPP) on September 6, 2013. Our comments on the PI are included directly on the attached copy of the labeling. We reviewed the draft carton and container labels submitted by the applicant on September 6, 2013. We have no comments on the carton and container labels (attached for reference). Our review of the PPI was conducted jointly with DMPP and was filed under separate cover on September 17, 2013.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Lynn Panholzer at 301-796-0616 or lynn.panholzer@fda.hhs.gov.

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

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/s/

LYNN M PANHOLZER
09/20/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 17, 2013
To:	Hylton Joffe, M.D., Director **Division of Bone, Reproductive and Urologic Products (DBRUP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Melissa Hulett, RN, BSN, MSBA Team Leader, Patient Labeling Team **Division of Medical Policy Programs**
From:	Robin Duer, MBA, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Lynn Panholzer, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	conjugated estrogens/ bazedoxifene
Dosage Form and Route:	tablets
Application Type/Number:	NDA 22-247
Applicant:	Wyeth

1 INTRODUCTION

On September 26, 2012, Wyeth submitted for the Agency's review a New Drug Application (NDA) for conjugated estrogens/bazedoxifene tablets indicated for the:

- treatment of moderate to severe vasomotor symptoms (VMS)
- treatment of moderate to severe symptoms of vulvular and vaginal atrophy
- prevention of postmenopausal osteoporosis

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Bone, Reproductive and Urologic Products (DBRUP) on November 19, 2012. DBRUP requested that DMPP and OPDP review the Applicant's proposed Patient Package Insert (PPI) for conjugated estrogens/ bazedoxifene tablets.

2 MATERIAL REVIEWED

- Draft conjugated estrogens/ bazedoxifene tablets PPI received on September 26, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on September 6, 2013
- Draft conjugated estrogens/ bazedoxifene tablets PPI received on September 26, 2012, revised by the Review Division throughout the review cycle, and received by OPDP on September 10, 2013
- Draft conjugated estrogens/ bazedoxifene tablets Prescribing Information (PI) received on September 26, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on September 6, 2013
- Draft conjugated estrogens/ bazedoxifene tablets Prescribing Information (PI) received on September 26, 2012, revised by the Review Division throughout the review cycle and received by OPDP on September 6, 2013
- Approved Premarin (conjugated estrogens tablets, USP) comparator labeling dated October 28, 2011
- DMPP PPI review for Cenestin (synthetic conjugated estrogens, A) dated February 15, 2013

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more

accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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09/17/2013

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: August 2, 2013

TO: Samantha Bell, Regulatory Project Manager
Gerald Willett, M.D., Medical Officer
Marcia Whittaker, M.D., Medical Officer
Division of Bone, 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
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Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
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SUBJECT: Evaluation of Clinical Inspections

NDA: 22247

APPLICANT: Wyeth Pharmaceuticals, Inc.

DRUG: bazedoxifene/conjugated estrogens

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of vasomotor symptoms (VMS) in postmenopausal women; treatment of vulvar and vaginal atrophy (VVA) in postmenopausal women; and prevention of postmenopausal osteoporosis (PMO)

CONSULTATION REQUEST DATE:	January 25, 2013
CLINICAL INSPECTION SUMMARY DATE:	August 3, 2013
DIVISION ACTION GOAL DATE:	October 3, 2013
PDUFA DATE:	October 3, 2013

I. BACKGROUND:

The Applicant submitted this NDA to support the use of bazedoxifene (BZA)/conjugated estrogens (CE) for the treatment of vasomotor symptoms (VMS) in postmenopausal women; treatment of vulvar and vaginal atrophy (VVA) in postmenopausal women; and prevention of postmenopausal osteoporosis (PMO).

The pivotal studies were the following:

Protocol 3115A1-303-US/EU/BR

"A Double-blind, Randomized, Placebo- And Active-Controlled Safety and Efficacy Study of Bazedoxifene/Conjugated Estrogens Combinations in Postmenopausal Women"

This was a two-year, outpatient, multicenter, double-blind, randomized, placebo- and active (raloxifene)-controlled study. The primary objective of this study was to evaluate the effects of bazedoxifene/CE combinations on the incidence of endometrial hyperplasia in postmenopausal women. The primary efficacy endpoint was endometrial hyperplasia after one year of therapy.

and

Protocol 3115A1-305-US

"A Double-blind, Randomized, Placebo Controlled, Efficacy and Safety Study Of Bazedoxifene/Conjugated Estrogens Combinations for Treatment of Vasomotor Symptoms Associated with Menopause"

This was an outpatient, multicenter, double-blind, randomized, placebo-controlled study. The primary objective of this study was to assess the efficacy and safety of two doses of bazedoxifene/CE compared with placebo for the treatment of moderate to severe vasomotor symptoms associated with menopause. The primary efficacy variables were the number and severity of hot flushes at Screening, Week 4, and Week 12 as recorded in the subject diaries.

and

Protocol 3115A1-306-WW

(b) (4)

(b) (4)

(b) (4)

and

Protocol 3115A1-3307-WW

"A Double-blind, Randomized, Placebo- and Active-Controlled Efficacy and Safety Study of the Effects of Bazedoxifene/Conjugated Estrogens Combinations on Endometrial Hyperplasia and Prevention of Osteoporosis in Postmenopausal Women"

This was a Phase 3, outpatient, multicenter, double-blind, randomized, placebo- and active-controlled study that included a breast density substudy, an osteoporosis substudy and a sleep substudy. The primary objectives of this study were to confirm the endometrial safety of BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg based on an endometrial hyperplasia incidence of less than 1% at Year 1 and to assess the effect of BZA/CE in preventing postmenopausal osteoporosis at Year 1. The primary efficacy endpoints were the incidence of endometrial hyperplasia at Year 1, and, for the osteoporosis substudy, the percent change from baseline in BMD of the lumbar spine at Year 1.

The clinical sites below were selected for inspection based on a combination of factors including large enrollment, reported availability of source documentation, and safety reporting based on experience with monotherapy.

Also, since this application is in support of a New Molecular Entity (NME), an additional inspection was conducted of the sponsor, Wyeth Pharmaceuticals, Inc.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
Edmund Baracat, M.D., Ph.D. 1017- Casa 6 -Paralso Sao Paulo, NA CEP04005-003	3115A1-303-US/EU/BR/ 447/ 889 (randomized)	6-17 May 2013	VAI
Sam StanleyMiller, M.D. 7711 Louis Pasteur Drive, Suite 300 San Antonio, TX 78229	3115A1-303-US/EU/BR/ 411/ 120	1–10 Apr 2013	VAI
John Christopher Gallagher, M.D. 601 North 30th Street, Suite 6712 Omaha, NE 68131	3115A1-303-US/EU/BR/ 375/ 73	11-15 Apr 2013	NAI
Christopher Hutchison, M.D. 4001 South 700 East, Suite 105 Salt Lake City, UT 84107	3115A1-305-US/ 538/ 26	10-29 Apr 2013	OAI. Pending final classification.
David Portman, M.D. 5965 East Broad Street, Suite 110 Columbus, OH 43213	3115A1-306-WW/ 649/ 21	11-15 Apr 2013	NAI
Phyllis Marx, M.D. 515 North State Street, Suite 2700 Chicago, IL 60654	3115A1-3307-WW/ 73/ 50	9-16 Apr 2013	NAI
David Portman, M.D. 99 North Brice Road, Suite 120 Columbus OH 43213	3115A1-3307-WW/ 37/ 25	3-11 Apr 2013	NAI
BMD Central Site, Helen Hayes Hospital 51 North, Route 9w West Haverstraw, NY 10993	3115A1-303-US/EU/BR and 3115A1-3307-WW	23 Apr-1 May 2013	NAI
Pfizer, Inc. 500 Arcola Road Collegeville, PA 19426-3982	3115A1-303-US/EU/BR and 3115A1-3307-WW	28 May-6 Jun 13	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. Edmund Baracat, M.D., Ph.D.
1017- Casa 6 -Paralso
Sao Paulo, NA CEP04005-003

a. What was inspected: At this site for Protocol 3115A1-303-US/EU/BR, 3284 subjects were screened and 889 subjects were enrolled in the study. The study records, including the informed consent forms, of 96 subjects were audited. Records reviewed included, but were not limited to, screening and enrollment logs, inclusion and exclusion criteria, monitor and IRB correspondence, source documents, and Case Report Forms (CRFs).

b. **General observations/commentary**: A Form FDA 483 was issued at the conclusion of the inspection noting that all source documents for 80 subjects including visit records, laboratory results, and informed consent forms were unavailable for review. Eight subject records had evidence of some missing study documents; four subject records had missing informed consent documents and six subject records (including two of the subjects with missing informed consent documents) had loss of various study binders containing information about study visits, CRFs, and study-related procedure reports. Documentation that all subjects met all of the inclusion criteria and none of the exclusion criteria was incomplete in that source documents for all subjects failed to record whether subjects did or did not meet the specific exclusion criterion regarding the use of any investigational drug within 60 days before screening. Select consent forms were not available for review for four subjects. The Form FDA 1572 was not promptly updated to reflect a change in IRBs. No major discrepancies were found in a comparison of data line listings with source documentation and CRFs.

c. **Assessment of data integrity**: Review of the site screening log ("Subject Master List") showed that the subject numbers of the 80 subjects reported to have missing source documents corresponded to the numbers of subjects listed as having been randomized at the site. Seventy eight (78) of these 80 subjects had at least one data clarification/query form generated by the study monitor that was reviewed and collected by the FDA field investigator at the time of inspection. While the screening log and data clarification forms provide some assurance that subjects existed, OSI can not verify data reliability for those 80 subjects with missing source records or for those found to have missing source data at the time of inspection. The review division should consider the potential implications of missing records (including under-reporting of adverse events or overstatement of efficacy) in deciding whether or not to rely upon data from this site.

2. Sam Stanley Miller, M.D.
7711 Louis Pasteur Drive, Suite 300
San Antonio, TX 78229

a. **What was inspected:** At this site for Protocol 3115A1-303-US/EU/BR, 253 subjects were screened, 120 subjects were enrolled, and 79 subjects completed the study. The study records, including the informed consent forms, of 69 subjects were audited. Records reviewed included, but were not limited to, financial disclosure, randomization, IRB and CRO correspondence, source documents, Case Report Forms (CRFs), adverse events, concomitant medications, early termination and screen failures, and test article accountability.

b. **General observations/commentary**: A Form FDA 483 was issued at the conclusion of the inspection noting the following:

1) Study subjects were not provided informed consent forms in language understandable to them. (b) (6)

2) Study records including original consent forms, source documents and CRFs were not available for review for Subjects 307154, 309797, 318973, 314586, 309796, 309794, 309806, 309815, 314560, 314561, 314563, 314582, and 318416.

3) Serious adverse events were not reported in a timely manner on five occasions for Subject 318966 (worsening depression), Subject 314591 (left breast ductal carcinoma), Subjects 309826 (basal cell and squamous cell carcinoma), and Subject 307143 (appendectomy).

4) Nine subjects had Visit 2B more than 21 days after Visit 2A, in violation of the protocol.

5) One subject underwent a drug washout and two subjects had vital signs assessed prior to signing consent forms.

6) Six subjects had study visits outside of specified time windows.

c. Assessment of data integrity: Dr. Miller responded in writing to the above observations in writing. The response was extensive and appears to address the various observations satisfactorily. Dr. Miller indicated that he has implemented corrective actions where needed, and overall, appears to have adequate documentation of those instances where deviations from protocol occurred. None of these observations appear to have had a significant effect on study efficacy or subjects' rights or safety. However, OSI is unable to verify data integrity for 13 subjects because their records were not available for review at the time of the inspection. The review division should consider the potential implications of missing records (including under-reporting of adverse events or overstatement of efficacy) in deciding whether to rely upon these data.

3. John Christopher Gallagher, M.D.
601 North 30th Street, Suite 6712
Omaha, NE 68131

a. What was inspected: At this site for Protocol 3115A1-303-US/EU/BR, 300 subjects were screened, 72 subjects were randomized, and 65 subjects completed the study. An audit of the study records of 30 subjects was conducted. Signed informed consent forms were present for each of these subjects. Records reviewed included, but were not limited to, sponsor, monitor, and IRB correspondence, financial disclosures, randomization schedules, subject charts, Case Report Forms (CRFs), inclusion/exclusion criteria, medication logs, primary endpoint (occurrence of endometrial hyperplasia), adverse events, concomitant medications, and test article accountability.

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.

4. Christopher Hutchison, M.D.
12391 South 4000 West, Suite 100
Salt Lake City, UT 84065

a. What was inspected: At this site for Protocol 3115A1-305-US, 22 subjects were enrolled, and 21 subjects completed the study. The study records of 19 subjects were reviewed. All enrolled subjects signed informed consent forms prior to study entry. Other records reviewed included, but were not limited to, source documents, case report forms (CRFs), line listings, training records, IRB correspondence, inclusion/exclusion criteria, laboratory testing, adverse event reporting, concomitant therapies, intercurrent illnesses, monitoring reports, financial disclosures, and test article accountability.

b. General observations/commentary: A Form FDA 483 was issued at the conclusion of the inspection. Observations included, but were not limited to, the following:

1) The investigator did not adhere to protocol. Specifically,

a) Subjects 243, 250, 255, 256, and 272 were enrolled into the study and completed the study while taking excluded medications such as Wellbutrin, Lexapro, Zoloft, Cymbalta, Neurontin, and Citalopram.

b) Subjects 237 and 264 were enrolled despite not experiencing 12 months of spontaneous amenorrhea, an inclusion criterion. Subject 264 also experienced uncontrolled hypertension, an exclusion criterion.

c) Trans-vaginal ultrasound (TVU) procedures were performed and read for five subjects prior to the technologist and reader completing the TVU Technologist Information Sheet and the TVU Reader Information Sheet prior to subject enrollment as required by the investigational plan. In addition, documentation of calibration and maintenance of the TVU equipment was unavailable for review.

d) Subject 234 underwent an endometrial biopsy despite having an endometrial wall thickness of only 2 mm. The protocol specified that such biopsies be performed if the endometrial wall exceeded 4 mm.

e) The investigator did not personally conduct or supervise the study as evidenced by the investigator's lack of signatures documenting review of enrollment records, concomitant medications, menstrual histories, and the uncontrolled hypertension experienced by one subject. There was also a lack of documentation of adequate training of staff personnel to conduct the study.

2) The investigator did not maintain adequate records.

a) Dates on all 49 completed ultrasound checklists were inconsistent with dates on ultrasound reports.

b) At least 15 instances of revisions of source documentation were made without explanation or documentation of investigator review.

3) Investigational drug records were inadequate.

a) Study drug was received at a secondary site and then transferred to the investigational site. There was no documentation available for review regarding storage conditions of the investigational product for a period of two weeks while held at the secondary site.

b) All Master Dispensing and Inventory Records completed had an incorrect address for the Investigator/site of dispensation.

c. **Assessment of data integrity**: Dr. Hutchison replied to the above observations in writing in a letter dated May 28, 2013. Dr. Hutchison prefaced his remarks with a statement that he had concerns regarding the management of the study by the SMO, (b) (4) Dr. Hutchison's clinical site, Granger Medical Clinic, disassociated itself from (b) (4) however, Dr. Hutchison attributed some of the noted deficiencies to inadequate management of the study by (b) (4) Dr. Hutchison, has, in general, acknowledged the deficiencies in study conduct and has provided SOPs and committed to staff training to avoid similar deficiencies in future studies.

This inspection was preliminarily classified OAI by the field investigator based on the number and nature of deficiencies revealed by the inspection. A Significant Action Meeting (SAM) will be held by OSI on August 29, 2013, to determine whether the observed deficiencies merit an OAI classification and subsequent Warning Letter. The outcome of this meeting will be communicated to DBRUP. In the interim, DBRUP may wish to conduct a sensitivity analysis to determine whether exclusion of data from this site would affect the overall outcome of the study.

5. David Portman, M.D.
5965 East Broad Street, Suite 110
Columbus, OH 43213
and
99 North Brice Road, Suite 120
Columbus OH 43213

a. **What was inspected:** At this site for Protocol 3115A1-306-WW, 49 subjects were screened, 21 subjects were enrolled, and 20 subjects completed the study. For Protocol 3115A1-3307-WW, 64 subjects were screened, 25 were randomized, and 20 completed the study. For Protocol 3115A1-306-WW an audit of the study records of 21 subjects was conducted. For Protocol 3115A1-3307-WW an audit of the study records of 25 subjects was conducted. Signed informed consent forms were present for all subjects in both studies. Records reviewed for both protocols included, but were not limited to, sponsor, monitor, and IRB communications, financial disclosures, Case Report Forms (CRFs), adverse events, protocol deviations, randomization, subject discontinuation, concomitant medications, and drug accountability. Some primary endpoint data for Protocol 306 (indices of vaginal maturation) and Protocol 3307 (bone marker laboratory values) could not be verified because the site was blinded to these results.

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 studies appear to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indications.

6. Phyllis Marx, M.D.
515 North State Street, Suite 2700
Chicago, IL 60654

a. **What was inspected:** At this site, for Protocol 3115A1-3307-WW, 122 subjects were screened, 50 subjects were randomized, and 39 subjects completed the study. All subjects signed informed consent forms prior to screening. Records reviewed included source documents, case report forms (CRFs), line listings including primary efficacy endpoint data, test article accountability, study monitoring, training records, and IRB records.

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.

7. BMD Central Site,
Helen Hayes Hospital,
West Haverstraw, New York

a. **What was inspected:** At this site for Protocols 303-US/EU/BR and 3115A1-3307-WW, the inspection focused on Drs. Sam Stanley Miller, John Christopher Gallagher, Edmund Baracat, David Jay Portman, and Phyllis Dreier Marx The inspection reviewed, but was not limited to, organization and personnel; staff responsibilities; monitoring responsibilities; scanning equipment and related software; SOPs; scanning equipment monitoring; site qualification documentation; training documentation; file, disk, and data storage; and phone logs. Subject files were selected from each of the clinical sites noted above, reviewed for protocol adherence, and the data compared with data listings.

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 assessments of bone mineral density for Studies 3115A1-303-US/EU/BR and 3115A1-3307-WW appear to have been conducted adequately. The data generated by this CRO and subsequently submitted by the sponsor may be used in support of the respective indications.

8. Pfizer Inc.
500 Arcola Road
Collegeville, PA 19426-3982

a. **What was inspected:** At this site for Protocol 3115A1-303-US/EU/BR, the inspection focused on three clinical investigators: Drs. Sam Stanley Miller (Site 411), John Christopher Gallagher (Site 375), and Edmund Baracat (Site 447). For Protocol 3115A1-3307-WW, the inspection focused on two clinical investigators: Drs. David Jay Portman (Site 37), and Phyllis Dreier Marx (Site 73). For both protocols, the inspection reviewed study records including, but not limited to, organization and personnel, selection and monitoring of investigators, Form FDA 1572s, financial disclosure forms, C.V.s, selection of monitors, monitoring procedures and activities, subject study participation, IRB practices and communications, test article integrity and accountability, adverse events, quality assurance, and annual reporting.

b. **General observations/commentary**: A Form FDA 483 was issued at the conclusion of the inspection. Observations included the delay in bringing into compliance an investigator (Site 447) who did not comply with the signed agreement. Specifically, at specified visits, source documents such as mammogram reports, ultrasound radiography reports, and transvaginal ultrasound reports and images for multiple subjects were not available for review by the monitors. Similarly, for Site 411, multiple open monitoring issues were not addressed over a period of several months. Attempts to bring this investigator into compliance consisted of repeated requests to provide requested records. Also, the reviews of site monitoring visit reports (SMVRs) from Sites 411, 375, and 447 were not reviewed in a timely manner, taking between 2-29 months for such review after completion of the monitoring visit.

c. **Assessment of data integrity**: The sponsor responded noting that it had implemented several SOPs to address issues such as record retention and escalating and reviewing issues in a timely manner. Based on inspections at the clinical sites (Sites 375, 411, and 447), the monitoring findings did not appear to have an effect on efficacy and safety outcomes for those subjects whose source records were available for review. Notwithstanding the monitoring issues, the study appears to have been conducted adequately. Use of data in support of the respective indication should be considered in context with known missing subject records; OSI cannot verify data integrity for subjects with known missing source records. The review division should consider the potential implications of missing records (including under-reporting of adverse events or overstatement of efficacy) in deciding whether to rely upon these data.

There were no observations related to study monitoring for Study 3307. The sponsor's conduct of the study appeared to be adequate and the data appear acceptable for use in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Gallagher, Miller, and Baracat were inspected for Protocol 3115A1-303-US/EU/BR. Dr. Gallagher was not issued a Form FDA 483. The final classification of this inspection was No Action Indicated (NAI). Drs. Baracat and Miller were each issued a Form FDA 483. The final classification of these inspections was Voluntary Action Indicated (VAI). The clinical data generated by Dr. Gallagher's site appear adequate in support of the respective indication. At Dr. Miller's site, the study records for 13 subjects were unavailable for review. As previously reported to FDA, there were a substantial number (80) of subjects reported to have missing source documents at Dr. Baracat's site. OSI is unable to verify data integrity for those subjects with missing source records or for those found to have missing source data at the time of inspection. The review division should consider the potential implications of missing records (including under-reporting of adverse events or overstatement of efficacy) in deciding whether to rely upon data from these sites.

The clinical investigator site of Dr. Hutchison was inspected for Protocol 3115A1-305-US. Dr. Hutchison was issued a Form FDA 483. The field investigator's recommended classification of this inspection was Official Action Indicated (OAI). (b) (4) DBRUP may wish to conduct a sensitivity analysis excluding the data from the site of Dr. Hutchison to assess the effect, if any, on study outcome.

The clinical investigator site of Dr. Portman was inspected for Protocol 3115A1-306-WW. In addition, Dr. Portman's site, as well as that of Dr. Marx, were inspected for Protocol 3115A1-3307-WW. Neither Dr. Portman nor Dr. Marx was issued a Form FDA 483. The final classification of these inspections was NAI. The clinical data generated by the sites of Drs. Portman and Marx appear adequate in support of their respective indications.

The sponsor, Pfizer, was inspected with respect to Protocols 3115A1-303-US/EU/BR and 3115A1-3307-WW. The sponsor was issued a Form FDA 483. The final classification of this inspection was VAI. Other than delays in bringing investigators into compliance with the protocol and reviewing site monitoring reports in a timely manner, the sponsor appears to have complied with regulatory requirements regarding its obligations as a sponsor. Use of data in support of the respective indication for Protocol 3115A1-303-US/EU/BR should be considered in context with known missing subject records; OSI cannot verify data integrity for subjects with known missing source records.

The CRO, Helen Hayes Hospital, was inspected with respect to Protocols 3115A1-303-US/EU/BR and 3115A1-3307-WW. The CRO was not issued a Form FDA 483. The final classification of this inspection was NAI. The clinical data generated by this CRO appear adequate in support of the respective indication.

Note: An inspection summary addendum will be generated if conclusions change from the pending classifications stated here upon review of the submitted reports.

{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}*

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08/02/2013

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:	March 11, 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 Strengths:	Duavee (Bazedoxifene and Conjugated Estrogens) Tablets, 20 mg/0.45 mg and 20 mg/0.625 mg
Application Type/Number:	NDA 022247
Applicant:	Wyeth Pharmaceuticals
OSE RCM #:	2012-2561

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

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Reference ID: 3291885

1 INTRODUCTION

This review evaluates the proposed packaging configuration, container labels, carton, and insert labeling for Duavee, NDA 022247 for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

Wyeth has developed a new treatment option in the management of menopausal health in women with a uterus that pairs Bazedoxifene, a third generation selective estrogen receptor modulator (SERM), developed by the Applicant, with Conjugated Estrogens (Premarin). The pairing of a SERM with one or more estrogens is described as a tissue selective estrogen complex (TSEC), which maintains the established benefits of estrogen therapy for menopausal symptoms of hot flashes, vulvar vaginal atrophy, and prevention of osteoporosis, while antagonizing certain estrogenic effects, such as stimulation of the uterus and breast. Bazedoxifene Acetate is currently approved and marketed for the treatment and/or prevention of osteoporosis in postmenopausal women in the EU, Switzerland, Korea, and Japan, and is under regulatory review in the US for the prevention and treatment of osteoporosis in postmenopausal women. Currently, the only SERM marketed in the US for the prevention and treatment of postmenopausal osteoporosis is Evista (Raloxifene).

1.2 REGULATORY HISTORY

NDA 022247 was officially submitted on October 3, 2012 and is therefore considered to be under PDUFA V. As an NME, it is part of "The Program", and will have a 12 month clock with additional regulatory milestones. The first proposed proprietary name, (b) (4) for this product was found unacceptable (b) (4) in OSE Review #2012-2382, dated November 20, 2012. The Applicant submitted the new proposed proprietary name, Duavee, on March 22, 2013 and is being evaluated under a separate cover in OSE Review #2013-759. Additionally, the March 22, 2013 submission included updated container labels and carton labeling.

1.3 PRODUCT INFORMATION

The following product information is provided in the March 22, 2013 proprietary name submission.

- Active Ingredient: Bazedoxifene Acetate and Conjugated Estrogens
- Indication of Use: Treatment of moderate to severe vasomotor symptoms and vulvar and vaginal atrophy associated with menopause and prevention of postmenopausal osteoporosis
- Route of Administration: Oral
- Dosage Form: Tablets
- Strengths: 20 mg/0.45 mg and 20 mg/0.625 mg
- Dose and Frequency: One tablet orally once daily

Reference ID: 3291885

- How Supplied: (b) (4) two blister packs of 15 tablets each in a carton. Professional blister packs of 7 tablets will be available.
- Storage: Controlled room temperature. Dispense and keep product in the original container. (b) (4) Protect from moisture. The Applicant has requested (b) (4) months of expiration dating period for the 20 mg/0.45 mg product strength (b) (4) After opening, (b) (4) product contained in the blister packs must be used within 60 days.
- Container and Closure System: (b) (4)
  - Blister cards: The blister card (one tablet per blister dome) consists of (b) (4) an aluminum foil laminate pouch. (b) (4) (b) (4)

2 METHODS AND MATERIALS REVIEWED

DMEPA reviewed the following labels and labeling.

2.1 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:

- (b) (4)
- Blister pack labels (30-count trade and 7-count professional sample) submitted March 22, 2013 (Appendix A)
- Pouch labeling (30-count trade and 7-count professional sample) submitted March 22, 2013 (Appendix B)

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

Reference ID: 3291885

- Carton labeling (30-count trade and 7-count professional sample) submitted March 22, 2013 (Appendix C)
- Professional labeling submitted December 20, 2012 (no image)

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our risk assessment of the Bazedoxifene and Conjugated Estrogens product design as well as the associated label and labeling.

3.1 PRODUCT PACKAGING CONFIGURATIONS

(b) (4)

3.1.2 Blister Pack

The Applicant is proposing two blister cards of 15 tablets each in a carton (commercial) or one card of 7 tablets in a carton (professional sample). The blister cards contain one tablet per blister dome and consist of (b) (4) a foil laminate pouch. (b) (4) Additionally, tablets should not be removed form blisters until immediately before administration to protect from moisture. After opening the foil pouch, product must be used within 60 days.

Our assessment of the blister cards found the design to be suitable for dosing and administration of this product. The proposed package of 2 blister cards, each containing 15 tablets per blister card allows for unit of use dosing and the proposed quantity is sufficient to allow for chronic therapy. The blister cards are not arranged in a way that

Reference ID: 3291885

could lead to dosing confusion. Each blister is labeled with the drug name, strength, and the warning statements related to the stability profile of the product.

3.2 PROPOSED IN-USE EXPIRATION DATES ((b) (4) BLISTER PACKS)

The Applicant has requested (b) (4) months (b) (4) of expiration dating period for the 20 mg/0.45 mg (b) (4) After opening, product (b) (4) contained in the blister packs must be used within 60 days after opening the foil pouch containing the blister card.

We had postmarketing experience with a product that offered similar storage requirements when first approved (i.e., Pradaxa). There were multiple medication errors that were occurring due to wrong storage technique of the product, such as (b) (4) transferring the product to medication dispenser and pill boxes. The possibility of similar errors occurring with the Bazedoxifene and Conjugated Estrogen product exists. (b) (4)

We expressed our concern to the CMC reviewer via an email communication dated January 23, 2013, and asked if she agreed with the Applicant's results of the in-use stability data submitted on October 19, 2012. (b) (4)

During the January 31, 2013 status meeting, the CMC reviewer informed us that her analysis of the Applicant's proposed in-use stability data found the results acceptabl (b) (4)

Based on these findings, DMEPA and CMC agreed that the (b) (4) 60-day expiration dates proposed by the Applicant for this product would have to be conveyed to the patients and the healthcare providers through prominent presentation of storage requirement warning statements on all product labels and labeling. Although the Applicant has included these warning statements in the labels and labeling, these statements lack prominence. We make recommendations for all labels and labeling in Section 5.

Reference ID: 3291885

3.3 LABELS AND LABELING

(b) (4)

The 20 mg/0.45 mg strength is presented in pink (b) (4) The corresponding tablets are also presented in the same colors. This color scheme is consistent across all the proposed packaging configurations.

The Duavee labels and insert labeling direct health care practitioners to dispense the tablets in their original container. Patients are also directed to keep the product in the original container ((b) (4) blister pack) and not to use the product after (b) (4) 60 days after opening the foil pouch containing the blister packs. Because of these requirements, increasing the prominence of these warning statements to store medication in the original container may help reduce the risk of errors related to improper storage. (b) (4)

4 RECOMMENDATIONS

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

4.1 COMMENTS TO THE DIVISION

DMEPA provides the following comments for consideration by the review Division prior to the approval of the NDA:

1. General comment: In light of the storage requirements associated with Duavee, we recommend the Applicant alert the public and healthcare practitioners of the proper storage of this product (i.e., Dear Healthcare Provider letters and warning notifications in every shipment of the product to the pharmacy).
2. We recommend revising the presentation of the established name throughout the insert labeling and Patient Labeling to replace the symbol '/' with 'and' (i.e., Bazedoxifene and Conjugated Estrogens).
3. Under sections 2.2, 2.3, and 2.4, 2.5, and 2.6 , Dosage and Administration, section 3, Dosage Forms and Strengths, section 11, Description, and section 16, How Supplied/Storage and Handling, in the full prescribing information, We recommend replacing all instances of the abbreviation 'CE' with Conjugated Estrogens for clarity.
4. Under section 17, Patient Counseling Information, in the full prescribing information, we recommend including a section for healthcare providers to communicate the proper storage of this product and the limitations associated with the proposed expiration dates once a container ((b) (4) foil pouch containing the blister card) is opened, to the patients. We recommend the following (or similar to) to be included in section 17:

Reference ID: 3291885

"17.1 Instructions for Patients

- Keep Duavee in the original container to protect from moisture. Do not place Duavee in pill boxes or pill organizers
- [redacted] (b) (4)
- If more than one blister package is dispensed to the patient, instruct them to open one foil pouch at a time
- [redacted] (b) (4)
- [redacted] (b) (4)

5. Under How should I take Duavee?, in Patient Labeling, include the following or similar to (note the use of bold font):

   - **Duavee comes in a** [redacted] (b) (4) **blister package.**

[redacted] (b) (4)

   - **Record the date you open the foil pouch in the space provided on the blister package label.**

[redacted] (b) (4)

6. Under How do I store Duavee?, in Patient Labeling, include the following statement to [redacted] (b) (4) the blister storage information: "Do not place [redacted] (b) (4) in pill boxes or pill organizers." [redacted] (b) (4)

Reference ID: 3291885

4.2 COMMENTS TO THE APPLICANT

A. General Comments

1. Delete or relocate the highlighted Pfizer logo that appears above or next to the proprietary name to the bottom of the label or the side panel (if applicable).
2. Revise the presentation of the established name by replacing the symbol '/' with the word 'and'. The revised presentation appears as: "Bazedoxifene and Conjugated Estrogens".
3. Unbold the dosage form 'tablets' so that it appears in the same font as the established name.
4. Unbold the 'Rx only' statement.
5. Ensure the dosage form presentation in the quantity statements (i.e., 7 tablets, 15 tablets, and 30 tablets) are consistent. Specifically, the dosage form is presented with a lower case 't' (i.e., tablets) on the blister pack labels (b) (4) Choose one presentation for all container labels and carton labeling.

(b) (4)

Reference ID: 3291885

(b) (4)

C. Blister card labels (30-count trade and 7-count professional sample)

1. Include the statement (b) (4) Consequently, delete the statement (b) (4) Additionally, deleting this statement will provide more space for improvements in the presentation of the important storage information.

2. Relocate the equivalency statement "Each tablet contains bazedoxifene equivalent to 22.6 mg of bazedoxifene acetate" to immediately below the storage information to help unclutter the top portion of the blister label. (b) (4)

3. (b) (4) The pharmacy staff would see the carton labeling or the foil pouch labeling, and with proper warning statements on those labels, the pharmacy staff should be alerted not to open the foil pouch due to the 60 day expiration date of the product.

4. Relocate the storage statement "After opening foil pouch, product must be used within 60 days." to appear below the dosage form (i.e., Tablets). Additionally increase the prominence of this statement by using bold font.

5. Include the statement "Date foil pouch opened:" to appear below "After opening foil pouch, product must be used within 60 days." after revisions in #3 above.

6. Revise the statements (b) (4) to read in bold font "Store product in original package to keep from moisture. Tablets should not be removed from blisters until immediately before administration. Do not place medication in pill boxes." See the example below after revisions in #2 through #5 above (please note the use of bold font).

Reference ID: 3291885

"**After opening foil pouch, product must be used within 60 days.**
Date foil pouch opened:

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to
15°C to 30°C (59°F to 86°F)[see USP Controlled Room Temperature]
Dosage and Use: See accompanying prescribing information."
Store product in original package to keep from moisture. Tablets should not be removed from blisters until immediately before administration. Do not place medication in pill boxes."

7. Ensure the lot number and the expiration date appears on all the blister card labels. As currently presented, a place holder does not appear on the labels.

D. Foil Pouch containg the Blister cards 30-count trade and 7-count professional sample)

1. Relocate the dosage form 'Tablets' so that it appears immediately below the established name.
2. Relocate the storage statement "After opening foil pouch, product must be used within 60 days." to appear below the product strength. Additionally increase the prominence of this statement by using bold font.
3. Revise the statement [redacted] (b) (4) to read "Dispense and store product in original package to protect from moisture." Additionally, relocate this statement to the principal display panel to appear below "After opening foil pouch, product must be used within 60 days."

   For example (note the use of bold font):

   Duavee
   (Bazedoxifene and Conjugated Estrogens)
   Tablets
   20 mg/0.45 mg

   After opening foil pouch, product must be used within 60 days.
   Dispense and store product in original package to protect from moisture.

   30 Tablets

4. Revise the statements [redacted] (b) (4) to read "Tablets should not be removed from blisters until immediately before administration. Do not place medication in pill boxes." Additionally, increase the prominence of these statements by using bold font. The statement [redacted] (b) (4) may be deleted after revisions in #3 above.

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5. Revise the equivalency statement and the ingredient statement [redacted] (b) (4)

6. Ensure the lot number and the expiration date appears on the foil pouch labeling. As currently presented, a place holder does not appear on the labeling.

E. Blister Carton Labeling (30-count trade and 7-count professional sample)

1. Relocate the storage statement "After opening foil pouch, product must be used within 60 days." to appear below the dosage form. Additionally increase the prominence of this statement by using bold font.

7. Revise the statement [redacted] (b) (4) to read "Dispense and store product in original package to protect from moisture." Additionally, relocate this statement to the principal display panel to appear below "After opening foil pouch, product must be used within 60 days."

   For example (note the use of bold font):

   Duavee
   (Bazedoxifene and Conjugated Estrogens)
   Tablets

   After opening foil pouch, product must be used within 60 days.
   Dispense and store product in original package to protect from moisture.

   30 Tablets

2. Revise the equivalency statement and the ingredient statement [redacted] (b) (4)

3. 30-count trade only: reduce the prominence of the quantity statement (i.e., 30 Tablets) by reducing the font size so that it does not compete with the strength statement.

4. Revise the statement 'Package includes 2 blister cards containing 15 tablets each.' to state: [redacted] (b) (4)

5. Ensure the lot number and the expiration date appears on the 7-count professional sample carton labeling. As currently presented, a place holder does not appear on the labeling.

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(b) (4)

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

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

Reference ID: 3291885

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
04/11/2013

CAROL A HOLQUIST
04/11/2013

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirements of Prescribing Information (SRPI) version 2 is 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.

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 is 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:

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).

Comment:

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

Reference ID: 3227122

Selected Requirements of Prescribing Information (SRPI)

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.

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:

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

NO

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

    Comment: *Currently none of the text in the box is 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**").

    Comment:

YES 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." 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

N/A 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 class) indicated for (indication)]."

    Comment:

Dosage Forms and Strengths

YES

Reference ID: 3227122

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:

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

NO 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment: *The current revision date is listed as 05/2012 and should be revised to "MM/YYYY"*

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

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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:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

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

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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

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:

YES 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:

YES 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

NO 42. All text is **bolded**.

Comment: *Only the heading is bolded.*

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

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YES 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

NO 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: *"Clinical" needs to be added prior to practice in the current statement*

NO 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: *Modification of statement is included*

Patient Counseling Information

NO 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: *Need to add "See FDA-approved patient labeling (Patient Information)"*

Reference ID: 3227122

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

/s/

SAMANTHA S BELL
12/06/2012

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 # 022247 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) (proposed) Established/Proper Name: bazedoxifene acetate/conjugated estrogens (BZA/CE) Dosage Form: tablet Strengths: BZA 20 mg/CE 0.45 mg; BZA 20 mg/CE 0.625 mg		
Applicant: Wyeth Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer, Inc. Agent for Applicant (if applicable):		
Date of Application: September 26, 2012 Date of Receipt: September 26, 2012 Date clock started after UN: October 3, 2012		
PDUFA Goal Date: October 3, 2013	Action Goal Date (if different):	
Filing Date: December 2, 2012	Date of Filing Meeting: November 20, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1, 4		
Proposed indication(s)/Proposed change(s): Treatment of vasomotor symptoms (VMS) in postmenopausal women Treatment of vulvar and vaginal atrophy (VVA) in postmenopausal women Prevention of postmenopausal osteoporosis.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***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.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

Reference ID: 3223325

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ 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): (b) (4) IND 062288, (b) (4)	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***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.***	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)? ***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*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		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			

Reference ID: 3223325

User Fee Status	Payment for this application:
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.	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				
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)].**				
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)]?** ***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***				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

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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)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
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)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

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

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

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☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **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**		
• If yes, were all of them submitted on time?				
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				
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.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
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			

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Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)]. ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***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].*** ***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…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***				

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:			**X**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**

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PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***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.*	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? ***If no, request in 74-day letter***	X			
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)? ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels			

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

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	☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	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? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***				
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	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				

[4] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

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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) ***If yes, specify consult(s) and date(s) sent:***		X		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** July 25, 2001; August 22, 2001 ***If yes, distribute minutes before filing meeting***	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** July 18, 2007 February 18, 2010; July 12, 2011 (CMC) ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** Submitted November 22, 2004; August 29, 2008 ***If yes, distribute letter and/or relevant minutes before filing meeting***	X			

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ATTACHMENT

MEMO OF FILING MEETING

DATE: November 20, 2012

BLA/NDA/Supp #:

PROPRIETARY NAME: (b) (4) (proposed)

ESTABLISHED/PROPER NAME: bazedoxifene acetate/conjugated estrogens (BZA/CE)

DOSAGE FORM/STRENGTH: BZA 20 mg/CE 0.45 mg; BZA 20 mg/CE 0.625 mg

APPLICANT: Wyeth Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):
Treatment of vasomotor symptoms (VMS) in postmenopausal women
Treatment of vulvar and vaginal atrophy (VVA) in postmenopausal women
Prevention of postmenopausal osteoporosis.

BACKGROUND:
Bazedoxifene/conjugated estrogens is a new molecular entity that combines a selective estrogen receptor modulator (SERM) with conjugated estrogens (Premarin®). (b) (4) The sponsor has submitted five Phase 3 clinical trials in this application as clinical efficacy and safety data to support BZA/CE for the indications listed above.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Samantha Bell	Y
	CPMS/TL:	Margaret Kober	Y
Cross-Discipline Team Leader (CDTL)	Theresa Kehoe		
Clinical	Reviewer:	Marcea Whitaker Gerald Willett	Y Y
	TL:	Theresa Kehoe	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		

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OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

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Clinical Pharmacology	Reviewer:	Sayed Al Habet	Y
	TL:	Myong-Jin Kim	Y
Biostatistics	Reviewer:	Sonia Castillo Kate Dwyer	Y Y
	TL:	Mahboob Sobhan	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Leslie McKinney	Y
	TL:	Alexander Jordan	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Donna Christner	Y
	TL:	Terrance Ocheltree	Y
Quality Microbiology *(for sterile products)*	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:		

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Bioresearch Monitoring (OSI)	Reviewer:	Roy Blay	Y
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety***	☒ YES Date if known: July 8 or 9, 2013 ☐ NO ☐ To be determined Reason:

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or efficacy issues ○ ***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***	
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• 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? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

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IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

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CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Julie Beitz **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): 3-6-13 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

	ACTIONS ITEMS
☒	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).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	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.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day

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	filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for NME NDAs in "the Program")
☐	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]
☐	Other

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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

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

/s/

SAMANTHA S BELL
11/29/2012

MARGARET M KOBER
11/29/2012