CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022247Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

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

Date: **18-Sep-2013**

From: **Donna Christner, Ph.D.** **and** **Hamid Shafiei, Ph.D.**
CMC Lead **Chemist**
DNDQA II/ONDQA **DNDQA II/ONDQA**

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

To: **CMC Review #1 of NDA 22247**

Subject: **Carton/Container Labeling**

The applicant modified the carton/container labeling in response to comments from DMEPA. There were no outstanding CMC issues concerning the carton/container labels. For completeness of the regulatory record, the trade presentations are reproduced below.

From a CMC standpoint, the application is recommended for APPROVAL.

5 Page(s) of draft labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 3376320

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/s/

DONNA F CHRISTNER
09/19/2013

HAMID R SHAFIEI
09/19/2013

MOO JHONG RHEE
09/19/2013
Chief, Branch IV

ONDQA Division Director's Memo
NDA 22-247, DUAVEE (conjugated estrogens and bazedoxifene) tablets
Date: 27-AUG-2013

Introduction

The DUAVEE Tablet is a film-coated tablet available in two strengths (0.45 mg/20 mg and 0.625 mg/20 mg conjugated estrogens/bazedoxifene). All excipients are commonly used in solid oral dosage forms. The tablet is designed to be taken once daily, without regards to meals.

All CMC-related deficiencies have been resolved for this application, and all related reviews are complete. There are no outstanding review deficiencies that would preclude a recommendation of approval from a CMC standpoint. An overall acceptable recommendation from the Office of Compliance was issued on 14-AUG-2013.

All CMC review issues have been resolved, and ONDQA recommends approval of this NDA.

Administrative

The original submission of this 505(b)(1) NDA was received on 26-SEP-2012 from Wyeth Pharmaceutical, Inc. Ten (10) CMC amendments were also reviewed during the review cycle. The comprehensive CMC assessment is captured in the following reviews, respectively: Chemistry Review #1 (04-JUN-2013, Dr. D. Christner and Dr. H. Shafiei), Addendum to Chemistry Review #1 (27-AUG-2013, Dr. D. Christner and Dr. H. Shafiei) and the Biopharmaceutics Review (05-AUG-2013, Dr. J. Duan).

The NDA is supported by NDA 4-782, IND (b) (4) 62288, (b) (4) and twelve (12) drug master files (DMFs). All DMFs were assessed for adequacy in the chemistry review.

Summary and Recommendation

Chemistry Review #1 (04-JUN-2013, Dr. D. Christner and Dr. H. Shafiei) includes a recommendation of a Complete Response based on several unresolved Chemistry, Manufacturing and Controls deficiencies. The Biopharmaceutics Review (05-AUG-2013, Dr. J. Duan) confirms non-agreement with the Applicant's proposed in vitro in vivo correlation (IVIVC); related comments were issued to the Applicant in late cycle communications, and there are no additional actions required to resolve these issues. The Addendum to Chemistry Review #1 (27-AUG-2013, Dr. D. Christner and Dr. H. Shafiei) confirms that the previously-identified deficiencies have all been resolved, and the review team makes a recommendation of approval for the NDA.

The 04-JUN-2013 Chemistry Review captures discussion and consideration of the approved USAN name (bazedoxifene acetate) relative to the free base as utilized in the established name and strength. I discussed this issue further with ONDQA's USAN Liaison (b) (4), 14-AUG-2013) as well as the Labeling and Nomenclature chair (Dr. R. Lostritto, 19-AUG-2013). Both parties agreed with the approach captured in the Chemistry Review, and all agreed that no further action was necessary with regard to the currently approved USAN name.

I concur that there are no outstanding CMC deficiencies for this NDA, and I concur with the team's recommendation of approval for this application.

As per the 27-AUG-2013 Addendum to Chemistry Review #1, the following expiration dating periods can be granted:

- ***36 months for the 0.45 mg/20 mg CE/BZA strength***

(b) (4)

Also, as per the Addendum, the (b) (4) ***blister configuration must be used within 60 days after opening the pouch.***

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/s/

SARAH P MIKSINSKI
08/28/2013

Memorandum

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

Date: **26-Aug-2013**

From: **Donna Christner, Ph.D.** **and** **Hamid Shafiei, Ph.D.**
CMC Lead **Chemist**
DNDQA II/ONDQA **DNDQA II/ONDQA**

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

To: **CMC Review #1 of NDA 22247**

Subject: **Final Recommendation**

CMC Review #1 dated 05-Jun-2013 noted the following issues that precluded an approval recommendation from the ONDQA perspective:

21 CFR 314.125(b)(1)

- A test and acceptance criterion for (b) (4) BZA in the drug product need to be included because adequate information has not been provided to ensure that the manufacturing process and other tests can (b) (4) (b) (4) impact the safety and efficacy of the drug product. The applicant agreed to set a specification, which would be submitted on 04-Jun-2013. Until the proposed specification is submitted, reviewed and found acceptable, this remains an outstanding issue.
- The applicant needs to address the (b) (4) phenomenon discovered during the drug product manufacturing site inspection and the Method Validation performed at the St. Louis laboratory. Until this issue is adequately resolved, an appropriate expiration dating period cannot be granted.

21 CFR 314.125(b)(13)

- The facilities involved in this application have not been confirmed in their compliance with cGMP.

21 CFR 314.125(b)(6)

- Label and labeling have not been finalized as of this review

21 CFR 25.15(a)

- Environmental Assessment has not been satisfactorily prepared.

Reference ID: 3363664

The issues have been resolved as follows:

21 CFR 314.125(b)(1)

1. *The applicant has set an appropriate specification and acceptance criteria* (b) (4) *in the drug product specification in the Amendment dated 04-Jun-2013. The method and validation have been reviewed and are adequate. See* ***Review Notes****.*

2. *The applicant has provided sufficient information in the Amendment dated 01-Aug-2013 to address the* (b) (4) *phenomenon, and has included adequate controls to assure product quality. See* ***Review Notes****.*

21 CFR 314.125(b)(13)

On 14-Aug-2013, the Office of Compliance made a final ACCEPTABLE recommendation for all manufacturing sites. See ***Attachment 1***

21 CFR 25.15(a)

As per the review dated 26-Aug-2013, the EA is acceptable.

21 CFR 314.125(b)(6)

The updated Physician's Insert was submitted on 16-Aug-2013. The CMC-related portions are acceptable. There were no CMC-related comments conveyed on the carton/container labels.

Clarification:

The Executive Summary of Review # 1 states the following:

The applicant has provided adequate justification for deletion of the following tests in the commercial stability studies (b) (4)
(b) (4)

(b) (4)

Reference ID: 3363664

Final Recommendation:

NDA 22247 is recommended for **APPROVAL** from the ONDQA perspective. The following expiration dating periods can be granted:

- *36 months for the 0.45 mg/20 mg CE/BZA strength* (b) (4)

The (b) (4) *blister configuration must be used within 60 days after opening the pouch.*

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/s/

DONNA F CHRISTNER
08/27/2013

HAMID R SHAFIEI
08/27/2013

MOO JHONG RHEE
08/27/2013
Chief, Branch IV

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date August 13, 2013

From Vipul Dholakia, Ph.D.
Compliance Officer
New Drug Manufacturing Assessment Branch
Division of Good Manufacturing Practice Assessment,
Office of Manufacturing and Product Quality

Subject Non Concurrence with Division of International Drug Quality's Withhold Recommendation for NDA 022-247 Bazedoxine Acetate/Conjugated Estrogen (b) (4) Tablets 20 mg/0.625 mg and 20 mg/0.45 mg

Thru Don Henry, Acting Branch Chief
New Drug Manufacturing Assessment Branch (NDMAB)
Division of Good Manufacturing Practice Assessment (DGMPA)

To Moo Jhong Rhee, Branch Chief, Branch IV, ONDQA Division II

Applicant: Wyeth Pharmaceutical, Inc.
235 East 42nd Street
New York, NY 10017

Establishment: Pfizer Ireland Pharmaceuticals.
Little Connell
Newbridge, County Kildare, Ireland
FEI: 3006785053

The Division of Good Manufacturing Practice Assessment (DGMPA) has completed a review of an establishment inspection report (EIR) covering a pre-approval inspection (PAI) of NDA 22-247, Bazedoxifene/Conjugated Estrogen (BZA/CE) (b) (4) Tablets 20 mg/0.45 mg and 20 mg/0.625 mg and GMP inspection conducted by Investigators Charisse K. Green and Microbiologist, Xiaokuang Lai from February 4, 2013 to February 8, 2013 at the Pfizer Ireland Pharmaceuticals facility. The PAI coverage included the NDA 22247 and the profile class (b) (4). During the GMP inspection, there were no significant GMP issues observed and Form -483 was not issued. (b) (4) (b) (4) (b) (4) DGMPA has reviewed the firm's July 31, 2013 written response to the product specific issue described in the EIR for (b) (4) of BZA/CE tablets and the (b) (4) issue discussed at the late cycle meeting held on June 26, 2013 with the agency.

The Division of Good Manufacturing Practice Assessment (DGMPA) does not concur with Division of International Drug Quality's (DIDQ) recommendation to withhold approval of NDA 22247 based on the product specific observation for Bazedoxifene/Conjugated Estrogens Tablets (b) (4) (b) (4)

A recommendation by DIDQ to withhold application of NDA 22247 Bazedoxifene Acetate/Conjugated Estrogen (b) (4) Tablets was based on the following GMP issues observed during the inspection:

1. (b) (4) (b) (4)

(b) (4)

The firm response has been found adequate and acceptable.

2. (b) (4)

(b) (4)

The firm response has been found adequate and acceptable.

3. The firm did not have data to support (b) (4) expiration date of BZA/CE 20 mg/0.45 mg tablets (b) (4)

During the PAI, it was observed that the stability data obtained for BZA/CE 20 mg/0.45 mg batches with (b) (4) months shelf life were within specifications; however these batches were manufactured (b) (4) The firm did not have stability data to support (b) (4) expiration date of BZA/CE 20 mg/045 mg tablets (b) (4)

In order to address this issue, the firm provided release and 3 month stability data on the planned confirmatory batches G85262 and G86484 (BZA/CE 20 mg/0.45 mg) manufactured with (b) (4) specifications. The release testing and 3 month stability data met the acceptance criteria (b) (4) for both BZA and CE dissolution (b) (4) The firm also committed to testing the stability of the product throughout its (b) (4) shelf life, and will provide 6 month stability data to the agency when available.

The firm response has been found adequate and acceptable.

CDER/OC/OMPQ/DGMPA Recommendation:

OMPQ/NDMAB does not concur with DIDQ's recommendation to withhold approval of NDA 022-247 Bazedoxine Acetate/Conjugated Estrogen (b) (4) Tablets 20 mg/0.625 mg and 20 mg/0.45 mg.

The corrections described in the firm's response should be further evaluated during next inspection of this facility. It remains the firm's responsibility to assure continued compliance with current good manufacturing practices

If you have any questions, please contact me at (301) 796-5065 or by email at Vipul.dholakia@fda.hhs.gov.

Vipul Dholakia, Ph.D.

cc:

DIDQ, Elizabeth Philpy (PAM),
NDMAB Acting Team Leader, Mahesh Ramanadham
CMS case #68920

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/s/

VIPULCHANDRA N DHOLAKIA
08/14/2013

DON L HENRY
08/14/2013

NDA 22247

DUAVEE
(conjugated estrogens and bazedoxifene) tablets
0.45 mg/20 mg and 0.625 mg/20 mg

Wyeth Pharmaceutical, Inc.
A wholly owned subsidiary of Pfizer, Inc.

Donna F. Christner, Ph.D.
Hamid R. Shafiei, Ph.D.

Review Chemist

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

CMC REVIEW
For the Division of Bone, Reproductive and Urologic Products

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CMC Review Data Sheet

1. NDA 22247

2. REVIEW #: 1

3. REVIEW DATE: 04-Jun-2013

4. REVIEWER(S): Donna F. Christner, Ph.D.
Hamid Shafiei, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission (SDN 1)	26-Sep-2012
Correspondence (SDN 4)	(03-Oct-2012 PDUFA fee)
Amendment Manufacturing site information (SDN 5)	19-Oct-2012
Amendment Manufacturing site information (SDN 7)	31-Oct-2012
Amendment Response to 74-day letter (SDN 16)	18-Jan-2013
Amendment updated trade name and labeling (SDN 22)	22-Mar-2013
Amendment Response to 18-Mar-2013 IR (SDN23)	05-Apr-2013
Amendment Response to 22-Mar-2013 teleconference (SDN 24)	05-Apr-2013
Amendment Response to Dissolution (SDN 27)	12-Apr-2013
Amendment Response for Alcohol Dose Dumping (SDN 28)	15-Apr-2013
Amendment Response to EA (SDN 30)	29-Apr-2013
Amendment Response to 09-May-2013 teleconference (SDN 038)	17-May-2013

7. NAME & ADDRESS OF APPLICANT:

Name: Wyeth Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer, Inc.
Address: 235 East 42nd Street
New York, NY 10017
Representative: Birming P. Wong
Director
Worldwide Safety and Regulatory
Telephone: 212-733-5177

Reference ID: 3319282

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: DUAVEE
   b) Non-Proprietary Name (USAN): bazedoxifene acetate and conjugated estrogens Code Name/#: PF-05212370
   c) Chem. Type/Submission Priority (ONDQA only):
   - Chem. Type: Type 1 and Type 4 (NME and New Combination)
   - Submission Priority: Standard (12 month, PDUFA V)

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

10. PHARMACOL. CATEGORY: Conjugated Estrogens, and Bazedoxifene acetate is an Estrogen agonist /antagonist

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 20 mg BZA/0.45 mg CE
    20 mg BZA/0.625 mg CE

13. ROUTE OF ADMINISTRATION: Oral

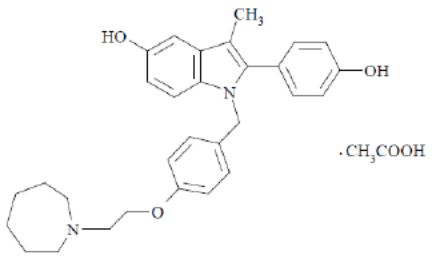
14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    ___X___SPOTS product – Form Completed (submitted 03-Jan-13)

    _____Not a SPOTS product

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

Bazedoxifene Acetate:

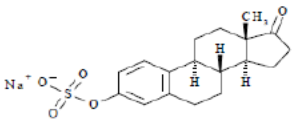


Empirical (molecular) formula: $C_{32}H_{38}N_2O_5$ or $C_{30}H_{34}N_2O_3 \cdot C_2H_4O_2$
Molecular weight (or Relative Molecular Mass): 530.65 (salt), 470.60 (free base)

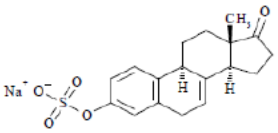
Reference ID: 3319282

Conjugated Estrogens:

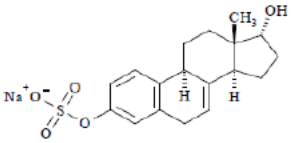
Figure 1-1: Chemical Structures of Conjugated Estrogens Components



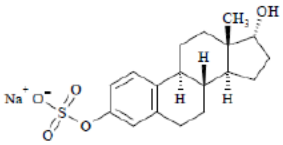
Estrone sodium sulfate



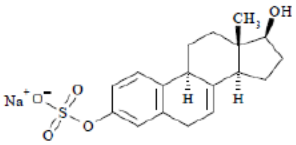
Equilin sodium sulfate



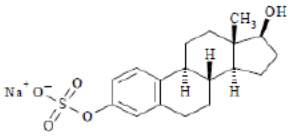
17α-dihydroequilin sodium sulfate



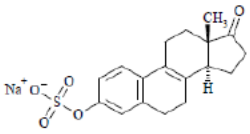
17α-estradiol sodium sulfate



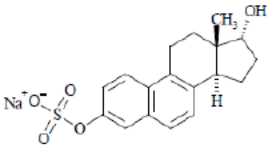
17β-dihydroequilin sodium sulfate



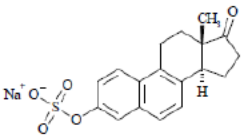
17β-estradiol sodium sulfate



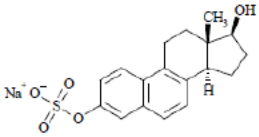
$\Delta^{8,9}$-dehydroestrone sodium sulfate



17α-dihydroequilenin sodium sulfate



Equilenin sodium sulfate



17β-dihydroequilenin sodium sulfate

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	ADEQUATE	22-Feb-2007 17-May-2013	Sheldon Markofsky, Ph.D. Hamid Shafiei, Ph.D.
	IV			1	ADEQUATE	29-Oct-2012	Donna Christner, Ph.D.
				1	ADEQUATE	29-Oct-2012	Donna Christner, Ph.D.
				1	ADEQUATE	26-Dec-2012	Donna Christner, Ph.D.
				1	ADEQUATE	29-Oct-2012	Donna Christner, Ph.D.
	III			3	ADEQUATE	24-Oct-2012	D. Klein, Ph.D. for NDA 21-402
	III			3	ADEQUATE	24-Mar-2010	R. Agarwal, Ph.D., Ph.D. for NDA 22-511
	III			3	ADEQUATE	29-Apr-2002	R. Frankewich, Ph.D. for NDA 21-156
	IV			3	ADEQUATE	24-Oct-2012	D. Klein, Ph.D. for NDA 21-402
	III			3	ADEQUATE	30-May-2003	L. Rocca, Ph.D. for NDA 21-323
	III			3	ADEQUATE	07-Mar-2008	B. Kurtyka, Ph.D. for NDA 22-262
				1	ADEQUATE	02-Jan-2013	Donna Christner, Ph.D.
	III			3	ADEQUATE	07-Jul-2010	C. Strasinger Ph.D. for (b) (4)
	III			1	ADEQUATE	02-Jan-2013	Donna Christner, Ph.D.
	III			1	ADEQUATE	31-Dec-2012	Donna Christner, Ph.D.
	III			3	ADEQUATE	13-Jul-1999	Thomas Oliver, Ph.D. for NDA 21-305

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	(b) (4) 62288 (b) (4)	(b) (4) BZA/CE combination therapy
NDA	04-782	Conjugated Estrogens

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	03-Jun-2013	
EES	Pending	03-Jun-2013	
Pharm/Tox	Impurities qualified	20-Mar-2013	Leslie McKinney, Ph.D.
Biopharm	Approval	29-May-2013	Kareen Riviere, Ph.D. John Duan, Ph.D.
LNC	See Attachment 1	03-Jun-2013	
Methods Validation	Pending	03-Jun-2013	
DMEPA	Pending	03-Jun-2013	
EA	Pending	03-Jun-2013	R. Bloom, Ph.D.
Microbiology	N/A	03-Jun-2013	

Reference ID: 3319282

The CMC Review for NDA 22247

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has ***not*** provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product

The Office of Compliance has ***not*** made the final recommendation for the facilities involved in this application.

Environmental Assessment has ***not*** been adequately prepared.

Label/labeling issues are ***not*** finalized as of this review.

Therefore, from the ONDQA perspective, this NDA is ***not*** recommended for approval per 21 CFR 314.125(b)(1) (6), and (13), and 21 CFR 25.15(a) in its present form until these issues are satisfactorily resolved.

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

None at this time.

II. Summary of CMC Assessments

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

(1) Drug Substances

Bazedoxifene

Bazedoxifene acetate is reported to be a tissue selective estrogen receptor modulator by the applicant. However, it is classified as an Estrogen agonist /antagonist by the FDA. It is a white to tan powder. (b) (4)

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[redacted] (b) (4)

The synthetic process for bazedoxifene acetate and description of commercial manufacturing processes for bazedoxifene acetate is provided in DMF [redacted] (b) (4) This DMF has been reviewed and has been found to be adequate to support this NDA.

Bazedoxifene acetate drug substances release specification includes: Description, Identification, Assay, Related Impurities, Residual Solvents, Water Content, [redacted] (b) (4) Content, Residue on Ignition, [redacted] (b) (4) Content, Heavy Metals, Particle Size by laser diffraction, and Polymorphic Purity. The proposed acceptance criteria in specification for bazedoxifene acetate are consistent with the current impurity limits recommended in ICH Q3A, Q3C, and Q3D. The proposed stability specification for bazedoxifene acetate is a subset of the release specification but only includes the testing and acceptance criteria that are considered relevant for the determination of the drug substance shelf-life. The stability specification includes Description, Identification, Strength (assay), Purity, Water Content, [redacted] (b) (4) Content, and Polymorphic Purity. The proposed specifications for release and stability testing of bazedoxifene acetate are considered satisfactory.

The proposed container closure system for storage of the commercial batches bazedoxifene acetate is [redacted] (b) (4). Full information is provided in DMF [redacted] (b) (4) and is acceptable. Furthermore, the use of the proposed container closure system is supported by the stability data provided in this application.

The applicant has proposed a retest period of [redacted] (b) (4) **months for bazedoxifene acetate drug substance when stored at** [redacted] (b) (4) based on the results of 36-month long-term stability at [redacted] (b) (4) 36-month accelerated stability at 25ºC/60% RH, and 6-month accelerated stability at 40ºC/75% RH from three primary stability batches of this drug substance, as well as additional supporting long-term and accelerated stability results from other developmental batches of this drug substance showing no significant changes in the drug substance strength and purity, no significant increase in drug substance degradation products, and no polymorphic form conversion or changes in polymorphic purity. **The proposed retest period is granted.**

Based on the review of the drug substance information provided in DMF [redacted] (b) (4) and in this NDA application, it is concluded that bazedoxifene acetate drug substance manufactured [redacted] (b) (4) is acceptable for use in the manufacture of the drug product, bazedoxifene acetate/conjugated estrogen tablets.

Conjugated Estrogens

Conjugated estrogens is a mixture of sodium salts of water-soluble sodium estrone and equilin sulfates and other estrogenic substance, extracted from pregnant mares' urine. Full information is cross-referenced to approved NDA 04-782.

[redacted] (b) (4) The drug substance is currently approved with a retest period of [redacted] (b) (4) months.

(2) Drug Product

The drug product is an oval, biconvex, [redacted] (b) (4) tablet [redacted] (b) (4). The Bazedoxifene (BZA) 20 mg/Conjugated Estrogens (CE) 0.45 mg tablets are pink with black branding on one side. [redacted] (b) (4)

The tablets consist of the currently approved commercial 0.45 mg [redacted] (b) (4) Premarin tablet [redacted] (b) (4)

Tablets are available for prescribing in [redacted] (b) (4) a blister package consisting of two blisters of 15 tablets each which are packaged in an aluminum pouch. The container closure systems are packaged [redacted] (b) (4) The drug product is labeled with instructions to keep the tablets in the container closure system and to use within [redacted] (b) (4) 60 days (for blisters) after opening.

The quality of the tablets is controlled by adherence to the following specification: Appearance, Identification A and B for CE, Identification by HPLC and UV for BZA, Total CE, CE Potency, Ratio [redacted] (b) (4), BZA Strength, Uniformity of Dosage Units for CE and BZA, BZA Degradation Products, Dissolution for CE and BZA [redacted] (b) (4)

The applicant has provided adequate justification for deletion of the following tests in the commercial stability studies [redacted] (b) (4)

The applicant requested [redacted] (b) (4) in the drug product specification. This is not acceptable and the applicant has agreed to set a specification to be submitted on 04-Jun-2013. Until the proposed test and acceptance criterion are

submitted, reviewed and found acceptable, this remains an outstanding issue. See Sections P.2.2.1, P.2.3 and P.5.6 for more complete discussion of this issue.

An expiration dating period cannot be set at this time. While the submitted stability data would support the requested expiration dating period, the to-be-marketed drug product uses [redacted] (b) (4) The clinical trial supplies and majority of the primary stability batches were manufactured [redacted] (b) (4) This product quality issue makes it difficult to know how much of the stability data can be used to set an appropriate expiration dating period. The applicant will need to address this issue in the NDA. See Section P.3.1 and **Attachment 6**.

[redacted] (b) (4)

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

The tablet is designed to be taken once daily, without regards to meals. Tablets should be swallowed whole. The recommendation is that the drug product be used at the lowest effective dose for duration consistent with the treatment goals. The applicant seeks the following indications:

- Treatment of Moderate to Severe Vasomotor Symptoms associated with Menopause
- Treatment of Moderate to Severe Vulvar and Vaginal Atrophy associated with Menopause
- Prevention of osteoporosis

C. Basis for Approvability or Not-Approval Recommendation

The NDA is ***not*** recommended for approval from the CMC perspective at this time for the following reasons:

21 <u>CFR 314.125(b)(1)</u>

- A test and acceptance criterion for [redacted] (b) (4) BZA in the drug product need to be included because adequate information has not been provided to ensure that the manufacturing process and other tests can [redacted] (b) (4) impact the safety and efficacy of the drug product. The applicant agreed to set a specification, which would be submitted on 04-Jun-2013. Until the proposed

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specification is submitted, reviewed and found acceptable, this remains an outstanding issue.

- The applicant needs to address the (b) (4) phenomenon discovered during the drug product manufacturing site inspection and the Method Validation performed at the St. Louis laboratory. Until this issue is adequately resolved, an appropriate expiration dating period cannot be granted.

21 CFR 314.125(b)(13)

- The facilities involved in this application have not been confirmed in their compliance with cGMP.

21 CFR 314.125(b)(6)

- Label and labeling have not been finalized as of this review

21 CFR 25.15(a)

- Environmental Assessment has not been satisfactorily prepared.

(See the **List of Outstanding Deficiencies** on p. 178)

III. Administrative

A. Reviewers' Signature:

(See appended electronic signature page)

Donna F. Christner, Ph.D.

Hamid R. Shafiei, Ph.D.

B. Endorsement Block:

(See appended electronic signature page)

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

C. CC Block: entered electronically in DFS

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/s/

DONNA F CHRISTNER
06/04/2013

HAMID R SHAFIEI
06/04/2013

MOO JHONG RHEE
06/05/2013
Chief, Branch IV

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

OND Division:	Division of Reproductive and Urologic Products
NDA:	22247
Applicant:	Wyeth
Stamp Date:	03-Oct-2012
PDUFA Date:	02-Oct-2013 (12 month clock for PDUFA V)
Trademark:	TBD
Established Name:	Bazedoxifene and conjugated estrogens
Dosage Form:	Tablet
Route of Administration:	Oral
Indication:	Treatment of moderate to severe vasomoter symptoms due to menopause Treatment of moderate to severe vulvar and vaginal atrophy Prevention of postmenopausal osteoporosis
CMC Lead:	Donna F. Christner, Ph.D.

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

Summary and Critical Issues:

A. Summary

The NDA is for a combination tablet containing Bazedoxifene, a New Molecular Entity, and Conjugated Estrogens. The application was officially submitted on 03-Oct-2012 and therefore is under PDUFA V. As an NME, it is part of "The Program", and will have a 12 month clock with additional regulatory milestones.

The drug product is an oval, biconvex, (b) (4) tablet containing Bazedoxifene (BZA) as the acetate salt and Conjugated Estrogens (CE). Two doses are available, with 20 mg of the BZA, dosed as the base, and two different CE doses. The BZA/CE (20mg/0.45 mg) tablet is pink with black branding on one side (b) (4)

The drug product is a combination product (b) (4) Drug product is packaged in (b) (4) blisters. (b) (4) The blister is then placed in an aluminum foil laminate pouch. (b) (4)

The applicant has requested (b) (4) months of expiration dating period for the BZA/CE (20mg/0.45 mg) tablet (b) (4) based on the submitted real time data.

B. Critical issues for review

It will need to be discussed within ONDQA management whether cross-reference to the approved NDA04-782 is sufficient for information on the CE API (b) (4) *It is a review decision* (b) (4)

Drug Substances

1. *For bazedoxifene, the DMF was originally reviewed in 2007 and found ADEQUATE, but there have been updates since that time and the DMF will require additional review. Tests and acceptance criteria provided in the NDA appear to be in line with typical limits for APIs. The applicant has provided methods, validation, and justification of specification; all will require review. Hamid Shafiei, Ph.D. has been assigned to review the bazedoxifene drug substance.*

2. *Bazedoxifene acetate is the approved USAN name, however, there is a new USP policy (official after May 2013) which states that drugs should be named according to the active moiety (free base) and not the salt form. Therefore, since the USP policy becomes official during the review cycle, this issue will be consulted to the Labeling and Nomenclature Committee chaired by Rik Lostritto, Ph.D.*

3. *All information on the conjugated estrogens is cross-referenced to the approved NDA 04-782.* (b) (4) *As outlined above, it will be a review decision* (b) (4)

4. *Given the long regulatory history of this drug substance, it would be valuable to have current CMC information on the CE API provided to this NDA.*

Drug Product

1. *Concerning the manufacturing process for the dosage form, the applicant has provided a flow chart, narrative, process control ranges and executed and master batch records. Taken together, they may provide enough information to fulfill the requirements for review. However, from a cursory review of the provided information, it does not appear that detailed ranges are provided. Once a more thorough review is performed of this section of the application, an IR request may be sent to the applicant.*

2. *The specification appears standard for the dosage form. The following items should be noted:*

   - (b) (4)

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(b) (4)

- *The applicant states* (b) (4) *An ONDQA BioPharm team consisting of Kareen Riviere, Ph.D. and John Duan, Ph.D. has been assigned to evaluate the dissolution parameters of the tablet.*
- *During development of the dosage form, it was reported (as outlined in the Drug Substance section of this review)* (b) (4) *It is a review issue on whether a specific test is needed at this time.*
- (b) (4) *It may be necessary to include microbial limits testing during stability. A consult may be sent to OPS Microbiology.*

3. *The applicant has provided the following information on Method validation for the drug substances and drug product:*

    - *For CE, the applicant states that the conjugated estrogens is the same as that used in the manufacture of Premarin tablets as outlined in NDA 04-782. The applicant requests a waiver for submission of further drug substance validation since it is already included in the cross-referenced NDA.*
    - *For BZA, the applicant states that bazedoxifene acetate samples and samples of both dosage strengths are available upon request.*

    The Methods validation request will be sent to the St. Louis laboratories to evaluate the BZA drug substance and the Strength, Identity, Dissolution, and Content Uniformity of both APIs in the drug product.

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C. Comments for 74-Day Letter

1. *Because the regulatory history of conjugated estrogens is very long, we request that the following currently approved information be submitted to NDA 22247*

    - *Manufacturing methods, starting with collection of the urine*
    - *Specifications (identity, strength, characterization, etc.)*
    - *Analytical methods and their validation reports if not USP methods*
    - *Overview of stability data and retest date*

    Provide specific references (Supplement numbers, submission and approval dates) for NDA 04-782 in support of the currently approved methods.

.

D. Recommendation:

This NDA is fileable from a CMC perspective. It has been designated as a team review, with Donna Christner, Ph.D. as the primary CMC reviewer for Conjugated Estrogens and drug product, Hamid Shafief. Ph.D. as the CMC reviewer with responsibility for the bazedoxifene review (drug substance and corresponding drug product issues), and Kareen Riviere, Ph.D. and John Duan, Ph.D. as the ONDQA BioPharm review team.

REGULATORY BRIEFING RECOMMENDATION: Office level

_____
Donna F. Christner, Ph.D.

Reference ID: 3223861

NDA Number: 22247	**Type: 1 NME and 4 New Combination**	**Established/Proper Name:** **Bazedoxifene and conjugated estrogens**
Applicant: Wyeth	**Letter Date: 26-Sep-2012**	**Stamp Date: 03-Oct-2012**

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

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

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**	X		*Inspection request submitted on 05-Nov-2012* *As of 14-Nov-2012:* *the Conjugated Estrogens manufacturing site in Canada is **ASSIGNED INSPECTION***

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7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		*Inspection request submitted on 05-Nov-2012.* *As of 14-Nov-2012:* *the bazedoxifene manufacturing site* (b) (4) *is* ***ASSIGNED INSPECTION*** *the* (b) (4) *site* (b) (4) *is* ***UNDER REVIEW*** *in the District Office.*
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		*Inspection request submitted on 05-Nov-2012.* *As of 14-Nov-2012:* *the* (b) (4) *packaging site is* ***ACCEPTABLE BASED ON PROFILE*** *the Ireland manufacturing and blister packaging site is* ***SUBMITTED TO DO.***

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9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

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

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion requested as per 21 CFR 25.31(b) for both APIs

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D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		Cross reference DMF (b) (4) for Bazedoxifene Cross reference NDA 04-782 for Conjugated estrogens
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Cross reference DMF (b) (4) for Bazedoxifene Cross reference NDA 04-782 for Conjugated estrogens
14.	Does the section contain information regarding the characterization of the DS?	X		Cross reference DMF (b) (4) for Bazedoxifene Cross reference NDA 04-782 for Conjugated estrogens
15.	Does the section contain controls for the DS?	X		Cross reference DMF (b) (4) for Bazedoxifene Cross reference NDA 04-782 for Conjugated estrogens
16.	Has stability data and analysis been provided for the drug substance?	X		Cross reference DMF (b) (4) for Bazedoxifene Cross reference NDA 04-782 for Conjugated estrogens (b) (4) retest period requested for BZA
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	Not a filing issue
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	Not a filing issue

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E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		Details of operating ranges do not appear to be provided and will be requested.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	Sponsor (b) (4) has data for the combination tablet.
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		(b) (4) The blister is (b) (4) (b) (4) placed in an aluminum foil laminate pouch. (b) (4)
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		(b) (4) for 20 mg BZA/0.45 mg CE based on 24 months of data (b) (4)
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	DoE performed to justify (b) (4) specifications for commercial batches. No regulatory relief requested.
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	N/A

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F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	X		Validation for Bazedoxifene drug substance and drug product. Validation for CE drug substance cross referenced to NDA 04-782. Methods will be sent to St. Louis labs.

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

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

DMF # (b) (4)	TYPE	HOLDER	ITEM REFERENCED (b) (4)	LOA DATE	COMMENTS
	II			28-Feb-2012	ADEQUATE on 22-Feb-2007. Updated and will require review.
	IV			17-Nov-2011	Needs review
					Needs review
					Needs review
					Needs Review
	III			03-Jun-2011	See ONDC Policies on (b) (4) Blisters*
	III			23-Sep-2010	
	III			11-Jan-2011	
	IV			15-Sep-2011	

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(b) (4)		(b) (4)		
	III		28-Jan-2011	
	III		01-Mar-2011	ADEQUATE on 07-Mar-2008
			21-Feb-2012	
	III		24-Apr-2012	
	III		29-Apr-2010	
	III		23-Feb-2012	
	III		19-Apr-2010	

**Policy on the Review of Container Closure Systems for Solid Oral Drug Products* (b) (4) *, 26-Apr-2001*
Policy on the Review of Blister Container Closure Systems for Oral Tablets (b) (4) *29-May-2002*

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

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

Reference ID: 3223861

{See appended electronic signature page}

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

{See appended electronic signature page}

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

Reference ID: 3223861

Attachment A: Nanotechnology product evaluating questions:

1, This review contains new information added to the table below: _____Yes; ___x____No Review date: 29-Oct-2012_____
2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes_____; No_____ ; Maybe (please specify)_____
3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.) _____ 3 b) What is the source of the nanomaterial?_____
4) Is the nanomaterial a reformulation of a previously approved product? Yes_____ No_____
5) What is the nanomaterial functionality? Carrier_____; Excipient_____; Packaging_____ API_____; Other_____ _____
6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble **(**e.g., gold nanoparticle**)** in an aqueous environment? Soluble _____; Insoluble_____
7) Was particle size or size range of the nanomaterial included in the application? Yes_____(Complete 8); No_____ (go to 9).
8) What is the reported particle size? Mean particle size_____ ; Size range distribution_____; Other_____
9) Please indicate the reason(s) why the particle size or size range was not provided: _____ _____
10, What other properties of the nanoparticle were reported in the application (See Attachment E)? _____
11) List all methods used to characterize the nanomaterial?_____ _____

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/s/

DONNA F CHRISTNER
11/30/2012

MOO JHONG RHEE
11/30/2012
Chief, Branch IV