

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022247Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022247

SUPPL #

HFD # 580

Trade Name Duavee

Generic Name conjugated estrogens/bazedoxifene

Applicant Name Wyeth Pharmaceuticals Inc., a wholly owned subsidiary of Pfizer, Inc.

Approval Date, If Known October 3, 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s). conjugated estrogens

NDA# 004782	Premarin tablet
NDA# 010402	Premarin injectable
NDA# 020216	Premarin cream
NDA# 021417	Premarin tablet
NDA# 020992	Cenestin
NDA# 021443	Enjuvia
NDA# 021609	Enjuvia
NDA# 011045	Milprem-200, Milprem-400
NDA# 020303	Premphase, Prempro
NDA# 020527	Premphase 14/14, Prempro
NDA# 021396	Prempro/Premphase
NDA# 021788	Synthetic Conjugated Estrogens A
NDA#	

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

3115A1-303-US/EU/BR
3115A1-304-WW
3115A1-305-US
3115A1-3307-WW

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

3115A1-303-US/EU/BR
3115A1-304-WW
3115A1-305-US
3115A1-3307-WW

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of

the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 3115A1-303-US/EU/BR

IND # 062288 YES NO
Explain:

Investigation #2 3115A1-304-WW

IND # 062288 YES NO
Explain:

Investigation #2 !

Investigation #3 3115A1-305-US
IND # 062288 YES NO
Explain:

Investigation #4 3115A1-3307-WW
IND # 062288 YES NO
Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
! YES ! NO
Explain: ! Explain:

Investigation #2

!

YES

!

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Samantha Bell

Title: Regulatory Health Project Manager

Date: October 3, 2013

Name of Office/Division Director signing form: Hylton Joffe

Title: Division of Bone, Reproductive, and Urologic Products, Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/

SAMANTHA S BELL
10/03/2013

HYLTON V JOFFE
10/03/2013

Bazedoxifene Acetate

1.3 Administration Information
1.3.3 Debarment Certification

1.3.3 DEBARMENT CERTIFICATION

Wyeth Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) of section 306 of the Federal Food, Drug, and Cosmetics Act in connection with application No. 21-962 and No. 22-213 for Bazedoxifene acetate.

Signed:



Gary L. Stiles, MD, FACC
Executive Vice President and Chief Medical Officer
Wyeth Pharmaceuticals

090177e18284601e\Approved\Approved On: 22-Dec-01 16:19

NDA 022247

BAZEDOXIFENE ACETATE/CONJUGATED ESTROGENS

DEBARMENT CERTIFICATION

[FD&C Act 306(k)(1)]

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

Birming P. Wong

Digitally signed by Birming P. Wong
DN: cn=US, ou=SAFE/Biopharma Association,
ou=46cbf8e1e7653ef40e17716d569239587d2e68c8, cn=Birming
P. Wong
Reason: I attest to the accuracy and integrity of this document
Date: 2012.09.19 10:28:26 -0400

September 19, 2012

Signature of Company Representative

Date

PFIZER CONFIDENTIAL

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

DATE: September 11, 2013

TO: File – NDA 022247

THROUGH: NA

FROM: Samantha Bell, Regulatory Health Project Manager

SUBJECT: Communication of PMR

The attached email communication was sent to Wyeth Pharmaceuticals on September 11, 2013 regarding a postmarketing study requirement.

From: Bell, Samantha
Sent: Wednesday, September 11, 2013 4:09 PM
To: 'Wong, Birming'
Subject: NDA 22247 Communication of PMR

Dear Ms. Wong,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for conjugated estrogens (CE)/bazedoxifene acetate (BZA), NDA 022247. We are reviewing the application and have the following comments.

Currently all conjugated estrogen products contain a class warning statement regarding the potential for increased levels of CE in the presence of 3A4 inhibitors. Given the concerns surrounding the ratio of CE to BZA in the dose ranging studies we believe that this would be an appropriate study for a Postmarketing Study Requirement (PMR). In terms of general study design, the study should be a multiple dose study and should employ the to-be-marketed dosage form given with a strong 3A4 inhibitor. Additionally, given the concerns noted regarding the effect of body weight in women with a BMI >27, either a second arm in the trial or an additional study that would enroll women of BMI's in the obese range should be included. While neither of these studies would produce any valid risk estimates per se (they are not powered for that consideration), the increase in CE levels and change in CE to BZA ratio would translate to some degree into a safety signal that could be translated into labeling.

To finalize the PMR, we will need to agree on timelines for final protocol submission, study completion, and submission of the complete study report to FDA.

Regards,
Samantha

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.9687
Fax 301.796.9897
samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
09/12/2013



NDA 022247

INFORMATION REQUEST

From: Shiley, Kimberly
Sent: Thursday, August 29, 2013 12:35 PM
To: 'birming.wong@pfizer.com'
Cc: Bell, Samantha; Wasilik, Maria
Subject: Information request for NDA 022247 conjugated estrogens/bazedoxifene

Greetings,

I am covering for Samantha Bell while she is out today. Please respond to all and provide the following as quickly as possible, but no later than noon EST on Tuesday, September 3, 2013:

- calculations used to generate the multiples of exposure under sections 8.1 and 13.1 of the prescribing information.

Thanks.

Kim Shiley, R.N., B.S.N.
Regulatory Health Project Manager
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993
Bldg 22, Room 5377
office: 301-796-2117
fax: 301-796-9897
kimberly.shiley@fda.hhs.gov

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/s/

KIMBERLY A SHILEY
08/29/2013

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

DATE: July 16, 2013

TO: File – NDA 022247

THROUGH: NA

FROM: Samantha Bell, Regulatory Health Project Manager

SUBJECT: Information Request

The attached email communication was sent to Wyeth Pharmaceuticals on July 16, 2013 regarding the environmental assessment (EA) proposal submitted on July 3, 2013.

From: Bell, Samantha
Sent: Tuesday, July 16, 2013 1:02 PM
To: 'Wong, Birming'
Subject: NDA 022247 Information Request (EA Proposal)

Dear Ms. Wong,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for conjugated estrogens/bazedoxifene acetate (BZA/CE), NDA 022247.

We reviewed your environmental assessment (EA) proposal submitted on July 3, 2013, and have the following comments, which must be addressed in the EA to ensure it contains sufficient information and analysis to enable us to determine whether the proposed action may significantly affect the quality of the human environment (21 CFR 25.15(a)) and ultimately whether we will prepare an environmental impact statement (EIS) or a finding of no significant impact (FONSI) (21 CFR 25.40(a)). Therefore, in the EA:

1. Provide clear justification for marker selection, addressing potential potency, environmental concentration, and other relevant factors for each of the BZA/CE components;

2. Account for the [REDACTED] (b) (4) data in your March 29, 2013 testing strategy and (b) [REDACTED] (b) (4) in your July 3, 2013 EA proposal [REDACTED] (b) (4)

3. Provide supporting information [REDACTED] (b) (4) in the development of estimated environmental concentrations; and

4. Estimate individual and cumulative risk to the environment (a) for the representative CE components in the formulation; (b) across both BZA and CE in the formulation and (c) for all marketed CEs by Wyeth.

Regards,
Samantha

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.9687
Fax 301.796.9897
samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
07/16/2013



NDA 022247

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Wyeth Pharmaceuticals, Inc.
235 East 42nd Street
New York, NY 10017

ATTENTION: Birming Wong
 Director, Worldwide Safety & Regulatory

Dear Mr. Wong:

Please refer to your New Drug Application (NDA) dated September 26, 2012, accepted October 3, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Bazedoxifene Acetate and Conjugated Estrogens Tablets.

We also refer to your correspondence, dated and received March 22, 2013, requesting review of your proposed proprietary name, Duavee. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Duavee, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. If **any** of the proposed product characteristics as stated in your March 22, 2013, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Marcus Cato, Safety Regulatory Project Manager, in the Office of Surveillance and Epidemiology, at (301) 796-3903. For any other information regarding this application, contact Samantha Bell, Regulatory Project Manager, in the Office of New Drugs (OND), at (301) 796- 9687.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
06/18/2013



NDA 022247

LABELING PMR/PMC DISCUSSION COMMENTS

Wyeth Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer, Inc.
Attention: Birming Wong
Director, Worldwide Safety & Regulatory
235 East 42nd Street
New York, NY 10017

Dear Ms. Wong:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bazedoxifene acetate/conjugated estrogens.

We also refer to our December 12, 2012, letter in which we notified you of our target date of June 15, 2013, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012.”

On September 26 and December 20, 2012, we received your proposed labeling submissions to this application, and have proposed revisions that are included as an enclosure.

At this time, we do not anticipate the need for any postmarketing requirements/commitments.

If you have any questions, call me at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Samantha Bell, B.S., B.A., R.A.C.
Regulatory Health Project Manager
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE: Content of Labeling

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

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/s/

SAMANTHA S BELL
06/14/2013



NDA 022247

DISCIPLINE REVIEW LETTER

Wyeth Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer, Inc.
Attention: Birming Wong
Director, Worldwide Safety & Regulatory
235 East 42nd Street
New York, NY 10017

Dear Ms. Wong:

Please refer to your October 3, 2012 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bazedoxifene acetate/conjugated estrogens.

Our primary reviews of the Clinical and Statistical sections of your submission are complete. We have identified the following deficiencies:

1.  (b) (4)

 (b) (4)

 (b) (4)

2.

(b) (4)



(b) (4)



3. The Office of Scientific Investigations has not completed its inspections and the results are pending at this time. Approval of the prevention of postmenopausal osteoporosis indication is contingent upon an acceptable determination regarding the content and reliability of the Trial 303 data.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Samantha Bell, Regulatory Project Manager, at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Theresa Kehoe, M.D.
Clinical/Cross Discipline Team Leader
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

THERESA E KEHOE
06/13/2013

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

DATE: May 31, 2013

TO: File – NDA 022247

THROUGH: NA

FROM: Samantha Bell, Regulatory Health Project Manager

SUBJECT: Information Request

The attached email communication was sent to Wyeth Pharmaceuticals on May 31, 2013 requesting clarification regarding supportive table 15.3 from Study 304.

From: Bell, Samantha
Sent: Friday, May 31, 2013 12:02 PM
To: 'Wong, Birming'
Subject: NDA 022247 Information Request

Dear Ms. Wong,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for conjugated estrogens/bazedoxifene acetate, NDA 022247.

We are reviewing the application and have the following additional information request. Please provide a written response by June 4, 2013.

For Study 304, please explain the findings in the supportive table 15.3 (page 187 of 1488) especially the row labeled "Month 12 biopsy or hyperplasia before Month 12". Were these subjects excluded? Should this have read "no Month 12 biopsy or hyperplasia before Month 12"? How do the items and number of subjects in this table correlate with your submitted datasets (which dataset and which dataset columns)?

Regards,
Samantha

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.9687
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samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
05/31/2013

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

DATE: May 29, 2013

TO: File – NDA 022247

THROUGH: NA

FROM: Samantha Bell, Regulatory Health Project Manager

SUBJECT: Information Request

The attached email communication was sent to Wyeth Pharmaceuticals on May 29, 2013 requesting clarification regarding financial disclosure.

From: Bell, Samantha
Sent: Wednesday, May 29, 2013 2:06 PM
To: 'Wong, Birming'
Subject: NDA 22247 Information Request

Dear Ms. Wong,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bazedoxifene acetate/conjugated estrogens, NDA 022247.

We are reviewing the application and have the following additional information request. Please provide a written response by June 4, 2013.

Regarding the financial disclosure information submitted in the application, clarify if the central radiologists were included in your reporting.

Regards,
Samantha

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
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/s/

SAMANTHA S BELL
05/29/2013



NDA 022247

INFORMATION REQUEST

Wyeth Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer, Inc.
Attention: Birming Wong
Director, Worldwide Safety & Regulatory
235 East 42nd Street
New York, NY 10017

Dear Ms. Wong:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bazedoxifene acetate/conjugated estrogens.

We are reviewing your application and have the following comments and information requests.

We request a prompt written response by June 10, 2013 in order to continue our evaluation of your NDA.

Despite our prior requests for clarification, you have not provided adequate information to conclusively show a bridge between the products you used in your Phase 3 program and your proposed to-be-marketed products. Based on poor quality submissions and inconsistent terminology between documents and across formulations, stock numbers, and batch numbers, we are unable to track the progression of changes for your product across the Phase 3 program and are unable to understand how these products compare to the proposed to-be-marketed products. This is a major deficiency. We strongly urge you to completely, succinctly, and clearly provide the information requested below.

Starting with the first product formulation through to your to-be-marketed product, provide in a single document the data in both text and tabular format that outlines the sequence of product changes and bioequivalence study results that led to further product changes. This document should include an explanation with the specific manufacturing differences (e.g. processes, (b) (4) procedures, manufacturing sites), stock numbers and batch numbers for the products used in each bioequivalence study and each Phase 3 study. This document will need to clearly provide evidence of an adequate bridge to the to-be-marketed products using consistent terminology that you define at the start of the document and adhere to throughout.

Additionally, clarify the to-be-marketed formulation in Study 1117 and its relation with the final to-be-marketed formulations in Studies 1122 and 1137.

If you have any questions, call Samantha Bell, Regulatory Project Manager, at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

HYLTON V JOFFE
05/24/2013

From: [Wong, Birming](#)
To: [Jennings, Kerri-Ann](#)
Subject: RE: NDA 22247 (BZA/CE) Information Request
Date: Friday, May 10, 2013 11:13:20 AM

Thank you Kerri-Ann,
I will share with the team right away.
Best regards,
Ming

From: Jennings, Kerri-Ann [mailto:Kerri-Ann.Jennings@fda.hhs.gov]
Sent: Friday, May 10, 2013 11:12 AM
To: Wong, Birming
Subject: NDA 22247 (BZA/CE) Information Request

Good morning Ming,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bazedoxifene/conjugated estrogens (BZA/CE) Tablets.

As discussed during our teleconference May 9, 2013, we are reviewing the application and have the following comments and information requests. We request a written response by Friday, May 17, 2013, in order to continue evaluation of your NDA.

Provide the following:

1. Include a test (b) (4) in the drug product specification at both release and stability with an acceptance criteria of NMT (b) (4)
2. The following dissolution acceptance criteria are recommended for BZA:

NMT (b) (4) at 15 minutes
NLT (b) (4) at 60 minutes

This recommendation is based on the mean in-vitro dissolution profiles of the pivotal clinical and primary stability batches for both strengths. Note that the setting of dissolution acceptance criteria is based on mean data (n=12 units) not on individual data; therefore, some batches may require Stage 2 and, occasionally, Stage 3 testing. Revise the acceptance criteria for the dissolution test accordingly.

Update the drug product specifications and the Stability Commitment accordingly in the appropriate sections (Modules 2 and 3) of the NDA.

Submit an amendment to NDA 22247.

Please confirm receipt of this email.

Thank you .

Regards,

Kerri-Ann

Kerri-Ann E. Jennings, MS, BSN, RN
LT, United States Public Health Service
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment II
Phone (301) 796-2919

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/s/

KERRI-ANN JENNINGS
05/10/2013

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

DATE: May 2, 2013

TO: File – NDA 022247

THROUGH: NA

FROM: Samantha Bell, Regulatory Health Project Manager

SUBJECT: Information Request

The attached email communication was sent to Wyeth Pharmaceuticals on May 2, 2013 requesting a sensitivity analysis for Study 3115A1-303 and a patient diary for Study 3115A1-305.

From: Bell, Samantha [mailto:Samantha.Bell@fda.hhs.gov]
Sent: Thursday, May 02, 2013 11:44 AM
To: Wong, Birming
Subject: NDA 22247 Information Request

Dear Ms. Wong,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bazedoxifene acetate/conjugated estrogens, NDA 022247.

We are reviewing the application and have the following additional information requests. Please provide a written response by May 9, 2013.

1. For Study 3115A1-303, submit a sensitivity analysis excluding subjects with missing source documentation for the total hip and femoral neck endpoints, including placebo data.
2. For Study 3115A1-305, submit a sample copy of patient diary distributed to patients.

Regards,
Samantha

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.9687
Fax 301.796.9897
samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
05/02/2013

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

DATE: April 26, 2013

TO: File – NDA 022247

THROUGH: NA

FROM: Samantha Bell, Regulatory Health Project Manager

SUBJECT: Information Request

The attached email communication was sent to Wyeth Pharmaceuticals on April 26, 2013 regarding an upcoming Office of Scientific Investigations (OSI) audit of Dr. Baracat's site (Site #447) for Study 3115A1-303-US/EU/BR.

From: Bell, Samantha
Sent: Friday, April 26, 2013 7:46 PM
To: 'Wong, Birming'
Cc: 'Liza R.'
Subject: NDA 22247 Information Request (OSI)

Dear Ms. Wong,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bazedoxifene acetate/conjugated estrogens, NDA 022247.

We are reviewing the application and have the following additional information request regarding the upcoming Office of Scientific Investigations (OSI) audit of Dr. Baracat's site (Site #447) for Study 3115A1-303-US/EU/BR.

In order to facilitate the OSI audit of Dr. Baracat's site (Site #447) for Study 3115A1-303-US/EU/BR, OSI requests that you identify and make available at the time of the audit, documents from the regulatory binder (investigator site file) that provide evidence that the subjects with missing source documents (i.e. subjects at Site #447 listed in the February 19, 2013 submission to NDA 22247, Module 1.11.3 Efficacy Information Amendment, Table 1) existed and participated in the trial. This may include, but is not limited to:

- Any communications from the site to you (the Sponsor), the Ethics Committee, or any of the study vendors about these subjects
- Screening/enrollment log
- Site visit log
- Lab requisitions for procedures performed (e.g. bone mineral density, endometrial biopsy)
- Drug accountability log

Sincerely,
Samantha

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.9687
Fax 301.796.9897
samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
04/26/2013

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

DATE: April 26, 2013

TO: File – NDA 022247

THROUGH: NA

FROM: Samantha Bell, Regulatory Health Project Manager

SUBJECT: Information Request

The attached email communication was sent to Wyeth Pharmaceuticals on April 26, 2013 requesting an additional dataset for Study 3115A1-304 and additional endometrial biopsy information Study 3115A1-304 and Study 3115A1-303.

From: Bell, Samantha
Sent: Friday, April 26, 2013 12:36 PM
To: 'Wong, Birming'
Subject: NDA 22247 Information Request

Dear Ms. Wong,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bazedoxifene acetate/conjugated estrogens, NDA 022247.

We are reviewing the application and have the following additional information requests. Please provide a written response by May 3, 2013.

Information requests concerning Study 3115A1-304:

1. According to your study report, two different formulations (B and C) were used in study 304. Provide a dataset providing information on formulation use (combine year 1 and extension year). In this dataset from Study 304 include the following columns:

- Study number
- Subject identification number
- Calendar start date of formulation B
- Calendar end date of formulation B
- Study day start date of formulation B
- Study day end date of formulation B
- Calendar start date of formulation C
- Calendar end date of formulation C
- Study day start date of formulation C
- Study day end date of formulation C
- Total days of formulation B
- Total days of formulation C
- Treatment name (TPNAME)
- Treatment code (TPCODE)
- Investigator text (INVTEXT)

Also provide a definition PDF.

2. In a separate table provide information on all subjects who had at least one endometrial biopsy reading of hyperplasia or malignancy. Use additional rows if one subject had multiple days on which hyperplasia/malignancy was found. Include the following table columns:

- Subject ID
- Treatment
- Study day relating to the endometrial biopsy with hyperplasia or malignancy
- Study day start date of formulation B

- Study day end date of formulation B
- Study day start date of formulation C
- Study day end date of formulation C

Information request concerning Study 3115A1-303:

We reference the following paragraph on page 51 of the study report :

“As part of an internal audit of clinical study files, a reconciliation of endometrial biopsy slides, blocks, and biopsy report worksheets stored with the Sponsor was performed with the endometrial biopsy results in the clinical study database. The reconciliation process revealed that results for some endometrial biopsies were available on hardcopy endometrial biopsy worksheets at the Sponsor but had not been received from clinical study sites on CRFs and, as a result, were not available in the clinical database. In addition, slides and blocks from unscheduled biopsies for some subjects were identified for which there were no data on the database. The study database was reopened and the biopsy data from the hardcopy worksheets was added to the clinical database. In addition, the samples with no available worksheets were sent to independent pathologists for evaluation, and the results from these evaluations were also added to the database. The data presented in this clinical study report (CSR) are based on the updated database. The overall results and or conclusion of the study was not affected by this process. See Supportive Tables 15.4, 15.5, and 15.6 for a summary of the biopsy results added by data analysis interval and for a listing of all biopsy results for subjects who had biopsy data added to the database.”

1. Provide a listing of subject ID numbers in 2 categories:

- a. Those who had biopsy data available from hardcopy worksheets and were added to the clinical database.
- b. Those who had samples with no available worksheets and required sample submission or resubmission to the independent pathologists.

2. In regard to the subjects in category 2 – were any of the original worksheets subsequently found?

3. Were there any cases in Study 303 where the paraffin blocks had to be recut before slides could be sent to the pathologists?

Sincerely,
Samantha

Samantha Bell, BS, BA, RAC

Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.9687
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samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
04/26/2013



NDA 022247

MID-CYCLE COMMUNICATION

Wyeth Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer, Inc.
Attention: Birming Wong
Director, Worldwide Safety & Regulatory
235 East 42nd Street
New York, NY 10017

Dear Ms. Wong:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bazedoxifene acetate/conjugated estrogens.

We also refer to the teleconference between representatives of your firm and the FDA on March 20, 2013. The purpose of the teleconference was to provide you with an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Samantha Bell, Regulatory Project Manager, at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Theresa Kehoe, M.D.
Medical Team Leader
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

MID-CYCLE COMMUNICATION

Meeting Date and Time: March 20, 2013, 10:00 A.M. to 11:00 A.M.

Application Number: NDA 022247
Product Name: Bazedoxifene acetate/conjugated estrogens
Proposed Indications: Treatment of vasomotor symptoms (VMS) in postmenopausal women
Treatment of vulvar and vaginal atrophy (VVA) in postmenopausal women
Prevention of postmenopausal osteoporosis (PMO)

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

Meeting Chair: Theresa Kehoe, M.D.
Meeting Recorder: Samantha Bell, B.S., B.A., R.A.C.

FDA ATTENDEES

Office of Drug Evaluation III

Julie Beitz, M.D., Director
Victoria Kusiak, M.D., Deputy Director
Maria Walsh, R.N., M.S., Associate Director for Regulatory Affairs
Giusseppe Randazzo, M.S., Regulatory Scientist

Division of Reproductive and Urologic Products

Hylton V. Joffe, M.D., M.M.Sc., Director
Theresa Kehoe, M.D., Clinical Team Leader
Marcea Whitaker, M.D., Medical Officer
Gerald Willett, M.D., Medical Officer
Margaret Kober, M.P.H., Chief, Project Management Staff
Samantha Bell, B.S., B.A., R.A.C., Regulatory Project Manager

Office of New Drug Quality Assessment (ONDQA)

Donna Christner, Ph.D., CMC Lead
Kareen Riviere, Ph.D., ONDQA Biopharmaceutics Reviewer

Office of Biostatistics (OB)

Mahboob Sobhan, Ph.D., Team Leader, Division of Biometrics III (DBIII)
Sonia Castillo, Ph.D., Statistical Reviewer
Kate Dwyer, Ph.D., Statistical Reviewer

Office of Clinical Pharmacology (OCP)

Myong Jin Kim, Pharm.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology III (DCPIII)

Sayed Al-Habet, Ph.D., Clinical Pharmacology Reviewer

Fang Li, Ph.D., Pharmacometrics Reviewer

Janice Pohlman, M.D., M.P.H., Team Leader, Office of Scientific Investigations (OSI)

Kimberly Taylor, M.B.A., M.P.H., Operations Research Analyst, Office of Planning and Informatics, Office of Planning and Analysis

(b) (4)

APPLICANT ATTENDEES

Alan Clucas, M.D., Vice President, Clinical Sciences

Elaine Daniels, M.D., Ph.D., Vice President, Clinical Sciences

Sebastian Mirkin, M.D., Sr. Director, Clinical Sciences

Gail Cawkwell, M.D., Ph.D., Vice President, Medical Affairs

Barry Komm, Ph.D., Sr. Director, Medical Affairs

Simon Jenkins, Ph.D., Sr. Director, Medicine Team Lead

Amanda Ellis, M.D., Sr. Director, Safety

Suna Barlas, Ph.D., Sr. Director, Statistics

Carol Cronenberger, Ph.D., Sr. Director, Clinical Pharmacology

Beth Kendsersky, Sr. Director, Global CMC

Karl Bratin, Ph.D., Sr. Research Fellow, Pharmaceutical Sciences

David Wright, Ph.D., Associate Research Fellow, Toxicology

Deborah Driscoll, M.S., Vice President, Quality Assurance

Fred Feldstein, J.D., Sr. Director, Quality Assurance

Alan Poirier, Director, Regulatory Intelligence

Frieda Houghton, Ph.D., Sr. Director, Regulatory Strategy

Randi Albin, Ph.D., Director, Regulatory Strategy

Birming Wong, M.S., Director, Regulatory Strategy

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response,

and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

1. We have concerns regarding the high number of study subjects with absence of source documentation, especially the high number of subjects with complete absence of source documentation. This will be taken into account as we evaluate efficacy and safety.
2. (b) (4)
Therefore, it appears that small reductions in systemic exposure to bazedoxifene may adversely impact the safety profile of your product. We are closely evaluating intrinsic and extrinsic factors that may potentially affect the pharmacokinetic (PK) characteristics of bazedoxifene and in particular the exposure, metabolism, and formulation performance.
3. We note multiple formulations used in the development program for conjugated estrogen/bazedoxifene and the difficulty in finding to-be-marketed formulations that are bioequivalent to the formulations used in the clinical trials. The formulation changes and rationale for new formulation development are not clear (see our information request below).
4. The following Quality issues were conveyed in a letter dated March 18, 2013.
 - Updated information is required for the manufacturing process, packaging operations and hold times for bulk tablets.
 - Specifications should be included (b) (4) in the drug product and additional supporting documentation provided to support the acceptance criteria. Specifications and Stability Commitment should be updated.
 - The acceptance criteria for the bazedoxifene dissolutions should be modified and specifications updated.
 - An Environmental Assessment should be submitted for both active pharmaceutical ingredients (APIs).

DISCUSSION AT THE MEETING:

The Applicant asked if the Agency could elaborate on Item Number 4 from the Filing Communication letter, “We are concerned that substantial evidence of effectiveness has not been provided for all of your proposed indications”. The Agency explained that for each indication, two supportive studies would normally be needed. If the missing source documentation affects the study analyses such that only a single study becomes supportive for the VVA and VMS indications, this could be a review issue. The Applicant asked if this would apply to the PMO indication. The Agency could not confirm at this time as the review is still ongoing. Wyeth asked if the Agency needs any additional information related to the source documentation. The Agency stated not at this time.

Wyeth asked if the Agency could provide a status of the 303 and 304 study review. For 304, the Agency believes there is a loss of uterine protection with the lower bioequivalence from formulation C. For 303, the Agency stated the review is ongoing for VMS and VVA and we could not elaborate further, and, for PMO, it appears that bazedoxifene reduces the estrogen effect at bone.

3.0 INFORMATION REQUESTS

At this time, outstanding information requests (IR) include:

1. The Quality IR letter dated March 18, 2013, requesting:
 - Updated manufacturing information
 - Inclusion of a specification [REDACTED] (b) (4) in the drug product
 - Revision of the bazedoxifene dissolution acceptance criteria
 - Submission of an Environmental Assessment

2. The clinical IR request dated March 19, 2013 detailed below:
General:

- a. Reference is made to the Information Amendment, Question 2, submitted February 15, 2013. For Tables 2, 3, 5 and Tables 6 through 8, provide the number of subjects and the mean change from baseline (SD) values for the placebo group in your sensitivity analyses.

Prevention of PMO Indication:

- a. To assess the effect of bazedoxifene/conjugated estrogen in patients with low bone mass, submit analyses of bone mineral density (BMD) (lumbar spine, total hip, femoral neck, radius) from Substudy II of Study 303 and Study 3307, including only subjects with baseline T-score values between -2.5 and -1, inclusive, that is, $-2.5 \leq$ baseline lumbar spine or total hip T-score ≤ -1 . Each study should be reported separately. The datasets used for analyses, including the baseline lumbar spine and total hip T-scores, should also be submitted. Provide a dataset for the 370 subjects (16%) taking bone active drugs in the Osteoporosis Substudies from Study 303. Include the subject number, substudy, treatment group, prohibited medication name, dose, indication, duration of treatment, and mean percent change in BMD from baseline at the lumbar spine and total hip. Include baseline values, mean percent change at year 1 and mean percent change at year 2 for all dose groups. Provide the same dataset for similar subjects in study 3307.
- b. Reference is made to lumbar spine BMD results from Table 3 (Information Amendment, Question 2, submitted February 15, 2013) and Table 9-11, p. 114 of Study 303 Clinical Study Report. Provide an explanation for the change in sample size in the original analysis when the sensitivity analyses were submitted.
- c. For study 3307, submit the SAS dataset PATINFO. It was referenced in the SAS primary efficacy analysis program BMD-ANCOVA.

Vulvar and Vaginal Atrophy Indication:

a.

(b) (4)

3. The following new information request was discussed at this meeting:

- a. Clearly identify the steps taken in your formulation development pathway. Due to the complexity of your formulation development pathway and the number of failed bioequivalence studies, we recommend you include a flow chart with an explanation of the objective of each study. Also, include summary text to explain the complexity of the formulation in a step-by-step manner including the pass and fail studies. We also suggest providing the information in a decision tree fashion or any other format that can be easily visualized. It is important to include the changes in formulation at each step. It is critical to show the link/bridging among all relevant formulations without missing any link all the way through to the final-to-be-marketed formulation. You may include the date of each study to clarify the flow and the links.

DISCUSSION AT THE MEETING:

Wyeth asked the agency to clarify the information request for the VVA indication regarding the

(b) (4)

Post-meeting Comments: Clarification is provided for Item 2(a) under Information Requests. Based on the World Health Organization osteoporosis classification, the low bone mass population should include subjects with T-score values between -2.5 and -1, meaning > -2.5 and < -1 .

We note that Wyeth has responded to the information requests above.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

- a. The major safety concern identified to date is the apparent narrow therapeutic range for uterine protection.
- b. Because estrogen is the primary component necessary for the indications sought, a Patient Package Insert will be required (21 CFR 310.515).

DISCUSSION AT THE MEETING:

There was no further discussion at the meeting.

5.0 ADVISORY COMMITTEE MEETING

It is anticipated that this application will be presented before the Advisory Committee for Reproductive Health Drugs.

DISCUSSION AT THE MEETING:

Wyeth asked if the Agency could elaborate on the focus of the Advisory Committee and if there is a scheduled date. The Agency explained the focus is still being developed, but the fact that this is the first combination estrogen product that does not contain a progestin will likely be a topic of discussion. The Agency also stated the meeting is currently scheduled for July 9, 2013.

Post-meeting Comment:

After further internal discussions, FDA has determined that an advisory committee meeting for your product is not necessary. We have determined that there is sufficient expertise within FDA to address the issues identified to date in the NDA.

6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

The proposed date for the Late Cycle Meeting is June 26, 2013.

Initial product labeling and PMR/PMC requests will be provided by June 14, 2013.

DISCUSSION AT THE MEETING:

The project manager will confirm the date and time for the Late Cycle meeting with the applicant.

Post Meeting Comment:

The Applicant has confirmed the date and time for the late cycle meeting, June 26, 2013, 11:00 A.M. to 12:30 P.M.

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/s/

THERESA E KEHOE
04/15/2013



NDA 22247

INFORMATION REQUEST

Wyeth Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer, Inc.
Attention: Birning P. Wong
Director, Worldwide Safety & Regulatory
235 E. 42nd Street
New York, NY 10017

Dear Ms. Wong:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bazedoxifene/conjugated estrogens (BZA/CE) tablets.

We are reviewing the Product Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

In order for FDA to take action on NDA 22247, the Environmental Assessment Staff must proceed with an evaluation of the environmental impact of this application. To this end, sufficient information must be available for the Agency to make a determination of whether approval of this specific application will significantly impact the environment. Please provide the following to assist the Agency in its decision-making.

1. Provide by April 30, 2013, the Bazedoxifene Environmental Risk Assessment (ERA) and study reports previously submitted to EMA.
2. Provide by July 31, 2013, or earlier, the Bazedoxifene Environmental Assessment (EA) in the format recommended in the CDER GFI: Environmental Assessment of Human Drug and Biologic Applications.
3. Provide by April 30, 2013, your response to FDA's request for an EA for Conjugated Estrogens as provided in the March 18, 2013, letter to your company. During the April 10, 2013, teleconference with FDA, we recommended that Pfizer submit a literature-based EA for CE, using data available on estrogens, estradiol equivalents and exposure models, in order to assess the relative risks to ecological species associated with conjugated estrogens. We also recommended that Pfizer continue with their plans to complete the ongoing and proposed environmental studies. During the teleconference, Pfizer disagreed with CDER's recommendation and maintained that the studies need to be completed in order to submit an adequate EA. Please explain why you disagreed with CDER's recommendation and indicate what data you can provide in order to allow us to

make a determination of whether Pfizer meets the environmental impact requirements for this NDA.

4. Provide a timeline for completion of the environmental studies for CE.

If you have any questions, call LT Kerri-Ann Jennings, Regulatory Project Manager, at (301) 796-2919.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

MOO JHONG RHEE
04/12/2013
Chief, Branch IV

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

DATE: March 21, 2013

TO: File – NDA 022247

THROUGH: NA

FROM: Samantha Bell, Regulatory Health Project Manager

SUBJECT: Information Request

The attached email communication was sent to Wyeth Pharmaceuticals on March 21, 2013 requesting additional information related to the formulation development pathway.

From: Bell, Samantha
Sent: Thursday, March 21, 2013 4:07 PM
To: 'Wong, Birming'
Subject: NDA 22247 Information Request

Dear Ms. Wong,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bazedoxifene acetate/conjugated estrogens, NDA 022247.

We are reviewing the application and have the following additional information request. Please provide a written response by April 5, 2013.

Please clearly identify the steps taken in your formulation development pathway. Due to the complexity of your formulation development pathway and the number of failed bioequivalence studies we recommend you include a flow chart with explanation of the objective of each study. Also, include summary text to explain the complexity of the formulation in step-by-step manner including the pass and fail studies. You may include the 90% CI limits and point estimates for BZA relevant PK Parameters (e.g., Cmax and AUC) in a tabular format for each formulation tested in each study.

If possible we also suggest providing the information in a decision tree fashion or any other format that can be easily visualized as a snapshot. It is important to include the changes in formulation at each step. It is critical to show the link/bridging among all relevant formulations without missing any link all the way through to the final-to-be-marketed formulation. You may include the date of each study to clarify the flow and the links.

Sincerely,
Samantha

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.9687
Fax 301.796.9897
samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
03/21/2013

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

DATE: March 19, 2013

TO: File – NDA 022247

THROUGH: NA

FROM: Samantha Bell, Regulatory Health Project Manager

SUBJECT: Information Request

The attached email communication was sent to Wyeth Pharmaceuticals on March 19, 2013 requesting additional analysis and datasets following review of the response to information request submitted February 15, 2013.

From: Bell, Samantha
Sent: Tuesday, March 19, 2013 11:46 AM
To: 'Wong, Birming'
Subject: NDA 22247 Information Request

Dear Ms. Wong,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bazedoxifene acetate/conjugated estrogens, NDA 022247.

We are reviewing your submission dated February 15, 2013 in response to our requests provided in the December 12, 2012 Filing Communication letter. We have the following additional information request. Please provide a written response by April 2, 2013.

General:

1. Reference is made to the Information Amendment, Question 2, submitted February 15, 2013. For Tables 2, 3, 5 and Tables 6 through 8, provide the number of subjects and the mean change from baseline (SD) values for the placebo group in your sensitivity analyses.

Prevention of PMO Indication:

2. To assess the effect of BZA/CE in patients with low bone mass, submit analyses of BMD (lumbar spine, total hip, femoral neck, radius) from Substudy II of Study 303 and Study 3307, including only subjects with baseline T-score values between -2.5 and -1, inclusive, that is, $-2.5 \leq$ baseline lumbar spine or total hip T-score ≤ -1 . Each study should be reported separately. The datasets used for analyses, including the baseline lumbar spine and total hip T-scores, should also be submitted.
3. Provide a dataset for the 370 subjects (16%) taking bone active drugs in the Osteoporosis Substudies from Study 303. Include the subject number, substudy, treatment group, prohibited medication name, dose, indication, duration of treatment, and mean percent change in BMD from baseline at the lumbar spine and total hip. Include baseline values, mean percent change at year 1 and mean percent change at year 2 for all dose groups. Provide the same dataset for similar subjects in study 3307.
4. Reference is made to lumbar spine BMD results from Table 3 (Information Amendment, Question 2, submitted February 15, 2013) and Table 9-11, p. 114 of Study 303 Clinical Study Report. Provide an explanation for the change in sample size in the original analysis when the sensitivity analyses were submitted.
5. For study 3307, submit the SAS dataset PATINFO. It was referenced in the SAS primary efficacy analysis program BMD-ANCOVA.

Vulvar and Vaginal Atrophy Indication:

6.  (b) (4)

Sincerely,
Samantha

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products

WO22 - Room 5379
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.9687
Fax 301.796.9897
samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
03/19/2013



NDA 22247

INFORMATION REQUEST

Wyeth Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer, Inc.
Attention: Birming P. Wong
Director, Worldwide Safety & Regulatory
235 E. 42nd Street
New York, NY 10017

Dear Ms. Wong:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bazedoxifene/conjugated estrogens (BZA/CE) tablets.

We are reviewing the Product Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

CMC:

1. The following information should be provided concerning manufacturing of the drug product.
 - During review of the manufacturing processes submitted in P.3.3 and the Master Batch Records in section 3.2.R, it has been determined that information critical to ensure consistent manufacturing of the drug product is not included in either section. Some of this information appears to be included in the Pharmaceutical Development Section P.2.3. For example, Table 3-23 in Section P.2.3 lists the Target Process Parameters (b) (4) and this information should be included in either Section P.3.3 or in the Master Batch Record. Similar information should be provided for each process step. Revise the manufacturing process description in section P.3.3 or update the master batch record in section 3.2.R to provide sufficient detail for each process step.
 - Submit master batch records for the packaging operations. These should include detailed information (b) (4) used during packaging.
 - Provide information on the hold time for bulk tablets prior to packaging in the primary container closure systems. Taking into account the in-use stability data for packaged product, (b) (4) hold times for bulk tablets will need to be justified by supporting data, or data will need to be provided that the tablets are tested prior to packaging and that they meet the specification. Provide information on storage conditions (temperature and RH) for the bulk tablets.

2. Propose a specification (b) (4) for the to-be-marketed product. (b) (4)

The following additional information should be provided for our review:

- Physico-chemical properties, especially solubility data, (b) (4) should be submitted (b) (4).
If major differences are seen, the justification should include information on why these differences do not impact safety and efficacy of the dosage form.
- (b) (4)
- Update the drug product specifications and the Stability Commitment accordingly.

Other drug product specifications are still under review and may be modified at a later time.

Biopharmaceutics:

The following dissolution acceptance criteria are recommended for BZA:

NMT (b) (4) at 15 minutes
(b) (4) at 40 minutes
Q = (b) (4) at 60 minutes

This recommendation is based on the mean in-vitro dissolution profiles of the pivotal clinical and primary stability batches (24 months) for both strengths. Note that the setting of dissolution acceptance criteria is based on mean data (n=12 units) not on individual data; therefore, some batches may require Stage 2 and, occasionally, Stage 3 testing.

Revise the acceptance criteria for the dissolution test accordingly and submit the updated table of specifications for the drug product.

Environmental Assessment:

(b) (4) information available to the Agency that requires the preparation of an environmental assessment (EA) based

on FDA's "extraordinary circumstances" provision (21 CFR 25.21). As specified below, information indicates that at the expected level of exposure, there is the potential for serious harm to the environment. This constitutes "extraordinary circumstances" under 21 CFR 25.21(a). In addition, controversy related to the effects of hormonally active substances in the environment (e.g., GLELC and NRDC, 2010; Docket # FDA-2010-P-0377), requires the preparation of an EA (see 40 CFR 1508.27(b)(4)).

1. Bazedoxifene Acetate (BZA), as a selective estrogen receptor modulator (SERM), has the potential for harm to the environment at the expected level of exposure ([EMA, 2009](#); [Vandenberg et al., 2012](#)).
2. Conjugated Estrogens (CEs), which also are hormonally active, have the potential for harm to the environment at the expected level of exposure ([Caldwell et al., 2012](#); [Rozovsky et al., 2002](#); [Tyler et al., 2009](#)). In addition, as a result of this application, there is the potential for a significant increase in the concentration of CEs in the environment.

As noted in FDA's "Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications" (July 1998), an EA typically addresses the potential for effects to sensitive species at environmentally relevant concentrations by comparing dose-response information to predicted or measured environmental concentrations due to patient use of the applicant's drug applications. The EA should consider the contribution of BZA and CE from this NDA and your other drug applications to the overall environmental burden of estrogenic and other hormonally active compounds. When preparing the EA for this application, consider the potential impact of environmental levels on aquatic organisms. Information from the open literature and, if available, ecotoxicity study results may be utilized. An EA adequate for approval is one that contains sufficient information to enable the agency to determine whether approval of this NDA may significantly affect the quality of the human environment.

(b) (4)

An Environmental Assessment (EA), as described in 21 CFR 25.40, is required for this NDA.

References

- Caldwell, D.J., Mastrocco, F., Anderson, P.D., Länge, R. and Sumpter, J.P., 2012. Predicted-no-effect concentrations for the steroid estrogens estrone, 17 β -estradiol, estriol, and 17 α -ethinylestradiol. *Environmental Toxicology and Chemistry*. 31, 1396-1406.
- EMA, 2009. Assessment Report for Conbriza. European Medicines Agency.
- GLELC and NRDC, 2010. Citizen petition to the FDA commissioner under the national environmental policy act and administrative procedure act requesting an amendment to a FDA rule regarding human drugs and biologics. The Great Lakes Environmental Law Center; The Natural Resources Defense Council, pp. 14.

Rozovsky, I., Hoving, S., Anderson, C.P., O'Callaghan, J. and Finch, C.E., 2002. Equine estrogens induce apolipoprotein E and glial fibrillary acidic protein in mixed glial cultures. *Neuroscience Letters*. 323, 191-194.

Tyler, C.R., Filby, A.L., Bickley, L.K., Cumming, R.I., Gibson, R., Labadie, P., Katsu, Y., Liney, K.E., Shears, J.A., Silva-Castro, V., Urushitani, H., Lange, A., Winter, M.J., Iguchi, T. and Hill, E.M., 2009. Environmental Health Impacts of Equine Estrogens Derived from Hormone Replacement Therapy. *Environmental Science & Technology*. 43, 3897-3904.

Vandenberg, L.N., Colborn, T., Hayes, T.B., Heindel, J.J., Jacobs, D.R., Jr., Lee, D.H., Shioda, T., Soto, A.M., vom Saal, F.S., Welshons, W.V., Zoeller, R.T. and Myers, J.P., 2012. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. *Endocrine Reviews*. 33, 378-455.

If you have any questions, call LT Kerri-Ann Jennings, Regulatory Project Manager, at (301) 796-2919.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

MOO JHONG RHEE
03/18/2013
Chief, Branch IV

From: Wong, Birming [<mailto:Birming.Wong@pfizer.com>]
Sent: Friday, March 01, 2013 3:24 PM
To: Jennings, Kerri-Ann
Cc: Bell, Samantha
Subject: RE: NDA 22247 Information Request

Hi Kerri Ann,
Thank you for your prompt response. I will share this with the team.
Regards,
Ming

From: Jennings, Kerri-Ann [<mailto:Kerri-Ann.Jennings@fda.hhs.gov>]
Sent: Friday, March 01, 2013 3:22 PM
To: Wong, Birming
Cc: Bell, Samantha
Subject: RE: NDA 22247 Information Request

Hi Ming,

In general, the team agrees with your proposal. However, in your report include data/information for the *in vitro* dissolution testing using different concentrations of alcohol + (b) (4).
(b) (4) In addition, include the data supporting your selection of the type and concentration of (b) (4) used in the testing.

Please submit the final report by April 15, 2013.

Thank you.

Regards,

Kerri-Ann

From: Wong, Birming [<mailto:Birming.Wong@pfizer.com>]
Sent: Wednesday, February 27, 2013 5:00 PM
To: Jennings, Kerri-Ann
Cc: Bell, Samantha
Subject: RE: NDA 22247 Information Request

Dear Kerri-Ann,

(b) (4)

Based on the feedback from ONDQA that was provided in the email from the Agency on February 13, 2013, Wyeth will conduct the *in vitro* drug release test in alcoholic medium using the highest dose strength of BZA/CE tablets (BZA 20 mg/CE 0.625 mg).

To address the Agency's recommendations, Wyeth proposes to conduct in vitro drug release testing as follows:

Alcohol (ethanol) will be mixed with 0.1 N HCl and with the proposed CE dissolution medium (0.1% SLS as specified in NDA 22-247 in 3.2.P.5.2 Analytical Procedures, Method STM-00003181) on a volume-to-volume (v/v) basis in order to achieve the concentrations of alcohol of 0%, 5%, 20% and 40%. In addition, it may be necessary to add a small amount of surfactant to the 0.1 N HCl solution. Twelve (12) tablets of BZA/CE will be tested at each concentration of alcohol. Dissolution samples will be collected every 15 minutes for a total of 2 hours and analyzed for dissolved CE.

A final report of the *in vitro* drug release test will be submitted to the NDA by the end of April 2013. The report will include individual dissolution values, mean dissolution values, standard deviations, comparison plots, and f2 similarity factors, as appropriate.

Does the Agency agree with Wyeth's proposal?

Thank you,
Ming

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/s/

KERRI-ANN JENNINGS
03/08/2013

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

DATE: February 21, 2013

TO: File – NDA 022247

THROUGH: NA

FROM: Samantha Bell, Regulatory Health Project Manager

SUBJECT: Information Request

The attached email communication was sent to Wyeth Pharmaceuticals on February 21, 2013 regarding an information request from biometrics related to SAS datasets for missing source documentation.

From: Bell, Samantha
Sent: Thursday, February 21, 2013 2:24 PM
To: 'Wong, Birming'
Subject: NDA 22247 Information Request

Dear Ms. Wong,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bazedoxifene acetate/conjugated estrogens, NDA 022247.

We are reviewing your submission dated February 15, 2013 in response to our requests provided in the December 12, 2012 Filing Communication letter. We have the following information request. We request a written response by March 1, 2013.

Submit for each study a SAS dataset with the subject identification numbers for those subjects with completely or partially missing source document information.

Sincerely,
Samantha

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.9687
Fax 301.796.9897
samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
02/22/2013

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

DATE: February 1, 2013

TO: File – NDA 022247

THROUGH: NA

FROM: Samantha Bell, Regulatory Health Project Manager

SUBJECT: Information Request

The attached email communication was sent to Wyeth Pharmaceuticals on February 1, 2013 regarding an information request from Biopharmaceutics.

From: Bell, Samantha
Sent: Friday, February 01, 2013 1:46 PM
To: 'Wong, Birming'
Subject: NDA 22247 Information Request

Dear Ms. Wong,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bazedoxifene acetate/conjugated estrogens, NDA 022247.

We are reviewing the application and have the following information request. We request a written response by February 18, 2013.

- 1) We are concerned that your product may release its entire contents (“dose dumping”) when used with alcohol, thereby leading to safety concerns. Therefore, we recommend that you conduct a drug-alcohol interaction study with your product. You should conduct *in vitro* drug release testing first using the highest strength according to the following guidelines:
 - a. The following alcohol concentrations for the *in vitro* dissolution studies (using 12 units each) are recommended: 0 %, 5 %, 10 %, 20 %, and 40 %.
 - b. Generally a range of alcohol concentrations in 0.1 N HCl and the QC dissolution medium is recommended. Since the optimal dissolution medium has not been identified for your product, dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (pH 1.2, 4.5, and 6.8) are recommended.
 - c. Report f_2 values to assess the similarity (or lack thereof) in the dissolution profiles.
 - Compare the shape of the dissolution profile to see if the modified release characteristics are maintained, especially in the first 2 hours.
 - The report should include the complete data (i.e., individual, mean, SD, comparison plots, f_2 values, etc.) collected during the evaluation of the *in vitro* alcohol induced dose dumping study.

- 2) For study report rpt-79146, provide the following data/information:
 - a) Raw data in SAS transport file format for the individual and mean *in vivo* concentrations used in the internal validations (study 3117X3-102-US and 3117X3-109-US), including those of the common reference PCP tablet (Batch #024080).
 - b) Raw data in SAS transport file format for the individual and mean *in vitro* dissolution and *in vivo* concentrations used in the external validations shown in Table 4-1 of study report of rpt-79146.
 - c) Clarify the formulae (b) (4) in the equation under Table 8.4.
 - d) Provide parameter estimates and diagnostics, including the estimate error (CV%) and the diagnostic parameters and plots.
 - e) Clarify what software was used for deconvolution and IVIVC correlation, and provide the control streams and outputs for the deconvolution and correlation analyses.

Regards,
Samantha

Samantha Bell, BS, BA, RAC

Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.9687

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samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
02/01/2013

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

DATE: January 31, 2013

TO: File – NDA 022247

THROUGH: NA

FROM: Samantha Bell, Regulatory Health Project Manager

SUBJECT: Information Request

The attached email communication was sent to Wyeth Pharmaceuticals on January 31, 2013 regarding an information request from biometrics related to study information needed.

From: Bell, Samantha [mailto:Samantha.Bell@fda.hhs.gov]
Sent: Thursday, January 31, 2013 11:47 AM
To: Wong, Birming
Subject: NDA 22247 Information Request

Dear Ms. Wong,
Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bazedoxifene acetate/conjugated estrogens, NDA 022247.

We are reviewing the application and have the following information request. We request a written response by February 7, 2013.

Provide the following dates for studies 3115A1-303, 3115A1-304, 3115A1-305, 3115A1-306, and 3115A1-3307:

Last visit for last subject
Database lock
Database treatment blind break (unblinding)

Regards,
Samantha

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
Silver Spring, MD 20993

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Fax 301.796.9897
samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
01/31/2013



NDA 022247

FILING COMMUNICATION

Wyeth Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer, Inc.
Attention: Birming Wong
Director, Worldwide Safety & Regulatory
235 East 42nd Street
New York, NY 10017

Dear Ms. Wong:

Please refer to your New Drug Application (NDA) dated September 26, 2012, received October 3, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for bazedoxifene acetate/conjugated estrogens.

We also refer to your amendments dated September 26; October 3, 19, 29, and 31; November 29; and December 5, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is October 3, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 15, 2013. In addition, the planned date for our internal mid-cycle review meeting is March 6, 2013. We are currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

1. We continue to be concerned about the number of subjects and study sites with missing source documents.
2. We note from trial 304 that an 18% decrease in the bioavailability of bazedoxifene results in a marked difference in endometrial protection.
3. We note a marked decrease in the number of venous thromboembolic events with bazedoxifene/conjugated estrogen combined when compared with bazedoxifene alone or conjugated estrogens alone. The biologic plausibility of these findings is unclear.
4. We are concerned that substantial evidence of effectiveness has not been provided for all of your proposed indications.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

In addition, we request that you submit the following information:

1. Provide a listing (including subject identification) and description of which source documents are missing for all subjects with missing source documents. This description should also include comments on whether original source documentation for central laboratory specimens (bone mineral density and endometrial biopsy) is available.
2. Provide safety and efficacy analyses excluding all subjects with missing source documentation.
3. Per the February 12, 2008, meeting minutes, resubmit the audit report [REDACTED] (b) (4) [REDACTED] for the BZA/Atorvastatin drug interaction study, Study Number 3068A1-126-EU.
4. Provide confirmation that Study Number 3068A1-126-EU is the only study that was conducted [REDACTED] (b) (4) [REDACTED]
5. Provide the list of studies and corresponding audits (if any) that were conducted or analyzed [REDACTED] (b) (4) [REDACTED]
6. For ease of review, submit to this application the following information pertaining to approved conjugated estrogens:
 - a. Manufacturing methods, starting with collection of the urine
 - b. Specifications (identity, strength, characterization, etc.)
 - c. Analytical methods and corresponding validation reports if not USP methods
 - d. Overview of stability data and retest date
 - e. Specific references (Supplement numbers, submission and approval dates) for NDA 004782 in support of the currently approved methods

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. All text in the Boxed Warning in the Highlights of the Prescribing Information (PI) and Full Prescribing Information should be bolded.
2. The current revision date is listed in the PI as “05/2012” and should be revised to “MM/YYYY”.
3. "Clinical" should be added prior to “practice” in the current introductory statement in Section 6.1 of the Adverse Reactions section of the PI.
4. “See FDA-approved patient labeling (Patient Information)” should be added just under the heading for Section 17 (Patient Counseling Information).

We request that you resubmit labeling that addresses these issues by January 7, 2013. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of

administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Samantha Bell, Regulatory Project Manager, at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

HYLTON V JOFFE
12/12/2012



NDA 022247

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Wyeth Pharmaceuticals, Inc.
235 E. 42nd Street
New York, NY 10017

ATTENTION: Birming Wong
 Director, Worldwide Safety & Regulatory

Dear Mr. Wong:

Please refer to your New Drug Application (NDA) dated and received September 26, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Bazedoxifene Acetate and Conjugated Estrogens Tablets, 20 mg/0.45 mg and 20 mg/0.625 mg.

We also refer to your correspondence dated and received September 26, 2012, requesting for review of your proposed proprietary name [REDACTED] (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reason:

[REDACTED] (b) (4)

Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proposed proprietary name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C. 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Marcus Cato, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3903. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Samantha Bell, at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
12/03/2012

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

DATE: November 27, 2012

TO: File – NDA 022247

THROUGH: NA

FROM: Samantha Bell, Regulatory Health Project Manager

SUBJECT: Information Request

The attached email communication was sent to Wyeth Pharmaceuticals on November 27, 2012 regarding an information request related to interim analysis charters and statistical analysis plans.

From: Bell, Samantha
Sent: Tuesday, November 27, 2012 3:35 PM
To: 'Wong, Birming'
Subject: NDA 022247 Information Request

Dear Ms. Wong,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bazedoxifene acetate/conjugated estrogens, NDA 022247.

We are reviewing the application and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

An interim analysis was cited in the statistical analysis plans for Studies 3115A1-3307-WW, 3115A1-303-US/EU/BR, and 3115A1-304-WW; however, an interim analysis charter could not be located in the application. Provide the location within the application where this information can be found or submit to the application the interim analysis charters.

Sincerely,

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.9687
Fax 301.796.9897
samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
11/27/2012

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

DATE: November 6, 2012

TO: File – NDA 022247

THROUGH: NA

FROM: Samantha Bell, Regulatory Health Project Manager

SUBJECT: Information Request

The attached email communication was sent to Wyeth Pharmaceuticals on November 6, 2012 regarding an information request related to multiple versions of MedDRA and safety databases.

From: Bell, Samantha
Sent: Tuesday, November 06, 2012 1:46 PM
To: 'Wong, Birming'
Subject: NDA 022247 Information Request

Dear Ms. Wong,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bazedoxifene acetate/conjugated estrogens, NDA 022247.

We are reviewing the application and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

We note that multiple different versions of MedDRA have been used for coding adverse events for bazedoxifene/CEE studies and bazedoxifene monotherapy studies. This approach significantly inhibits our ability to conduct standardized MedDRA queries in our review of the safety of your bazedoxifene/CEE product. As outlined in the attached memo from the MedDRA Maintenance and Support System Organization (MSSO), the reports in a project should all be coded with the same version of MedDRA and preferably, the most recent version of MedDRA.

We request that you re-submit the safety databases for all bazedoxifene/CEE studies, the bazedoxifene/CEE integrated summary of safety, bazedoxifene monotherapy studies, and the bazedoxifene monotherapy integrated summary of safety using a single MedDRA version, preferably the most recent version of MedDRA. Please provide a timeline for this submission by 11/12/2012.

If recoding of the safety databases cannot be conducted in a timely manner, justify the impact of the various versions of MedDRA and clearly outline for each study which version of MedDRA was used and which MedDRA preferred terms are coded in multiple System Organ Classes (SOCs) based on the different MedDRA versions.



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Sincerely,

Samantha Bell, BS, BA, RAC
Regulatory Health Project Manager
FDA/Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
WO22 - Room 5379
10903 New Hampshire Avenue
Silver Spring, MD 20993

Phone 301.796.9687
Fax 301.796.9897
samantha.bell@fda.hhs.gov

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/s/

SAMANTHA S BELL
11/06/2012

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

DATE: October 22, 2012

TO: File – NDA 022247

THROUGH: NA

FROM: Samantha Bell, Regulatory Health Project Manager

SUBJECT: Information Request

The attached email communication was sent to Wyeth Pharmaceuticals on October 22, 2012 regarding an information request from the Office of Scientific Investigation (OSI).

From: Bell, Samantha
Sent: Monday, October 22, 2012 9:43 AM
To: Wong, Birming
Subject: NDA 022247 Information Request

Dear Ms. Wong:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bazedoxifene acetate/conjugated estrogens, NDA 022247

We are reviewing the application and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

The summary level data set provided for part III of the Office of Scientific Investigation request is currently in an unusable format for the site selection tool. We request that you join the seven individual datasets (clinsite-gn.xpt, clinsite-hf.xpt, clinsite-hy.xpt, clinsite-mb.xpt, clinsite-os.xpt, clinsite-pn.xpt, and clinsite-vm.xpt) into one dataset. Also, provide the following variables shown in black in the table below:

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Sincerely,

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/s/

SAMANTHA S BELL
10/22/2012



NDA 022247

**NDA ACKNOWLEDGEMENT
USER FEES RECEIVED**

Wyeth Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer, Inc.
Attention: Birming Wong
Director, Worldwide Safety & Regulatory
235 East 42nd Street
New York, NY 10017

Dear Ms. Wong:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for bazedoxifene acetate/conjugated estrogens.

You were notified in our letter dated October 2, 2012, that your application was not accepted for filing due to non-payment of fees. This is to inform you that the Agency has received all required fees and your application has been accepted as of October 3, 2012.

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 2, 2012 in accordance with 21 CFR 314.101(a).

The NDA number cited above should be included at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions regarding this application, contact Samantha Bell, Regulatory Project Manager, at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph., M.P.A
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MARGARET M KOBER
10/10/2012
Chief, Project Management Staff



NDA 022247

UNACCEPTABLE FOR FILING

Wyeth Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer, Inc.
Attention: Birming Wong
Director, Worldwide Safety & Regulatory
235 East 42nd Street
New York, NY 10017

Dear Ms. Wong:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: bazedoxifene acetate/conjugated estrogens

Date of Application: September 26, 2012

Date of Receipt: September 26, 2012

Our Reference Number: NDA 022247

We have not received the appropriate user fee for this application. An application is considered incomplete and cannot be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 979107
St. Louis, MO 63197-9000

Checks sent by courier should be addressed to:

U.S. Bank
Attention: Government Lockbox 979107
1005 Convention Plaza
St. Louis, MO 63101

When submitting payment for an application fee, include the User Fee I.D. Number, the Application number, and a copy of the user fee coversheet (Form 3397) with your application fee payment. When submitting payment for previously unpaid product and establishment fees, please include the Invoice Number(s) for the unpaid fees and the summary portion of the invoice(s) with your payment. The FDA P.O. Box number (P.O. Box 979107) should be included on any check you submit.

The receipt date for this submission (which begins the review for filability) will be the date the review division is notified that payment has been received by the bank.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you wish to send payment by wire transfer, or if you have any other user fee questions, please call Bev Friedman or Mike Jones at 301-796-3602.

If you have any questions regarding this application, contact Samantha Bell, Regulatory Project Manager, at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph., M.P.A
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MARGARET M KOBER
10/02/2012
Chief, Project Management Staff

Meeting Minutes

Date: August 22, 2001 **Time:** 3:00 - 4:30 PM **Location:** Parklawn; Potomac Room

IND: 62,288 **Name:** TSE-424 and Premarin (conjugated estrogens) tablets

Indications: Relief of vasomotor symptoms (VMS), (b) (4) prevention of osteoporosis in postmenopausal women

Type of Meeting: End-of-Phase 2, Chemistry, Manufacturing and Quality Control and Clinical Pharmacology and Biopharmaceutics

External Constituent: Wyeth-Ayerst

Meeting Chair: Mr. John Hunt **External Constituent Lead:** Dr. Katherine Penhale

Meeting Recorder: Ms. Diane Moore

FDA Attendees:

Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Eric Duffy, Ph.D. – Division Director, Division of New Drug Chemistry II (DNDC II; HFD-820)

David Lin, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

John Hunt - Deputy Director, Division of Pharmaceutical Evaluation II (DPE II; HFD-870)

Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, (DPBII) @ DRUDP (HFD-580)

Johnny Lau, R.Ph., Ph.D. – Pharmacokinetic Reviewer, (DPEII) @ DRUDP (HFD-580)

Sheldon Markofsky, Ph.D. – Chemist, Division of Metabolic and Endocrine Drug Products (DMEDP; HFD-510)

Hae-Young Ahn, Ph.D. – Pharmacokinetic Team Leader, DPEII @ DMEDP (HFD-510)

Karl Lin, Ph.D. - Statistician, DMEDP (HFD-510)

External Participants:

Samuel Sisenwine, Ph.D. – Chief Scientist, Drug Safety and Metabolism

Dan Minck, Ph.D. – Associate Director, Reproductive Toxicology

Gerald Fisher, Ph.D. – Senior Vice President, Drug Safety and Metabolism

Nirdosh Jagota, Ph.D. – Director, CMC Regulatory Affairs

Arwinder Nagi, Ph.D. – Associate Director (b) (4)

(b) (4)

Katherine Penhale- Associate Director, Worldwide Regulatory Affairs (WWRA)

Susan Wilson- Senior Regulatory Coordinator (WWRA)

James Ermer, M.S.- Associate Director, Clinical Pharmacokinetics Department, Clinical Research and Development (R&D)

External Attendees via Teleconference:

Allen A. Kutz, Ph.D. – Director, Analytical R&D, Chemical and Pharmaceutical Development

Karel F. Bernady, Ph.D. – Senior Director, CMC, North America

Simon Jenkins, Ph.D. – Director, Project Management

Yong J. Lee, Ph.E. – Section Head, Physical Pharmacy Section, Chemical and Pharmaceutical Development

Brent A. Harrington – Senior Principal Statistician, Biometrics Research

Asif Talaf – Senior Research Scientist II, Analytical R&D, Stability

Paul Scrimo – Regulatory Coordinator, WWRA

Meeting Objective:

To discuss the sponsor's proposed Chemistry, Manufacturing and Quality Control and Clinical Pharmacology and Biopharmaceutics proposals from the July 2, 2001, meeting package for the combination of conjugated estrogens and TSE-424.

Background:

Pre-IND meeting held with DRUDP on November 8, 2000, for Premarin plus TSE-424. The sponsor met with DMEDP separately for a clinical End of Phase 2 meeting with TSE-424 alone. DRUDP held a teleconference with the sponsor to discuss clinical issues on July 25, 2001. A regulatory letter with chemistry issues was sent to the sponsor on August 8, 2001.

Discussion Points: (See attached overheads)

- the sponsor confirmed that the tablet to be used in the Phase 3 clinical trials is the same as the to-be-marketed formulation (b) (4)
- the sponsor is using sinker weights throughout the entire time of dissolution testing

Decisions reached:

- **Question 1: Synthesis:**
The proposed commercial manufacturing process for drug substance is (b) (4)
(b) (4)
(b) (4) provided in Attachment I.
 - a) Does the FDA agree with our proposal to manufacture commercial batches of drug product (b) (4) (b) (4)?
 - b) The drug substance equivalence for clinical and commercial batches will be demonstrated by comparing the impurity profiles and physico-chemical properties of both substances. Is this acceptable to the FDA?
- **Answer to Question 1a:**
 - this question was addressed in the August 8, 2001, Agency letter; the Agency recommended that a change control protocol be provided for all of the above mentioned (b) (4) (b) (4) and listed what should be included in the protocol (see attached overheads for sponsor's response)
 - the Agency noted that the change control strategy protocol must be part of the NDA submission; the sponsor indicated that this agreement would be part of their global agreement (b) (4)
- **Answer to Question 1b:**
 - in the August 8, 2001 letter; the Agency agreed that the drug substance equivalence for clinical and commercial batches can be demonstrated by showing that the impurity profiles and physico-chemical properties of both substances are substantially the same, as long as both substances meet the drug substance specifications; it was requested of the sponsor that the drug substance specifications include a limit (b) (4) (see overheads for sponsor's response)
 - the Agency also noted that the drug substance specifications included a limit (b) (4)
(b) (4)
(b) (4)
(b) (4)

- the sponsor noted that if a new supplier revises the process, the Agency will be informed of the change
- **Question 2: Drug Substance Stability:**
 - a) Does FDA agree with our proposed stability program and protocol supporting the primary stability studies for an NDA filing?
- **Answer to Question 2a:**
 - except for the number of batches in the stability program, in the August 8, 2001 letter, the Agency agreed with the drug substance stability program and protocol for the batches manufactured at (b)(4) Wyeth-Ayerst and recommended that the sponsor monitor for individual impurities and degradants as well as for total impurities and assay (b)(4) in their stability program; the sponsor agreed to do this (see overheads)
 - b) Does FDA agree with our plan to qualify the alternate (b)(4) site for an NDA filing?
- **Answer to Question 2b:**
 - in the August 8, 2001 letter, the Agency recommended that the sponsor provide two batches of accelerated stability and two batches of long-term stability data for the drug substance (b)(4) (see overheads for sponsor's response)
 - the sponsor indicated that they would submit stability data on one batch upon submission of the original NDA and follow with stability data on additional batches during NDA review; the data will be submitted to the associated drug master file (DMF)
 - the Agency noted that the sponsor should submit a correspondence to the NDA that the DMF has been updated with additional stability data; the sponsor is in the process of determining the logistics of this issue
 - two batches each of accelerated stability and long-term stability (b)(4) are needed to measure consistency between the sites; the data reviewed may impact the drug substance stability; the sponsor is recommended to refer to the guidance entitled, "Stability Testing of Drug Substances and Drug Products"
 - the Agency will convey to the sponsor further comments regarding the final number of batches needed for the stability program for the drug substances manufacturer (b)(4) at a future time
- **Question 3. Drug Product:** The Conjugated Estrogens (b)(4) tablets used as the component for the manufacture of the combination product (CE/TSE-424) for Phase 3 clinical studies are identical to those used for the commercial product (Premarin[®]) in terms of (b)(4) site of manufacture. Assuming that the dissolution profiles of clinical batches are similar to that of commercial batches for the conjugated estrogens component (F_2 factor $>$ or $=$ to 50), does the FDA agree that it is not necessary to conduct a bioequivalency study for the Conjugated Estrogens component of the combination tablet when demonstrating the equivalency of Phase 3 clinical and proposed commercial products? The bioequivalency study need only demonstrate the equivalency of the TSE-424 component of the formulation.
- **Answer to Question 3:**
 - an *in vitro* dissolution test is needed to compare clinical batches with the to-be-marketed batches to substantiate the lack of difference between the clinically-tested formulation and the to-be-marketed formulation
 - a question was raised with the sponsor following the meeting (b)(4)

- (b) (4)
- dissolution profiles for the combination tablet (b) (4) will be needed
 - a waiver of an *in vivo* study can be granted on the basis on comparative dissolution data
- **Question 4a: Dissolution Methods:** Does the FDA agree that the media, pH and method (including W-A approach/rationale for developing specification) used for dissolution testing of conjugated estrogens in CE/TSE-424 tablets are acceptable for a NDA filing?
- **Answer to Question 4a:**
- no, the sponsor should continue to follow the current USP 24 *in vitro* dissolution method and acceptance criteria for the conjugated estrogens in CE/TSE-424 tablets; these include the 2 hr, 5 hr and 8 hr time-points for the combination Premarin plus TSE-424 product
- Question 4b:** Does the FDA agree that the media, pH and method (including W-A approach/rationale for developing specifications) used for dissolution testing of TSE-424 in CE/TSE-425 tablets are acceptable for a NDA filing?
- **Answer to Question 4b:**
- no, regarding the dissolution method for TSE-424, the sponsor should provide its justification for the following:
 - (b) (4) RPM paddle speed
 - use of SLS in the dissolution medium
 - use of a (b) (4) quantity of SLS
 - three dissolution media should be tested in the dissolution method with full profiles
 - (b) (4)
(b) (4) it was recommended that the sponsor consult the guidance entitled, "Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation"
 - (b) (4)
 - more supportive information is needed for TSE-424 alone
 - (b) (4) three time-points are needed according to USP 24
 - the Agency suggested that bio-data from the sponsor's ongoing pilot study with the 0.625 mg CE/40 mg TSE-424 and 0.625 mg CE/10 mg TSE-424 tablets, could possibly be used to help assess the *in vitro* dissolution methods and specifications for both CE and TSE
 - (b) (4)
(b) (4) Agency suggested that the sponsor conduct a pilot bio-study to detect possible *in vivo* bioavailability consequences
- **Question 5. Drug Product Stability:** Does the FDA agree with our proposed drug product stability program and protocol supporting the NDA expiry dating studies for both primary and alternate drug product manufacturing sites?
- **Answer to Question 5:**
- short-term accelerated data should be submitted from the alternate site
 - (b) (4) the design is acceptable
(b) (4)

- [redacted] (b) (4) in terms of product protection, the assertion that the difference is acceptable must be justified; more emphasis should be given on the blister pack [redacted] (b) (4)
 - complete testing for registration is ideal; however, if it is not appropriate to revise registration post-approval, it is recommended that the sponsor resubmit a more appropriate protocol with more rigorous testing; the Agency would consider less rigorous testing post-approval
 - the sponsor will provide supportive data from clinical batches or submit a new revised protocol
 - the stability matrix design needs more statistical power
 - because TSE is a new molecular entity, additional stability testing is needed; [redacted] (b) (4) design should include all time points
 - the Agency recommended that the sponsor discuss the [redacted] (b) (4) stability program in more depth with the Division of Metabolic and Endocrine Drug Products (DMEDP) in an End-of Phase 2 meeting
 - the power of the statistical test to analyze the expiration period must be justified
- **Question 6, biopharm.** An alternate site of manufacture [redacted] (b) (4) is being considered [redacted] (b) (4)
- [redacted]
- [redacted]
- [redacted]
- **Answer to Question 6:**
 - if the highest strength clinically-tested-formulation and the to-be-marketed formulation are bioequivalent (both TSE-424 and conjugated estrogens), a waiver for the bioequivalence study of lower strengths can be granted, provided the [redacted] (b) (4) *in vitro* dissolution profiles for both conjugated estrogens and TSE-424 are acceptable
 - a change in protocol is needed for the change in suppliers
 - accelerated stability data is needed on at least one batch of [redacted] (b) (4) TSE-424 from each facility

Comments:

- regarding impurity profiles for CE and the TSE-424 product, the Agency recommended that because high purity liquid chromatography (HPLC)/mass spectrophotometry instrumentation is now more universal, this methodology can be used to establish an impurity profile
- HPLC testing at different wavelengths may be needed to detect the impurities

Action Items:

Item:	Responsible Person:	Due Date:
• schedule teleconference to discuss pharmacology issues	Ms. Moore and Dr. Kuijpers	upon completion of pharmacology review
• submit revised protocol for registration testing	Wyeth-Ayerst	prior to NDA submission
• send copy of meeting minutes	Ms. Moore	one month

{See appended electronic signature page}

{See appended electronic signature page}

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

drafted: dm/8.31.01/TSE424MM82201.doc

Concurrence:

T.Rumble 9.6.01/ J.Lau 9.7.01/S.Markofshy, D.Lin 9.10.01/, J.Hunt 9.18.01, 9.27.01

Response not received from E.Duffy, H.Ahn, K.Lin

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/s/

Diane V. Moore
9/27/01 11:40:04 AM

John P. Hunt
9/27/01 11:56:34 AM

Minutes of Teleconference

Date: July 25, 2001 **Time:** 2:30 – 3:30 PM **Location:** Parklawn; Conf. Room “K”

IND 62,288: **Drug Name:** TSE-424 and Premarin (conjugated estrogens) tablets

Indications: relief of vasomotor symptoms (VMS), [REDACTED] (b) (4) prevention of osteoporosis in postmenopausal women

Type of Meeting: Clinical End-of-Phase-2 Guidance

Sponsor: Wyeth-Ayerst

Meeting Chair: Dr. Daniel Shames

Meeting Recorder: Ms. Diane Moore

FDA Attendees:

Daniel Shames, M.D. – Deputy Director, DRUDP (HFD-580)

Shelley Slaughter, M.D., Ph.D. – Team Leader, DRUDP (HFD-580)

Scott Monroe, M.D. – Medical Officer, DRUDP (HFD-580)

Diane Moore – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Johnny Lau, R.Ph., Ph.D. – Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

David Hoberman – Statistician – Division of Biometrics II (DBII) @ DRUDP (HFD-580)

External Participants:

Ginger Constantine, M.D. - Vice President, Women’s Health Care, Clinical Research and Development

James Pickar, M.D. – Assistant Vice President, Women’s Health Care, Clinical Research and Development

Sheila Ronkin, M.D. – Director, Women’s Health Care, Clinical Research and Development

Philip Mayer, Ph.D. – Senior Director, Clinical Research and Development, Clinical Pharmacokinetics Department

Robert Northington, Ph.D. – Associate Director, Clinical Biostatistics

Samuel Sisenwine, Ph.D.- Chief Scientist, Drug Safety and Metabolism

Nirdosh Jagota, Ph.D. – Director, CMC Regulatory Affairs

Arwinder Nagi, Ph.D. – Associate Director [REDACTED] (b) (4)

[REDACTED] (b) (4)
Joseph Sonk, Ph.D. – Therapeutic Area Head, Women’s Health Care, Assistant Vice President, Worldwide Regulatory Affairs

Kathryn Penhale – Associate Director, Worldwide Regulatory Affairs

Paul Scrimo – Regulatory Coordinator, Worldwide Regulatory Affairs

Susan Wilson – Senior Regulatory Coordinator, Worldwide Regulatory Affairs

Simon N. Jenkins, Ph.D. – Director, Project Management

Meeting Objective:

To discuss the sponsor's proposed Phase 3 clinical development plan and study proposed in the June 26, 2001, background package for the combination of conjugated estrogens and TSE-424.

Background:

Wyeth-Ayerst submitted background packages dated May 25, June 26, and July 2, 2001.

Decisions reached:

- **Toxicology and Drug Metabolism**
The toxicology and drug metabolism studies that are in progress or planned, together with the completed studies, will support the registration of CE/TSE-424 for the treatment of vasomotor symptoms and vaginal atrophy and the prevention of osteoporosis in postmenopausal women. Wyeth-Ayerst has presented the toxicology and drug metabolism development plan to FDA in a series of meetings pertaining to this compound (Pre-IND meetings for TSE-424 in a combination with CE, 8 November 2000, 30 November 2000, and 11 December 2000). At these meetings, the development program was considered adequate to support registration of CE/TSE-424. The planned reproductive studies with TSE-424 were added based on comments received at the TSE-424 End of Phase II meeting with the FDA on 9 May 2001 and from an EMEA advice received in March 2001. Does the FDA concur with this proposal?
 - **Answer:** Premarin is an approved drug, therefore, no pharmacology issues are noted; DRUDP defers to DMEDP for pharmacology comments regarding TSE-424
- **Clinical**
 1. **The CE/TSE-424 trial 3115A-303-US will include 8 treatment arms; CE 0.45 mg combined with 10 mg, 20 mg, or 40 mg of TSE-424, CE 0.625 mg combined with 20 mg, 30 mg or 40 mg of TSE-424, an active comparator (CE 0.45 mg/medroxyprogesterone acetate [MPA] 1.5 mg), and placebo. Does the FDA agree with the proposed doses for this trial?**
- **FDA response:**
 - the clinical study needs to define the lowest effective dose of TSE-424 that prevents endometrial hyperplasia with the chosen dose of conjugated estrogens (CE)
 - at least one dose of TSE-424 + CE in the trial should demonstrate ineffectiveness for prevention of endometrial hyperplasia; whichever CE dose(s) is/are chosen to be combined with TSE-424 (0.45 or 0.625) for the VMS and osteoporosis claims needs/need to have a corresponding lowest effective dose of TSE-424 for the prevention of endometrial hyperplasia
 - the Division is concerned that the lowest dose selected for the 0.45 mg arm (10 mg of TSE-424) may be fully effective in terms of endometrial protection
 - the sponsor indicated that approval will be sought for only one estrogen dose
 - the original study proposal contained eight arms (treatment regimens); the sponsor now proposes to drop the active comparator (Prempro/Premphase) arm; additional information regarding comparison bleeding patterns obtained from having the comparator arm would be useful information, but it is not a requirement for the endometrial safety study; the information could be useful in demonstrating a benefit with the drug over existing therapies
- 2. **Does FDA agree that a successful outcome to the CE/TSE-424 trial 3115A1-303-US is sufficient for filing for the treatment of vasomotor symptoms and the treatment of vaginal atrophy indication?**
- **FDA response:**
 - although one robust trial with a well-known estrogen and a well-known progestin might be sufficient to support safety and efficacy for the combination for an HRT indication, the TSE-424

product is a new molecular entity and is not as well characterized as a well-known progestin product might be; in addition, although the clinical trial we are now reviewing is a large trial, it is anticipated that only 300 patients will complete a full year of treatment on the to-be-marketed combination product; therefore, two clinical trials should be performed using the TSE-424 + CE product; the second trial should be a confirmatory study with the to-be-marketed dose of TSE-424 + CE

- the second trial should be a 1-year endometrial protection trial focused on the proposed to-be-marketed dose; the dose can be determined from the 1-year interim data from the previous 2-year trial; the second study should be adequately powered to give the requisite statistical limits so that it can stand alone; the risk of endometrial hyperplasia should have an upper bound of a one-sided 95% confidence interval (CI) that does not exceed 4%; the protocol should be proposed by the sponsor for review
 - for clarification, the first trial should be a 2-year trial that demonstrates that the combination drug prevents endometrial hyperplasia for the endometrial protection claim; the confirmatory trial should be a 1-year trial that demonstrates protection of the endometrium
 - for clarification, the outcome of Study 303 does not pertain to the filing of an NDA; rather the NDA is filed if adequate data is submitted to perform a substantive review
 - two trials with one including an active control makes the drug development plan less risky; a justification may be needed to support this new combination compared to standard therapy if there are any safety or efficacy concerns
 - the sponsor proposes to use (b) (4) for the second study instead of Prempro; a proposal should be submitted for review
- **Additional Comments:**
- the criteria for efficacy for relief of vasomotor symptoms is the demonstration of the reduction of frequency and severity of moderate-to-severe hot flushes by Week 4 and maintained through Week 12; the protocol currently does not include the Week 4 endpoint
 - regarding the evaluation of women with uterine bleeding that occurs more than three months after a normal endometrial biopsy, the protocol mentions that first the patient is assessed by transvaginal ultrasound (TVU); if the TVU is 8 mm or more, a biopsy or other intervention is recommended; the cut-off for a required biopsy should be a double wall endometrial thickness >4 mm instead of 8 mm or more; the Agency recommends that any woman with a double wall thickness of >4 mm or a focal abnormality undergo endometrial biopsy (EMB)
 - June 26 package included a pediatric waiver request; the granting of the pediatric waiver will be determined during the review of the NDA submission

Action Items:

- | Item: | Responsible Person: | Due Date: |
|--------------------------------|----------------------------|------------------|
| • submit revised protocol | Wyeth-Ayerst | ASAP |
| • send copy of meeting minutes | DRUDP | one month |

Signature, minutes preparer

Concurrence, Chair

Post meeting addendum: On July 25, 2001, the sponsor was given the following additional comments from the Medical Officer:

- the Division requests that the sponsor confirm that in Study 303 all patients will undergo endometrial biopsy and approximately 1/3 will also have annual TVU and hysteroscopy/directed biopsies if warranted
- the Division suggested that the sponsor add an intermediate visit prior to Week 12, particularly for patients in the VMS arm to ensure that patients are correctly filling out the patient diaries
- the Division recommends that an additional serum chemistry liver function test be added at the Month 9 visit
- the definition for serious adverse events on page 69 of the background package differs somewhat from the ICH regulations; the definitions should be reworded

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

CE/TSE-424 Clinical Trial Design

- Current proposal is for Placebo-only control
- In support of Placebo-control trials for demonstration of safety and efficacy, Wyeth reviewed:
 - The Statute
 - Regulations
 - Specifies active control where placebo use is deemed unethical
 - Not applicable for CE/TSE-424
 - FDA Guidances
 - Endometrium
 - Menopausal Symptoms
 - Osteoporosis

CE/TSE-424 Clinical Trial Design

- CE/TSE-424 is a combination of a well-characterized estrogen, Premarin[®], and a tissue selective estrogen TSE-424, shown to be safe through Phase II evaluation.
- The proposed 7-arm study design, which incorporates a Placebo control, is adequate to define the risk/benefit profile of CE/TSE-424.

Pre-IND Premarin + TSE-424
Meeting Minutes-July 25, 2001
Page 7

drafted: dm/7.26.01/I62288MM725901.doc

Concurrence:

J.Hunt 7.26.01/S.Monroe 7.30.01, 8.6.01/J.Lau 8.2.01/T.Rumble, S.Slaughter, A.Parekh 8.6.01
D.Hoberman, D.Shames, S.Slaughter 8.24.01

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/s/

Diane V. Moore
8/24/01 02:45:14 PM

Daniel A. Shames
8/24/01 03:17:04 PM

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 022247

LATE-CYCLE MEETING MINUTES

Wyeth Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer, Inc.
Attention: Birming Wong
Director, Worldwide Safety & Regulatory
235 East 42nd Street
New York, NY 10017

Dear Ms. Wong:

Please refer to your New Drug Application (NDA), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for conjugated estrogens/bazedoxifene acetate.

We also refer to the late cycle meeting (LCM) between representatives of your firm and the FDA on June 26, 2013.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Samantha Bell, Regulatory Project Manager at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Theresa Kehoe, M.D.
Medical Team Leader
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: June 26, 2013, 11:00 A.M. to 12:30 P.M.
Meeting Location: White Oak, Building 22, Room 1415

Application Number: NDA 022247
Product Name: Conjugated estrogens/bazedoxifene acetate
Proposed Indications: Treatment of vasomotor symptoms (VMS) in postmenopausal women
Treatment of vulvar and vaginal atrophy (VVA) in postmenopausal women
Prevention of postmenopausal osteoporosis (PMO)

Sponsor/Applicant Name: Wyeth Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer, Inc.

Meeting Chair: Theresa Kehoe, M.D.
Meeting Recorder: Samantha Bell, B.S., B.A., R.A.C.

FDA ATTENDEES

Office of New Drugs, Office of Drug Evaluation III

Julie Beitz, M.D., Director
Victoria Kusiak, M.D., Deputy Director
Maria Walsh, R.N., M.S., Associate Director for Regulatory Affairs
Giuseppe Randazzo, M.S., Regulatory Scientist

Division of Bone, Reproductive, and Urologic Products (DBRUP)

Hylton V. Joffe, M.D., M.M.Sc., Director
Theresa Kehoe, M.D., Clinical/Cross Discipline Team Leader
Stephen Bienz, M.D., Medical Officer
Marcea Whitaker, M.D., Medical Officer
Gerald Willett, M.D., Medical Officer
Leslie McKinney, Ph.D, Pharmacology / Toxicology Reviewer
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff
Samantha Bell, B.S., B.A., R.A.C., Regulatory Health Project Manager
Lisa Soule, M.D., Clinical Team Leader

Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP)

Myong Jin Kim, Pharm.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology III (DCP III)
Sayed Al-Habet, Ph.D., Clinical Pharmacology Reviewer, DCP III
LaiMing Lee, Ph.D., Clinical Pharmacology Reviewer, DCP III

Fang Li, Ph.D., Pharmacometrics Reviewer, Division of Pharmacometrics (DPM)
Yaning Wang, Ph.D., Pharmacometrics Team Leader, DPM
E. Dennis Bashaw, Pharm.D., CAPT, USPHS, Director, DCP III

Office of Biostatistics (OB), Division of Biometrics III (DBIII)

Mahboob Sobhan, Ph.D., Team Leader
Sonia Castillo, Ph.D., Statistical Reviewer
Kate Dwyer, Ph.D., Statistical Reviewer

Office of New Drug Quality Assessment (ONDQA)

Donna Christner, Ph.D., CMC Lead
John Duan, Ph.D., ONDQA Biopharmaceutics Reviewer
Kareen Riviere, Ph.D., ONDQA Biopharmaceutics Reviewer
Hamid Shafiei, Ph.D., CMC Reviewer
Kerri-Ann Jennings, M.S., B.S.N., R.N., LT, USPHS, Regulatory Health Project Manager

Office of Pharmaceutical Science (OPS)

Nakissa Sadrieh, Ph.D., Associate Director for Research Policy and Implementation
James Laurenson, Environmental Scientist/Toxicologist

Office of Surveillance and Epidemiology

Adrienne Rothstein, Pharm.D., Team Leader, Division of Pharmacovigilance (DPV) 1
Jane Gilbert, M.D., Ph.D., Medical Officer, DPV 1
Samantha Cotter Pharm.D., BCPS, FISMP, Safety Evaluator, DPV 1
David Money, R.Ph., M.P.H., CDR, USPHS, Epidemiologist, Division of Epidemiology II
Cynthia LaCivita, Pharm.D., Division of Risk Management
Manizheh Siahpoushan, Pharm.D., Safety Evaluator, Division of Medication Error Prevention and Analysis

Office of Compliance

Vipul Dholakia, Ph.D., Interdisciplinary Scientist – Chemist, Office of Manufacturing and Product Quality, Office of Compliance

Office of Scientific Investigations (OSI)

Janice Pohlman, M.D., M.P.H., Team Leader
Roy Blay, Ph.D., Reviewer

[REDACTED] (b) (4)

SPONSOR ATTENDEES

Elaine Daniels, M.D., Ph.D., Vice President, Clinical Sciences
Sebastian Mirkin, M.D., Sr. Director, Clinical Sciences
Steve Romano, M.D., Sr. Vice President, Head of Medicines Development Group
Simon Jenkins, Ph.D., Sr. Director, Medicine Team Lead

Amanda Ellis, M.D., Sr. Director, Safety
Suna Barlas, Ph.D., Sr. Director, Statistics
William McKeand, M.S., Associate Director, Clinical Pharmacology
Carol Cronenberger, Ph.D., Sr. Director, Clinical Pharmacology
Beth Kendsersky, Sr. Director, Global CMC
John Groskoph, M.B.A., Sr. Director, Global CMC
Loren Wrisley, Sr. Director, Pharmaceutical Sciences, Analytical R&D,
Jon Ericson, MS, Associate Research Fellow, Environmental Sciences,
Deborah Driscoll, M.S., Vice President, Quality Assurance
Frieda Houghton, Ph.D., Sr. Director, Regulatory Strategy
Randi Albin, Ph.D., Director, Regulatory Strategy
Birming Wong, M.S., Director, Regulatory Strategy

1.0 BACKGROUND

The applicant submitted a New Drug Application (NDA) for conjugated estrogens/bazedoxifene acetate (CE/BZA) on September 26, 2013. CE/BZA pairs conjugated estrogens (Premarin®) with bazedoxifene, an estrogen agonist/antagonist (also referred to as a Selective Estrogen Receptor Modulator or SERM). Conjugated estrogens are composed of multiple estrogens that demonstrate estrogen receptor agonist activity. Bazedoxifene acetate demonstrates both tissue selective estrogen receptor agonist and antagonist activity.

The goal of this meeting was to share information and to discuss any substantive review issues that the Agency has identified to date including additional information that may be needed to address the identified issues and our objectives for the remainder of the review.

2.0 LCM Agenda

1. Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues –Please refer to the background information for FDA’s assessment of each issue.

- a. (b) (4) dissolution failures discovered during the drug product manufacturing site inspection and the Method Validation performed at the St. Louis laboratory

Additional information is required to determine how the noted (b) (4) phenomenon (b) (4)

(b) (4) will affect the quality of the proposed to-be-marketed drug product and support use of the data from the primary stability batches to set an expiration dating period. The following information must be submitted to the NDA for our review before this application may be approved:

- i. A timeline outlining when the issue was first identified and the steps taken to address the issue.
- ii. Tabulation of all drug product batches identifying (b) (4)

- iii. Detailed information on the drug product lot identified in the report provided to the Office of Compliance (b) (4)

This detailed information should include:

- a. (b) (4)

- b. The impact on dissolution
- c. The container closure system used
- iv. Release and stability data on the planned confirmatory batch manufactured (b) (4) that conforms to the (b) (4) acceptance criteria. At a minimum, we request 6 months of data on tablets held at both long term and accelerated conditions to determine if the stability data submitted in the NDA can be used as supportive for expiration dating purposes

Meeting Discussion:

Wyeth/Pfizer posed several clarifying questions:

- 1) Regarding the ballooning statement: Wyeth is interested in obtaining further information on FDA's method validation testing performed on Batch F25952 at the St. Louis laboratory. Therefore, it would be helpful if the Agency could provide clarification on the following:
 - a) Did the (b) (4) observed by the St. Louis laboratory result in failure of the BZA dissolution criteria, the CE dissolution criteria, both, or neither?
 - b) Can the FDA share the dissolution data obtained by the St. Louis laboratory?

The Agency confirmed that the St. Louis laboratory did observe (b) (4) but their testing has not yet been completed. The Agency expressed concern for the quality of the tablet once marketed (e.g. trouble swallowing, clinical ramifications). Pfizer provided a history (b) (4) Pfizer stated they believe the (b) (4) problem has been corrected and it will not impact clinical performance. Pfizer will be submitting information to support this conclusion.

- 2) Regarding FDA requests 2ai. and 2aii:

Wyeth proposes to provide by July 31, 2013 the requested information (2ai., 2aii.) for:

- The one Formulation B batch described above. This will include all information specific to the (b) (4) event as was recorded at the time.
- Three ICH CE 0.625 mg/BZA 20 mg stability batches stored at long term 25° C/60% RH conditions for 6, 12, and 18 months; intermediate 30° C/75% RH conditions for 12 months; and at accelerated 40° C/75% RH conditions for 6 months.

- 3) Regarding FDA request 2aiv., Wyeth proposes to provide by July 31, 2013:

- The additional ICH batch stability data (36 months for the CE 0.45 mg/BZA 20 mg tablet batches and 18 months for the CE 0.625 mg/BZA 20 mg tablet batches stored at 25°C/60% RH)
- Release data on six validation lots that were recently manufactured (b) (4)

- Full initial data and 3 months dissolution data on the CE 0.45 mg/BZA 20mg confirmatory batch manufactured (b) (4) to further support the proposed expiry dating.

The Agency asked Pfizer to submit the technical report shared with the Office of Compliance (b) (4)

The Agency stated Pfizer should submit any available additional stability and supporting data to facilitate the Agency's review.

b. Environmental Assessment has not been adequately prepared

In order to allow for compliance with the EA requirements to support approval of this NDA in this cycle, you should submit a literature-based EA for conjugated estrogens, using data available on estrogens, estradiol equivalents and exposure models, in order to assess the risks to ecological species associated with this application. The EA can be updated in 2015 once the planned studies are completed.

Meeting Discussion:

Wyeth/Pfizer posed the following clarifying questions:

1) Wyeth proposes to provide the requested EA information by July 31st, 2013:

- a) The EA (described under #2 below) for Conjugated Estrogens (CE) and a post-approval commitment to provide an updated CE EA based on our GLP study data (described under #3 below).
- b) The EA for Bazedoxifene (BZA).

2) The EA for CE will use available ecotoxicity data along with literature and modeled data (b) (4)

Literature and modeled data will primarily be used to support the physical-chemical and fate sections of the EA.

3) Wyeth will update the EA for CE with physical-chemical, fate, and ecotoxicity GLP study reports as a post-approval commitment by March 31st, 2015. The updated EA will be based on Pfizer's GLP data currently being generated on estrone and 17 β -dihydroequilin and will replace the literature cited and modeled data once available. Pfizer proposes the additional GLP study reports be provided at the time of the updated CE EA on March 31st, 2015.

Does the Agency agree with Wyeth's proposals and approaches outlined above to address the substantive review issue concerning Environmental Assessment?

The Agency agreed to the proposal from Question 1. The Agency did not agree with the proposal described in Question 2, and requested that Pfizer submit literature and modeled data based on relative importance of estradiol and other relevant estrogenic components present in CE or in excretion products. (b) (4)

(b) (4) The Agency reiterated the need for literature data on estradiol and other relevant estrogenic components in order to complete the Environmental Assessment, and explained that the Agency does focus on the parent compounds, unless data can justify that the metabolites should be assessed. Pfizer will submit to the Agency their justification regarding which markers for CE should be included in the EA (b) (4)

(b) (4) If needed, a teleconference will be held to discuss this matter further. The Agency could not comment on the proposal in Question 3 at this time, regarding whether the proposed EA data to be submitted as a post-market commitment will actually replace the July 31, 2013 EA. However, the Agency did commit to reviewing any new EA and adding it to the file.

- c. A test and acceptance criterion for (b) (4) bazedoxifene in the drug product is needed

Review of your June 4, 2013 amendment is ongoing.

Meeting Discussion:

The amendment dated June 4, 2013, is still under review at this time. However, the proposal to drop the test (b) (4) was not clear. Any request to delete a test after approval must be submitted in a Prior-Approval supplement with adequate data to support the request.

- d. Facilities inspections have been completed and the final recommendation is pending at this time

We will evaluate the stability data of the drug product (b) (4) (b) (4) to determine if the facility is capable of manufacturing a product of acceptable quality that conforms to application expectations.

Meeting Discussion:

(b) (4) Pfizer confirmed they responded to the Establishment Inspection Report in April and asked about the status. The Agency stated it would need to review the July 31 data Pfizer intended to submit prior to making any decision regarding the inspection.

- e. Inadequate information currently available related to bridging all formulations to the final to-be-marketed formulation

We await your planned June 19, 2013 submission for further review.

Meeting Discussion:

Based upon Clinical Pharmacology's preliminary assessment of the June 19, 2013, amendment, it appears that clinical formulations A and B are bridged to the final to-be-marketed formulations. However, the Chemistry/Manufacturing/Controls (CMC) review of the amendment is ongoing.

- f. The data available do not support approval of the conjugated estrogens 0.625 mg/bazedoxifene 20 mg dose for any indication

(b) (4)

Meeting Discussion:

Pfizer asked if the Agency could explain further. The Agency discussed the basis for this conclusio (b) (4)

[Redacted]

Pfizer asked if the Agency would provide further advice for a path forward to approval for this strength. The Agency stated that we are open to discussing a path forward after this review cycle. (b) (4)

[Redacted]

Post-Meeting Comment:

(b) (4)

[Redacted]

- g. The data available do not support approval of the proposed indication for treatment of moderate and severe vulvar and vaginal atrophy associated with menopause

(b) (4)

[Redacted]

Meeting Discussion:

The Agency provided their rationale for why the data were not supportive. There was no further discussion.

h. Content and reliability of data from Trial 303

Question to Pfizer/Wyeth: How were adverse events, reported to FDA on May 23, 2013, from a trial that was completed in 2006 uncovered seven years later? How can we assure that there was adequate capture and recording of adverse events in the conjugated estrogens/bazedoxifene development program, most notably in Trial 303?

Meeting Discussion:

The Agency confirmed that eight inspections have been completed; however, the final recommendation is pending. The Agency asked if Pfizer could explain why approximately ten percent of the subject files from Site 447 is missing. Pfizer attributed the missing files to closure of the site and the movement of those files between the site and the storage facilities. The Agency expressed its concern regarding the missing files. Furthermore, the Agency stated its expectation that the loss of subject files under the circumstances described by the applicant would result in the loss of sequential subject files rather than what appear to be randomly numbered files. Pfizer stated that they conducted both internal and third-party quality assurance inspections and determined that the pattern of missing subject files was random in nature. Pfizer also confirmed that they were unable to identify the reason(s) for the missing files.

Regarding Pfizer's recent report of previously unreported adverse events, Pfizer explained that Site 447 was inspected in January 2013 and four discrepancies between source files and case report forms were noted. Pfizer stated that none of these recently reported adverse events changed the adverse event profile. The Agency asked Pfizer whether they believed that all adverse events had been captured. Pfizer said that they conducted additional internal audits and believed the safety profile to be complete.

3. Major labeling issues

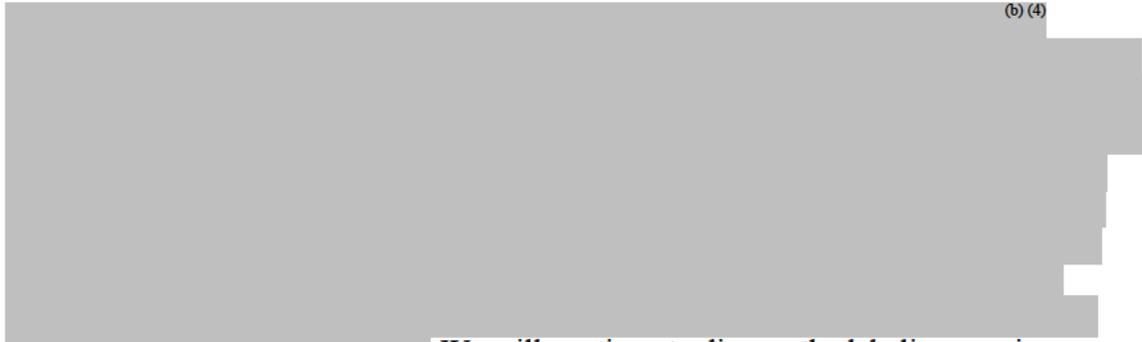
- All references to the product should be in conjugated estrogens/bazedoxifene format.
- Estrogen class labeling should be included in product labeling
- The approved indications should include "in women with a uterus".
- Limiting use in patients aged > 75 years.
- Use is not recommended in patients with renal or hepatic impairment.
- (b) (4)

Meeting Discussion:

The Agency explained that the limitation of use in patients up to 75 years old is based upon the lack of clinical data in patients > 75 years from the conjugated estrogens/bazedoxifene Phase 3 studies and the results of the age-effect pharmacokinetic study from the bazedoxifene monotherapy NDA. In the conjugated estrogens/bazedoxifene Phase 3 studies, patients up to 65 years were enrolled in the VMS and VVA studies and patients up to 75 years were enrolled in the PMO studies. The pharmacokinetic study

assessing the effect of age on bazedoxifene exposure showed that elderly subjects (>75 years) had a 2.6-fold increase in bazedoxifene exposure compared to younger subjects (51 to 64 years), which may result in loss of efficacy.

(b) (4)



We will continue to discuss the labeling moving forward.

4. Information Requests

Meeting Discussion:

Pfizer asked if they could expect any further discipline review (DR) letters. The Agency stated that all DR letters have either been sent or the information has been included in the late cycle meeting background package.

5. Postmarketing Requirements/Postmarketing Commitments

No Postmarketing Requirements or Commitments have been identified at this time

Meeting Discussion:

There was no further discussion at the meeting.

Wrap up and Action Items

Meeting Discussion:

The Agency's review of the July 31 submission will be important for this application. We plan to continue labeling discussions. We acknowledge the interest to discuss the path forward for approval of the high dose strength.

Note that this application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

THERESA E KEHOE
07/25/2013



NDA 022247

**LATE CYCLE MEETING
BRIEFING PACKAGE**

Wyeth Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer, Inc.
Attention: Birming Wong
Director, Worldwide Safety & Regulatory
235 East 42nd Street
New York, NY 10017

Dear Ms. Wong:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for bazedoxifene acetate/conjugated estrogens.

We also refer to the Late-Cycle meeting (LCM) meeting scheduled for June 26, 2013.
Attached is our briefing package, including our agenda for this meeting.

If you have any questions, call Samantha Bell, Regulatory Project Manager, at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Briefing Package

LATE-CYCLE MEETING BRIEFING PACKAGE

Meeting Date and Time: June 26, 2013, 11:00 A.M. to 12:30 P.M.
Meeting Location: White Oak, Building 22, Room 1415

Application Number: NDA 022247
Product Name: Bazedoxifene acetate/conjugated estrogens
Proposed Indications: Treatment of vasomotor symptoms (VMS) in postmenopausal women
Treatment of vulvar and vaginal atrophy (VVA) in postmenopausal women
Prevention of postmenopausal osteoporosis.

Sponsor/Applicant Name: Wyeth Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer, Inc.

INTRODUCTION

The purpose of a Late-Cycle meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues, whether it will be reviewed by the Agency in the current review cycle, and, if so, whether the submission would constitute a major amendment and trigger an extension of the PDUFA goal date. If you submit any new information in response to the issues identified in this briefing package prior to this LCM, we may not be prepared to discuss that new information at this meeting.

OVERVIEW OF ISSUES IDENTIFIED TO DATE

In addition to the contents of this briefing document, please also refer to the following Discipline Review (DR) letters already provided to you:

Office of New Drug Quality Assessment – March 18, 2013
Clinical Pharmacology – May 24, 2013
Clinical/Statistical – June 13, 2013

CURRENT SUBSTANTIVE REVIEW ISSUES

Chemistry, Manufacturing, and Control (CMC) Issues:

This NDA has not provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Items 1, 2, 3, and 4 are deficiencies that will need to be resolved prior to approval of this NDA.

1. An expiration dating period cannot be set at this time. While the submitted stability data would support the requested expiration dating period, the findings from the drug product site inspection demonstrated that the to-be-marketed drug product (b) (4) resulting in dissolution failures. This (b) (4) phenomenon was also evident during the Method Validation performed at the St. Louis laboratory. Because the clinical trial supplies and majority of the primary stability batches were manufactured (b) (4)

(b) (4) This product quality issue discovered during the site inspection makes it difficult to determine from the information provided in the NDA how much of the stability data can be used to set an appropriate expiration dating period. You will need to address this issue in the NDA. Until this issue is adequately resolved, an appropriate expiration dating period cannot be granted.

We note that during the inspection of the Pfizer Ireland site, dissolution failures on stability were attributed (b) (4)

(b) (4) Additional information is required to determine how this will affect the quality of the proposed to-be-marketed drug product and support use of the data from the primary stability batches to set an expiration dating period. We note that some information has been submitted to the Office of Compliance as part of their inspectional investigation, but we request that the following information be submitted to the NDA for our review before this application may be approved:

- i. A timeline outlining when the issue was first identified and the steps taken to address the issue.
- ii. Tabulation of all drug product batches identifying (b) (4)

- iii. Detailed information on the drug product lot identified in the report provided to the Office of Compliance (b) (4)

(b) (4) This detailed information should include:

- a. (b) (4)

- b. The impact on dissolution
- c. The container closure system used
- iv. Release and stability data on the planned confirmatory batch manufactured (b) (4) that conforms to the (b) (4) acceptance criteria. At a minimum, we request 6 months of data on tablets held at both long term and accelerated conditions to determine if the stability data submitted in the NDA can be used as supportive for expiration dating purposes

2. Environmental Assessment has not been adequately prepared.

As outlined in 21CFR 25.15(a), "All applications or petitions requesting agency action require the submission of an EA or a claim of categorical exclusion..... Failure to submit an adequate EA for an application or petition requesting action by the agency of a type specified in § 25.20, unless the agency can determine that the action qualifies for exclusion under §§ 25.30, 25.31, 25.32, 25.33, or 25.34, is sufficient grounds for FDA to refuse to file or approve the application or petition."

An environmental assessment for bazedoxifene and for conjugated estrogens is required before this NDA may be approved, as outlined in the information request letter dated March 18, 2013. We acknowledge that you plan to submit the environmental assessment for bazedoxifene by July 31, 2013. For your environmental assessment for conjugated estrogens, we acknowledge your intent to conduct environmental studies, and you propose a completion date of 2015. However, this proposed plan would not meet the environmental assessment (EA) requirements before the end of the review cycle. An adequate EA is required prior to approval.

In order to allow for compliance with the EA requirements to support approval of this NDA in this cycle, you could submit a literature-based EA for conjugated estrogens, as described in our April 12, 2013 Information Request (IR) letter, using data available on estrogens, estradiol equivalents and exposure models, in order to assess the risks to ecological species associated with this application. The EA can be updated in 2015 once the planned studies are completed.

- 3. A test and acceptance criterion for (b) (4) bazedoxifene acetate 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 adequately control the amount (b) (4). Data indicate that (b) (4) can impact the safety and efficacy of the drug product.

We acknowledge your Amendment 040 submitted June 4, 2013. A review of this amendment is ongoing and a final decision regarding this deficiency is pending.

- 4. Facilities inspections have been completed and the final recommendation is pending at this time. We will evaluate the stability data of the drug product (b) (4)

(b) (4) to determine if the facility is capable of manufacturing a product of acceptable quality that conforms to application expectations.

5. Although not an approvability issue for this NDA submission, your proposed IVIVC is not acceptable at this time due to the following reasons.

(b) (4)

In addition, the following concerns should be noted:

(b) (4)

(b) (4) This information is valuable and can be used for further development of this product. If you want to pursue further the IVIVC model, conduct the following:

- a. Build an IVIVC model using the bazedoxifene acetate/conjugated estrogens tablet data and validate the model.
- b. Show the robustness of the model.

Clinical Pharmacology Issues:

1. This NDA does not support approval at this time due to inadequate information currently available related to bridging all formulations to the final to-be-marketed (TBM) formulation. An IR letter was sent on May 24, 2013 requesting a document clearly outlining the complicated formulation development and bridging of all formulations to the TBM formulation.

We acknowledge your intent to submit a response to our May 24, 2013 Information Request on June 20, 2013. We will need to review this amendment and find satisfactory evidence of bridging before the NDA may be approved. Therefore, a final decision regarding this deficiency is pending.

Clinical and Statistical Issues:

1. [REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4)

2. [REDACTED] (b) (4)

[REDACTED] (b) (4)

3. Approval of the prevention of postmenopausal osteoporosis indication is contingent upon an acceptable determination regarding the content and reliability of the Trial 303 data. One major concern is the missing source documentation described below. We are still determining the extent to which we can rely on data from patients with missing source

documentation and the extent to which we can rely on data from a study site that has extensive missing source documentation.

Seven of eight inspections requested by the Office of Scientific Investigations (OSI) have been completed by the Office of Regulatory Affairs. For Trial 303, three clinical sites were inspected. Based upon preliminary review of informal investigator reports and Form FDA 483s, other than the missing source documentation at Site #447 (further described below), no critical regulatory violations impacting data reliability have been identified to date. Four source documents were noted to be missing at a second site for Trial 303. Preliminary evaluation and classification of the clinical site inspection for Trial 305 is pending. For Trial 306, no significant regulatory violations were identified at the clinical site inspected; this same site was also inspected for Trial 3307 and there were no significant regulatory violations. Based upon preliminary information from a second site inspected for Trial 3307, no critical regulatory violations have been identified to date. Final reports from several inspections are not yet available for review and may change OSI conclusions.

One concern regarding the reliability of the data for Trial 303 is the issue of missing source documentation. In a submission to the NDA on February 15, 2013, you reported 286 subjects with missing source documentation. Of these, complete sets of source documents were missing in 257 subjects. At a single site (447) that enrolled 889 subjects, 83 complete sets of source documents were reported missing. Based on a preliminary report, at the time of inspection by the Office of Scientific Investigations, 80 complete sets of source documents were missing. Among these were five subjects whose records were apparently found; an additional two subjects where source documentation was thought to be present but were found missing at the time of inspection; and 6 additional subjects, not previously reported, found to have partially missing records.

We also note a submission to the NDA on May 23, 2013, reporting additional adverse events for Trial 303, a trial that was completed in 2006. This raises concern regarding the adequate capture and reporting of adverse events for this trial, although this was not a significant regulatory violation noted during OSI's site inspections.

Pharmacology Toxicology Issues: none

Based on the substantive issues outlined above, the conjugated estrogens 0.45 mg / bazedoxifene 20 mg tablet appears acceptable for the treatment of vasomotor symptoms associated with menopause and may be acceptable for the prevention of postmenopausal osteoporosis. These determinations are pending successful resolution of the CMC issues and demonstration of adequate bridging between the formulations used in trials during the development program and the to-be-marketed formulation.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

This application's risk versus benefit assessment does not necessitate a REMS.

LCM AGENDA

1. Introductory Comments – 5 minutes (Regulatory Project Manager/Cross-Discipline Team Leader)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issue(s) –45 minutes: Please refer to the background information for FDA’s assessment of each issue.

- a. (b) (4) dissolution failures discovered during the drug product manufacturing site inspection and the Method Validation performed at the St. Louis laboratory. Additional information is required to determine how the noted (b) (4) phenomenon (b) (4) will affect the quality of the proposed to-be-marketed drug product and support use of the data from the primary stability batches to set an expiration dating period. The following information must be submitted to the NDA for our review before this application may be approved:

- i. A timeline outlining when the issue was first identified and the steps taken to address the issue.
- ii. Tabulation of all drug product batches identifying (b) (4)

(b) (4)

- iii. Detailed information on the drug product lot identified in the report provided to the Office of Compliance (b) (4)

This detailed information should include:

- a. (b) (4)
- b. The impact on dissolution
- c. The container closure system used
- iv. Release and stability data on the planned confirmatory batch manufactured (b) (4) that conforms to the (b) (4) acceptance criteria. At a minimum, we request 6 months of data on tablets held at both long term and accelerated conditions to determine if the stability data submitted in the NDA can be used as supportive for expiration dating purposes

- b. Environmental Assessment has not been adequately prepared

In order to allow for compliance with the EA requirements to support approval of this NDA in this cycle, you should submit a literature-based EA for conjugated estrogens, using data available on estrogens, estradiol equivalents and exposure models, in order to assess the risks to ecological species associated with this application. The EA can be updated in 2015 once the planned studies are completed.

- c. A test and acceptance criterion for [REDACTED] (b) (4) bazedoxifene in the drug product is needed

Review of your June 4, 2013 amendment is ongoing.

- d. Facilities inspections have been completed and the final recommendation is pending at this time

We will evaluate the stability data of the drug product [REDACTED] (b) (4) [REDACTED] to determine if the facility is capable of manufacturing a product of acceptable quality that conforms to application expectations.

- e. Inadequate information currently available related to bridging all formulations to the final to-be-marketed formulation

We await your planned June 20, 2013 submission for further review.

- f. The data available do not support approval of the conjugated estrogens 0.625 mg/ bazedoxifene 20 mg dose for any indication

[REDACTED] (b) (4)

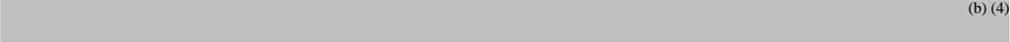
- g. The data available do not support approval of the proposed indication for treatment of moderate and severe vulvar and vaginal atrophy associated with menopause

[REDACTED] (b) (4)

- h. Content and reliability of data from Trial 303

Question to Pfizer/Wyeth: How were adverse events, reported to FDA on May 23, 2013, from a trial that was completed in 2006 uncovered seven years later? How can we assure that there was adequate capture and recording of adverse events in the conjugated estrogens/bazedoxifene development program, most notably in Trial 303?

3. Major labeling issues – 15 minutes

- All references to the product should be in conjugated estrogens/bazedoxifene format.
- Estrogen class labeling should be included in product labeling
- The approved indications should include “in women with a uterus”.
- Limiting use in patients aged > 75 years.
- Use is not recommended in patients with renal or hepatic impairment.
-  (b) (4)

4. Information Requests – 5 minutes

5. Postmarketing Requirements/Postmarketing Commitments – 5 minutes

No Postmarketing Requirements or Commitments have been identified at this time

6. Wrap up and Action Items – 5 minutes

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

/s/

HYLTON V JOFFE
06/14/2013