

**CENTER FOR DRUG
EVALUATION AND RESEARCH**

APPLICATION NUMBER:

21-864

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

21-864

NAME OF APPLICANT / NDA HOLDER

Wyeth

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

TRADENAME

ACTIVE INGREDIENT(S)

Levonorgesrel
Ethinyl Estradiol

STRENGTH(S)

90 ug
20 ug

DOSAGE FORM

Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

6,500,814

b. Issue Date of Patent

12/31/2002

c. Expiration Date of Patent

09/03/2018

d. Name of Patent Owner

Wyeth

Address (of Patent Owner)

5 Giralda Farms

City/State

Madison, New Jersey

ZIP Code


07940

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

e. **Name of agent or representative** who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

 General Counsel
Wyeth

Address (of agent or representative named in 1.e.)

5 Giralda Farms

City/State

Madison, New Jersey

ZIP Code

07940

FAX Number (if available)

Telephone Number

(973) 660-5000

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) 1, 2, 3 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) See, Attachment A


5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)	Date Signed
	5/5/05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Randall Brenner	
Address. 500 Arcola Road	City/State Collegeville, PA
ZIP Code 19426	Telephone Number (484) 865-3792
FAX Number (if available) (484) 865-9060	E-Mail Address (if available) Brenner1@wyeth.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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EXCLUSIVITY SUMMARY

NDA # 21-864

SUPPL # 000

HFD # 580

Trade Name Lybrel™

Generic Name levonorgestrel 90mcg/ethinyl estradiol 20mcg

Applicant Name Wyeth Pharmaceuticals, Inc.

Approval Date, If Known 22-MAY-2007

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:

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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 years

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).

NDA# 20-683

Alesse (levonorgestrel 100 mcg/ethinyl estradiol 20 mcg)

NDA#

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:

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"):

313-NA & 315-EU

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
IND # 65,693 YES ! NO
! Explain:

Investigation #2
IND # 65,693 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: John C. Kim, R.Ph., J.D.
Title: Regulatory Health Project Manager
Date: 22-MAY-2007

Name of Office/Division Director signing form: Daniel Shames, M.D., F.A.C.S.
Title: Deputy Office Director, ODEIII

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Daniel A. Shames
5/22/2007 02:38:01 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-864 Supplement Type (e.g. SE5): N/A Supplement Number: 000

Stamp Date: 27-MAR-2005 PDUFA Goal Date: 22-MAY-2007

HFD 580 Trade and generic names/dosage form: Lybrel™ (90 mcg levonorgestrel// 20mcg ethinyl estradiol) Tablets

Applicant: Wyeth Pharmaceuticals, Inc Therapeutic Class: 3010600 Oral Contraception

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
 No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
 Disease/condition does not exist in children
 Too few children with disease to study
 There are safety concerns
 Other: Safety and efficacy of Lybrel tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same for post pubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

NDA 21-864

Page 3

This page was completed by:

{See appended electronic signature page}

John C. Kim, R.Ph., J.D.

Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STAFF at 301-796-0700**

(Revised: 10/10/2006)

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On Original**

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___Partial Waiver ___Deferred ___Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

LNG/EE Continuous-Use

1.3 Administrative Amendment
1.3.3 Debarment Certification

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. 21-864 for LNG/EE Continuous-Use.

Signed: _____

 1/21/05

Henrietta Ukwu, M.D.
Vice President
Worldwide Regulatory Affairs

Appears This Way
On Original

Wyeth Pharmaceuticals
P.O. Box 8299
Philadelphia, PA 19101-8299

Robert DiGregorio, D.O.
— Director I
Global Regulatory Affairs
(484) 865-8424
digregr@wyeth.com



May 11, 2007

NDA 21-864
Levonorgestrel/Ethinyl Estradiol Continuous Use
Sequence No. 0049

Scott Monroe, M.D., Acting Director
Division of Reproductive and Urologic Products
Food and Drug Administration
Center for Drug Evaluation and Research
HFD 580, Room 18B-17
5901-B Ammendale Road
Beltsville, MD 20705-1266

**RE: Amendment to a Pending Application:
Proposed Post Marketing Commitment**

Dear Dr. Monroe:

Reference is made to NDA 21-864, submitted to the FDA on May 27, 2005, for Levonorgestrel 90µg/Ethinyl Estradiol 20µg, continuous use regimen, oral contraception. Reference is also made to our May 4, 2007, teleconference in which the FDA requested that Wyeth conduct a post marketing of thromboembolic events study among women prescribed Lybrel.

The purpose of this letter is for Wyeth to agree to conduct a study as a Phase IV commitment, upon approval of Lybrel™, as outlined below:

Description of Commitment – To conduct and submit a final study report for a post marketing study of thromboembolic events among women prescribed Lybrel, compared to women prescribed cyclic oral contraceptives containing 20 mcg ethinyl estradiol. This study will be a prospective claims database study and will enroll enough participants to achieve 80% power to detect a relative risk of 2.0.

Protocol Submission - Protocol submission within 60-days of approval.

Study Start – Within 4-months of product launch.

Study Status Update - Status updates to be provided annually.

Final Report – Within 5 years from start of this study. In the event that Lybrel uptake is lower than anticipated, Wyeth will negotiate an extension of the study timelines to achieve an adequate sample size.

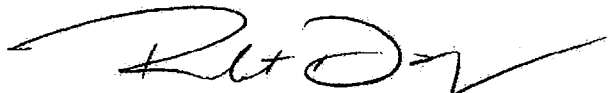
Wyeth

eCTD Information

This submission has been provided entirely in eCTD format; therefore, no table of contents has been provided. The FDA Viewer will display the content of the submission in its correct CTD location. Information related to the electronic format of this submission has been provided immediately after the signatory page.

If there are questions regarding this submission, please contact me at 484-865-8424 or Don Lewis, Manager, Global Regulatory Affairs at 484-865-8021.

Sincerely,



Robert DiGregorio, D.O., F.A.C.O.O.G.
Director I
Global Regulatory Affairs

CC. Mr. John Kim, R.Ph., J.D., Regulatory Health Project Manager

Appears This Way
On Original

DATE: May 11, 2007

INFORMATION ALERT
CONFIDENTIAL

SUBJECT/LEAD COMPONENT: On May 22, 2007 FDA plans to approve Wyeth Pharmaceutical's Lybrel™ (90 mcg levonorgestrel and 20 mcg ethinyl estradiol) Tablets, a continuous use oral contraceptive.

WHY THIS INFORMATION IS IMPORTANT FOR THE SECRETARY NOW: Lybrel™ will be the first continuous use oral contraceptive to be approved by FDA. This will have media interest.

SUMMARY OF ISSUE, BACKGROUND, AND DEPARTMENT RESPONSE/ACTION:

- LNG/EE combination pills have been previously marketed by Wyeth Pharmaceuticals and other firms for this indication at comparable or higher doses using monthly or extended regimens, but had not yet been approved for continuous use.
- Lybrel is a low dose combination oral contraceptive containing 28 days of LNG/EE tablets per pill pack to be taken continuously with no hormone free period between packs. This regimen differs from current oral contraceptives regimens which have a placebo or "pill free" period that usually lasts 4 or 7 days.
- Two one-year, Phase 3 studies were submitted with the NDA to support the efficacy and safety.
- Serious adverse events reported were consistent with those observed with other low dose oral contraceptives, i.e., deep venous thrombosis and pulmonary emboli, cholecystitis and uterine fibroids. The most common drug related adverse events were headache and nausea.
- The sponsor has agreed to a Phase IV Commitment to conduct a post-marketing study of thromboembolic events associated with this continuous use regimen.

CONTACT:

Tom Kuchenberg, OS ES, 202-205-8644
Lee Lemley, FDA/OEP 301-443-5392
Indya Mungo, FDA OES, 301-827-4440

Drafted: LLemley, 5/3/07

5/7/07

NDA 21-864

INFORMATION REQUEST

Wyeth Pharmaceuticals, Inc.
 Attention: Robert Digregorio, D.O.
 Director, Global Regulatory Affairs
 P.O. Box 8299
 Philadelphia, PA 19101-8299

Dear Dr. Digregorio:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lybrel (levonorgestrel/ethinyl estradiol).

We are reviewing your submission and have the following requests for information. We request that you provide a written response no later than 12 noon on Friday May 11, 2007.

1. In regard to Table 10.4.2.4-1 (page 160) of the final report for Study 313-NA, explain why the number of observations for the time point "posttreatment" is only 1179 if there were 2114 baseline measurements.
2. In Item 4 of our Information Request of May 4, 2007, we requested that you provide additional calculations similar to those represented in Table 10.4.2.4-1 (page 160) of the final report for Study 313-NA. Include in the requested tables an additional entry based on the change in the last on-treatment or first posttreatment value from baseline for all subjects for which a post baseline value is available. Also provide a similar calculation for the subjects represented in Table 10.4.2.4-1.
3. Provide "standard" shift tables for hemoglobin and hematocrit values for Study 313-NA and each treatment group in Study 315. In the shift tables include the time points of Pill Pack 7, Pill Pack (12, 13 or posttreatment), and last post baseline measurement.
4. Provide values for the following Table based on changes in hemoglobin concentrations from baseline. Provide a separate Table for Study 313-NA and each treatment group in Study 315.

Changes in Hemoglobin concentrations (baseline to last post baseline measurement)

Category (gms Hg/dl)	Number of subjects	Percent of total subjects
> 2.0		
2.0 to > 1.5		
1.5 to > 1.0		
1.0 to > 0.5		
0.5 to > 0.0		
0.0 to 0.0		
-0.5 to < 0.0		
-1.0 to < -0.5		
-1.5 to < -1.0		
-2.0 to < -1.5		
< -2.0		

NDA 21-864

Page 2

We ask that you email your responses to project managers John Kim (John.Kim@fda.hhs.gov) and Ayoub Suliman (Ayoub.Suliman@fda.hhs.gov). We also request that you formally submit your responses to the NDA.

If you have any questions, please call John Kim at 301-796-0932 or Ayoub Suliman at 301-796-0630.

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/s/

Ayoub Suliman
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CSO

2. For Table 4-7 (page 50) in the Advisory Committee Background Document, provide actual subject numbers and race for each subject. Provide similar information for the 4 subjects with an estimated date of conception that occurred within 14 days post-treatment.
3. Confirm that the data in Table 6-1 (page 66) in the Advisory Committee Background Document represents data from Study 313-NA only.
4. Provide Tables similar to that of Table 10.4.2.1.4-1 (page 160) of Final Report for Study 313-NA that are based on (1) only subjects who withdrew because of a bleeding-related AE and (2) all subjects who withdrew primarily because of bleeding (considered to be either an AE or because of subject choice not listed as an AE).
5. Provide in Table format the information represented in Figures SF 1-3, SF 1-4, SF 1-5, SF 1-6, SF 1-7, and SF 1-8. Several of the Figure headers appear to be incomplete. Figures SF 1-3 and SF 1-4 appear to be incomplete. For each of the requested Tables, also provide information for the final laboratory assessment in addition to that for Pill Packs 7 and 13.

If you have any questions, please call Ayoub Suliman at 301-796-0630 or John Kim at 301-796-0932.

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/s/

Ayoub Suliman
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

1/9/07

PDUFA GOAL DATE EXTENSION

NDA 21-864

Wyeth Pharmaceuticals
Attention: Robert DiGregorio, D.O., F.A.C.O.O.G.
Director, Global Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. DiGregorio:

Please refer to your August 21, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lybrel™ (levonorgestrel and ethinyl estradiol).

On December 22, 2006, we received your December 22, 2006, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is May 22, 2007.

If you have any questions, call John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 796-0932.

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 Kober

1/9/2007 02:46:06 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-864

Wyeth Pharmaceuticals
Attention: Robert DiGregorio, D.O., F.A.C.O.O.G.
Director I, WWRA (WHC)
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. DiGregorio:

Please refer to your May 27, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lybrel™ (levonorgestrel and ethinyl estradiol).

We also refer to the teleconference between representatives of your firm and the FDA on October 31, 2006. The primary purpose of this teleconference was to discuss the use of pooled data in the Lybrel efficacy analysis.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 796-0932.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Acting Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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MEMORANDUM OF TELECONFERENCE MINUTES

DATE: October 31, 2006 **TIME:** 11:30 am – 12:30 pm
PHONE NUMBER: 1-866-643-3861
APPLICATIONS: NDA 21-864
DRUG NAME: Lybrel™ (levonorgestrel and ethinyl estradiol)
SPONSOR: Wyeth Pharmaceuticals
TYPE OF MEETING: Type A, End-of-Review
MEETING CHAIR: Scott Monroe, M.D.
MEETING RECORDER: John Kim, R.Ph., J.D.

FDA PARTICIPANTS:

Daniel Shames, M.D. – Acting Deputy Director, Office of Drug Evaluation III
Scott Monroe, M.D. – Acting Director, Division of Reproductive and Urologic Products (DRUP)
Shelley R. Slaughter, M.D., Ph.D. – Medical Team Leader, DRUP
Phill Price, M.D. – Medical Officer, DRUP
Mahbood Sobhan, Ph.D. – Acting Team Leader, Division of Biometrics II
John Kim, R.Ph., J.D. – Regulatory Health Project Manager, DRUP

WYETH PARTICIPANTS:

Ginger Constantine, M.D. – Vice President, Clinical Research and Development
Gary Grubb, M.D, M.P.H. – Senior Director, Clinical Research and Development
Henrietta Ukwu, M.D. – Vice President, Global Regulatory Affairs (GRA)
Sam Maldonado, M.D. – Assistant Vice President, GRA
Robert DiGregorio, D.O. – Director I, Global Regulatory Affairs
Don Lewis M.S. – Manager, GRA
Bob Northington, Ph.D. – Director, Clinical Biostatistician
Kathleen Young, Ph.D. – Associate Director, Project Management

BACKGROUND:

The Sponsor received an approvable letter dated June 27, 2006, for NDA 21-864 (Lybrel™). The approvable letter included the following statement:

“Clinical issues remain unresolved. The three primary areas of concern are the pregnancy rate demonstrated in the US trial, the discontinuation rate, and the unpredictable bleeding pattern. Taken together, these three areas of concern create a questionable risk/benefit ratio for Lybrel. Therefore, we plan to convene a public meeting to receive input from external contraceptive experts and other stakeholders. We believe that this discussion is needed prior to making a final decision regarding the approvability of your application.”

Following this action, the Sponsor requested an End-of-Review teleconference to discuss the clinical concerns that prompted the Agency to seek an advisory committee meeting. The Sponsor subsequently submitted a detailed chronology of communications with the Division to support the Sponsor's intention to pool the efficacy data from the United States (313-NA) and European (315-EU) studies. Pooling of the efficacy data across the two studies would result in a slightly lower overall Pearl index for the combined studies than for the larger U.S. study alone. The Sponsor requested this additional teleconference to reach agreement on pooling of these data.

DISCUSSION POINTS

- Dr. Monroe stated that he did not intend to challenge the detailed chronology of events to support the pooling of U.S. and European data at this time because, in his opinion, pooling of the data was not the critical issue in the decision not to approve Lybrel™ during the first review cycle or in the decision to seek input and guidance from an Advisory Committee.
- The Division stated that pooling of data from U.S. and non-U.S. studies generally has been permissible to increase power and to provide an additional level of assurance when outcomes across studies are comparable. However, if the findings from the studies differ, as is the case in the Applicant's submission, the findings from each study are independently assessed to determine if they support the safety and effectiveness of the drug product. Trial 313-NA is much larger (includes more months of treatment) and has a higher Pearl Index and discontinuation rate and more unexpected/unplanned bleeding than the European trial.
- The Division further explained that the data from Study 315-EU have not been ignored, but the Division has given more importance to the findings from Study 313-NA because this study was considerably larger and the patient population is likely to be more relevant to the U.S. population that would use Lybrel should it be approved for marketing.
- The Applicant stated that the Pearl Index for NuvaRing® was similar to that for Lybrel, but was approved under similar circumstances where by the European data were more favorable than the U.S. data.
- Regarding the Advisory Committee (AC) meeting, the Applicant was informed that they could present the findings from 313-NA and 315-EU studies as an integrated analysis if they chose to do so, but that the Division will present the findings as individual trials. The Applicant can request another teleconference to discuss the logistics of the AC meeting. The Division does not believe at this time that the format of the AC meeting will deviate from the usual format of an AC meeting.

ACTION:

- Project Manager to convey meeting minutes within 30 days.

{See appended electronic signature page}

Scott Monroe, M.D.
Acting Director

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/s/

Scott Monroe
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MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: October 6, 2006

TO: John Kim, Regulatory Project Manager
Phil Price, M.D., Medical Officer
Division of Reproductive and Urologic Drug Products

THROUGH: Constance Lewin, M.D., M.P.H.
Chief, Good Clinical Practice Branch I (GCPB1, HFD-46)
Division of Scientific Investigations (DSI)

FROM: Roy Blay, Ph.D.
Reviewer, GCPB1, DSI, HFD-46

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-864

APPLICANT: Wyeth

DRUG: Lybrel™ (levonorgestrel/ethinyl estradiol)

PROTOCOL: 0858A2-313-NA, "A Phase 3, Multicenter, Open-label Study to Evaluate the Safety and Efficacy of Levonorgestrel 90µg and Ethinyl Estradiol 20µg in a Continuous Daily Regimen for Oral Contraception"

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Contraception

CONSULTATION REQUEST DATE: April 26, 2006

DIVISION ACTION GOAL DATE: October 13, 2006

PDUFA DATE: February 22, 2007

I. BACKGROUND

The indication for the investigational drug Lybrel™ is contraception. The drug is a combination of levonorgestrel and ethinyl estradiol. The primary study objective is to evaluate the safety and contraceptive efficacy of this combination drug in a continuous use regimen. Lybrel™ is not a New Molecular Entity.

The following sites were selected for inspection because of their relatively large enrollments and some concerns regarding the adequacy of their study records.

II. RESULTS (by site):

Name	City, Country	Protocol	Insp. Date	EIR Received Date	Final Classification
James Simon, M.D.	Laurel, MD	0858A2-313-NA	4-18 August 2006	18 Sep 06	VAI
Donald Edger, M.D.	Lexington, KY	0858A2-313-NA	18-24 July 2006	14 August 2006	VAI
James Maly, M.D.	Lincoln, NE	0858A2-313-NA	18-21 July 2006	21 August 2006	VAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations from regulations. Data unreliable.

Protocol # 0858A2-313-NA

1. Site No. 006604, 26 subjects

James Simon, M.D.
Women's Health Research Center
14201 Laurel Park Drive
Suite 104
Laurel, MD 20707

- a. The records of the 26 enrolled subjects were audited. The audit included, but was not limited to, review of the primary efficacy endpoint, diary cards, laboratory results, adherence to inclusion/exclusion criteria, adverse event reporting, informed consent, and drug accountability.
- b. There were no limitations to the inspection.
- c. The inspection revealed two instances of recordkeeping deficiencies (a missing consent form and an erroneous report to the IRB regarding the number of subjects enrolled) and two instances of delayed reporting of serious adverse events (pregnancy) to the sponsor.
- d. The data appear acceptable in support of the relevant indication.

2. Site No.002118, 22 Subjects
Donald Edger, M.D.
Central Kentucky Research
Associates, Inc.
3475 Richmond Road, 3rd floor
Lexington, KY 40509
 - a. The records for all 22 enrolled subjects were audited. The audit included, but was not limited to, review of the primary efficacy endpoint, adherence to inclusion/exclusion criteria, adverse event reporting, informed consent, and drug accountability.
 - b. There were no limitations to the inspection.
 - c. The inspection revealed some recordkeeping deficiencies involving diary card and case report form discrepancies and deviations from protocol involving follow up of increased cholesterol/triglyceride levels.
 - d. The data appear acceptable in support of the relevant indication.

3. Site No. 004421, 23 subjects
James Maly, M.D.
Women's Clinic of Lincoln, PC
220 Lyncrest Drive
Lincoln, NE 68510
 - a. All subjects' records were audited for informed consent. The number of subjects' records audited for data integrity was not stated in the EIR. The audit included, but was not limited to, review of the primary efficacy endpoint, adherence to inclusion/exclusion criteria, adverse event reporting, informed consent, and drug accountability.
 - b. There were no limitations on the inspection.
 - c. The inspection revealed that two subjects were at minimal risk for pregnancy (one subject used an additional contraceptive agent and the other subject had a partner with a vasectomy), a protocol violation. DSI recommends that the review division consider whether the data from these two subjects (#s 4401 and 4406) should be excluded from the safety and efficacy analyses.
 - d. With the possible exclusion of data from subjects 4401 and 4406 as noted above, the data appear acceptable in support of the relevant indication.

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III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL
RECOMMENDATIONS

The inspections of Drs. Simon, Edger, and Maly identified regulatory deficiencies related to protocol compliance and recordkeeping, as discussed above. DSI recommends that the review division consider excluding the data for subjects 4401 and 4406 at Dr. Maly's site, as they were at minimal risk for pregnancy; otherwise, the data appear acceptable in support of the respective indication.

No follow up activities are needed at this time.

{See appended electronic signature page}

Roy Blay, Ph.D.
Reviewer, Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

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/s/

Andrea Slavin
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Constance Lewin
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MEDICAL OFFICER
Roy Blay is on leave; Andrea Slavin finalized the
document and entered it into DFS on his
behalf.



NDA 21-864

ACKNOWLEDGEMENT LETTER

Wyeth Pharmaceuticals
Attention: Robert DiGregorio, D.O., F.A.C.O.O.G.
Director, Global Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. DiGregorio:

We acknowledge receipt on August 22, 2006, of your August 21, 2006, resubmission to your new drug application for Lybrel™ (levonorgestrel and ethinyl estradiol).

We consider this a complete, class 2 response to our June 27, 2006, action letter. Therefore, the user fee goal date is February 22, 2007.

If you have any question, call me at (301) 796-0932.

Sincerely,

{See appended electronic signature page}

John C. Kim, R.Ph., J.D.
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

John C. Kim
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-864

Wyeth Pharmaceuticals
Attention: Robert DiGregorio, D.O., F.A.C.O.O.G.
Director, Global Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. DiGregorio:

Please refer to your May 27, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lybrel™ (levonorgestrel and ethinyl estradiol).

We also refer to your August 9, 2006, correspondence, containing a chronology of communications that pertain to Wyeth's intent of using a combined analysis of the two Phase 3 studies, 0858A2-313-NA and 0858A2-315-EU, to support registration in the United States.

We further refer to your August 18, 2006, correspondence, received August 21, 2006, requesting a teleconference to discuss the contents of your August 9 submission. We have considered your request and concluded that the meeting is unnecessary because the contents of your submission do not require clarification.

If you have any questions, call John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 796-0932.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Acting Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Scott Monroe
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-864

Wyeth Pharmaceuticals
Attention: Robert DiGregorio, D.O., F.A.C.O.O.G.
Director I, WWRA (WHC)
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. DiGregorio:

Please refer to your May 27, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lybrel™ (levonorgestrel and ethinyl estradiol).

We also refer to the teleconference between representatives of your firm and the FDA on July 31, 2006. The purpose of this end of review teleconference was to discuss the June 27, 2006, approvable letter.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 796-0932.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D., F.A.C.S.
Acting Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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MEMORANDUM OF TELECONFERENCE MINUTES

DATE: July 31, 2006 **TIME:** 1 pm – 2 pm
PHONE NUMBER: 1-866-643-3861
APPLICATIONS: NDA 21-864
DRUG NAME: Lybrel™ (levonorgestrel and ethinyl estradiol)
SPONSOR: Wyeth Pharmaceuticals
TYPE OF MEETING: Type A, End-of-Review
MEETING CHAIR: Daniel Shames, M.D.
MEETING RECORDER: John Kim, R.Ph., J.D.

FDA PARTICIPANTS:

Daniel Shames, M.D. – Acting Deputy Director, Office of Drug Evaluation III
Scott Monroe, M.D. – Acting Director, Division of Reproductive and Urologic Products (DRUP)
Mark Hirsch, M.D. – Acting Deputy Director, DRUP
Shelley R. Slaughter, M.D., Ph.D. – Medical Team Leader, DRUP
Phill Price, M.D. – Medical Officer, DRUP
Leslie McKinney, Ph.D. – Pharmacology/Toxicology Reviewer, DRUP
Myong-Jin Kim, Pharm.D. – Clinical Pharmacology Reviewer, Office of Clinical Pharmacology
Mahbood Sobhan, Ph.D. – Acting Team Leader, Division of Biometrics II
Margaret Kober, R.Ph., M.P.A. – Chief, Project Management Staff, DRUP
John Kim, R.Ph., J.D. – Regulatory Health Project Manager, DRUP

WYETH PARTICIPANTS:

Ginger Constantine, M.D. – Vice President, Clinical Research and Development
Eileen Helzner, M.D. – Assistant Vice President, Clinical Affairs, Global Medical Affairs (GMA)
Gary Grubb, M.D., M.P.H. – Senior Director, Clinical Research and Development
Amy Marren, M.D., Director, Clinical Affairs, GMA
Lynne Smith, M.B.A. – Principal Biostatistician
Henrietta Ukwu, M.D. – Vice President, Global Regulatory Affairs (GRA)
Sam Maldonado, M.D. – Assistant Vice President, GRA
Robert DiGregorio, D.O. – Director I, Global Regulatory Affairs
Don Lewis M.S. – Manager, GRA
Simon Jenkins, Ph.D. – Sr. Director, Project Management
William McKeand, Ph.D. – Assistant Director

BACKGROUND:

The Sponsor requested this meeting in response to an approvable letter dated June 27, 2006, for NDA 21-864 (Lybrel™). The approvable letter indicated the following:

1. The application does not contain sufficient stability data to support approval of the product manufactured using the revised _____ method. Submit 3 months of real time and accelerated stability data on the three lots of drug product manufactured by the revised _____ method.
2. Clinical issues remain unresolved. The three primary areas of concern are the pregnancy rate demonstrated in the US trial, the discontinuation rate, and the unpredictable bleeding pattern. Taken together, these three areas of concern create a questionable risk/benefit ratio for Lybrel. Therefore, we plan to convene a public meeting to receive input from external contraceptive experts and other stakeholders. We believe that this discussion is needed prior to making a final decision regarding the approvability of your application.

b(4)

The purpose of this teleconference is to discuss the clinical concerns that prompted the Agency to seek an advisory committee meeting. The issue regarding stability data will be discussed in a separate meeting (*scheduled for August 15, 2006*).

DISCUSSION POINTS:

The discussions that follow were generated from the Sponsor's specific questions.

QUESTION#1: *What are the specific concerns prompting the Division to request an Advisory Committee Meeting?*

FDA Response: As stated in the approvable letter, the Agency has three main concerns that prompted the request of an Advisory Committee Meeting: efficacy issues, discontinuation rate, and cycle control.

Regarding efficacy

Reference was made to the March 8, 2006, meeting where concerns over 7 pregnancies were discussed in detail. The Sponsor provided additional data that included serum hCG and information on the timing of the pregnancies. After further review, the Agency agreed that the overall number of pregnancies was 23 rather than 30. This resulted in an overall Pearl Index (PI) of 2.38 with a 95% CI of 1.51 to 3.37 in the 313-NA trial. There were at least 15 method failures in women less than 35 years of age with a PI of 1.55 and an upper bound of the 95% CI as high as 2.56. The life analysis had an upper bound of the 95% CI of 5.5.

Regarding discontinuation rate

When reviewing only the 313-NA trial, the discontinuation rate was almost 58%. Of those who discontinued due to significant adverse events, 54% discontinued due to bleeding which is considered significant.

Regarding cycle control

The Agency noted that a purported rationale for the development of the Lybrel™ continuous regimen oral contraceptive was sustained amenorrhea for women taking this regimen for contraception. This was not the case in the US clinical trial and the number of subjects who bled through the trial was high for a product intended to provide sustained amenorrhea.

Regarding pooling of 313-NA and 315-EU data

The Sponsor inquired as to whether the Agency reviewed the Statistical Analysis Plan (SAP) for Study 313-NA and 315-EU describing the plan for a pooled analysis. The Agency stated that it could not locate any information prior to the submission of the November 8, 2004 SAP for 313-NA that described the Sponsor's intent to pool the data from the two trials to support efficacy of the drug product for registration in the US. The Agency asked the Sponsor to provide the explicit information that prior to the completion of the US study, the Sponsor had informed the Agency of their intent to support registration in the US with a combined primary efficacy analysis of Study 313-NA and 315-EU. The primary review team indicated that not only would the Sponsor have had to inform the Agency of their intent to pool the efficacy data from the two studies, but the Sponsor would have also had to prospectively define how the data would be pooled. The Sponsor indicated that a chronology for the plan to use the two trials will be submitted for review (*received August 11, 2006*). This submission will outline when the SAP documents were submitted to the FDA and when the studies were completed and unblinded. The Sponsor further indicated that their plan to pool data from the Studies 313-NA and 315-EU was indicated in the briefing document for the pre-NDA meeting and cancellation of this meeting by the Agency suggested the Agency had no concerns with this plan.

b(4)

Regarding submission of a complete response

The Agency clarified that the second cycle review begins once a complete response is received (i.e. when both deficiencies are addressed). Specifically, 1) the stability data and 2) the unresolved clinical concerns must be addressed. Because no new data or information is being requested for the clinical issues and because a decision depends on the Advisory committee results, a response addressing the chemistry issue could initiate the clock. Such a complete response would trigger result in a 6-month review if submitted prior to the Advisory Committee Meeting.

QUESTION#2: *What specific questions does the Division expect to ask of the Advisory Committee?*

FDA Response: The Agency cannot address this question at this time.

QUESTION#3: *Does the Division plan to present to the Advisory Committee additional analyses or sub-analyses of the data submitted in the NDA?*

FDA Response: The Agency cannot address this question at this time.

ACTION:

- The Sponsor is to provide a chronology detailing plans to combine the two studies. *(Submitted August 11, 2006)*
- The Agency will provide an update regarding the date of the Advisory Committee Meeting. *(December 2006 or January 2007)*
- Project Manager to convey meeting minutes within 30 days.

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/s/

Daniel A. Shames
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-864

Wyeth Pharmaceuticals
Attention: Frederick A. (Simon) Golec, Jr., Ph.D.
Director II, Global Regulatory Affairs - CMC
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Golec:

Please refer to your May 27, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lybrel™ (levonorgestrel and ethinyl estradiol).

We also refer to your July 18, 2006, correspondence requesting a Chemistry, Manufacturing and Controls (CMC) meeting to discuss the contents of the June 27, 2006, approvable letter for Lybrel™.

We further refer to the preliminary draft responses that were sent to you on August 7, 2006, and to the response from Dr. Marijo Doedée to Mr. John Kim, requesting to cancel the teleconference.

The preliminary draft comments have been fully vetted and will be the official minutes of our planned teleconference.

If you have any questions, call John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 796-0932.

Sincerely,

{See appended electronic signature page}

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

Enclosure

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE (PLANNED): March 8, 2006 **TIME:** 1 pm – 2:30 pm

TELECONFERENCE# (PLANNED): 1-800-643-3861
Pass code# 5383492

APPLICATION: NDA 21-864

DRUG NAME: Lybrel™ (levonorgestrel and ethinyl estradiol)

SPONSOR: Wyeth Pharmaceuticals

TYPE OF MEETING: Type A, End-of-Review CMC

MEETING RECORDER: John Kim, R.Ph., J.D.

FDA PARTICIPANTS (PLANNED):

Elaine Morefield, Ph.D. – Director, Pre-Marketing Assessment Division II (PMAD II),
Office of New Drug Quality Assessment (ONDQA)
Moo Jhong Rhee, Ph.D. – Branch Chief, PMAD II, ONDQA
Donna Christner, Ph.D. – Pharmaceutical Assessment Lead, PMAD II, ONDQA
Scott Monroe, M.D. – Acting Director, Division of Reproductive & Urologic Products (DRUP)
Shelley R. Slaughter, M.D., Ph.D. – Medical Team Leader, DRUP
Phill Price, M.D. – Medical Officer, DRUP
Ameeta Parekh, Ph.D. – Team Leader, Office of Clinical Pharmacology (OCP)
Myong-Jin Kim, Pharm.D. – Clinical Pharmacology Reviewer, OCP
Margaret Kober, R.Ph., M.P.A. – Chief, Project Management Staff, DRUP
John Kim, R.Ph., J.D. – Regulatory Health Project Manager, DRUP

WYETH PARTICIPANTS (PLANNED):

Joseph De Vito, Ph.D. – Vice President, Women's Health Quality
Parimal Desai, Ph.D. – Vice President, Pre-Clinical Development
Marijō Doëdée, Ph.D. – Associate Director, Global Regulatory Affairs, Conformance
Frederick A. (Simon) Golec Jr., Ph.D. – Director II, Global Regulatory Affairs, CMC
Nirdosh Jagota, Ph.D. – Assistant Vice President, Worldwide Regulatory Affairs, CMC
Allan Kutz, Ph.D. – Assistant Vice President, Analytical and Quality Sciences
Phil Mayer, Ph.D. – Assistant Vice President, Clinical Pharmacology
Arwinder Nagi, Ph.D. – Senior Director, Pharmaceutical Development

BACKGROUND:

The Sponsor requested this meeting at the end of first cycle NDA review of Lybrel™ in response to the Approvable Letter dated June 27, 2006. The Sponsor is seeking guidance for plans to submit 3 months of real time and accelerated stability data on three lots of drug product manufactured by the revised _____ method.

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DISCUSSION POINTS:

The sponsor has asked the following questions in the meeting package:

QUESTION#1: *Wyeth will be updating the analytical methods to clearly describe the procedure for identifying and quantifying, as appropriate, the known leachables. Does the FDA concur that Wyeth can submit these updated methods along with the requested stability data?*

FDA response: Yes.

QUESTION#2: *Acknowledging that the FDA has not reviewed the May 22, 2006 amendment to the NDA, Wyeth would like to discuss the justification for reverting to the USP dissolution method for the _____ product. Would the FDA agree to have this discussion?*

FDA response: Upon reviewing the May 22, 2006, amendment, we agree that your justification for reverting to the USP dissolution method with the tighter acceptance criteria of NLT (Q) in 30 minutes for both levonorgestrel (LNG) and ethinyl estradiol (EE) is acceptable. Therefore, further discussion is unnecessary.

QUESTION#3: *Acknowledging the significant decrease in EE strength observed upon storage under ICH light conditions, Wyeth proposes to add a _____ statement to the labeling. Does the FDA concur?*

FDA response: If the 3 month stability data does not show a significant decrease in EE strength, addition of a _____ statement to the labeling would be adequate. We request that you submit a color mock-up of the labels for the container and carton.

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/s/

Moo-Jhong Rhee
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Chief, Branch III

7/28/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-864

Wyeth Pharmaceuticals
Attention: Frederick A. (Simon) Golec, Jr., Ph.D.
Director II, Global Regulatory Affairs - CMC
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Golec:

Please refer to your May 27, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lybrel™ (levonorgestrel and ethinyl estradiol).

We also refer to your July 18, 2006, correspondence, received July 19, 2006, requesting a Chemistry, Manufacturing and Controls (CMC) meeting to discuss the contents of the June 27, 2006, approvable letter for Lybrel™.

Based on the statement of purpose, objectives, and proposed agenda, we consider the teleconference a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The teleconference is scheduled for:

Date: August 15, 2006
Time: 12 noon – 1 pm
Call-in number: 1-866-643-3861
Passcode: 5383492

CDER Participants: Drs. Elaine Morefield, Moo Jhong Rhee, Donna Christner, Scott Monroe, Shelley R. Slaughter, Phill Price, Ameeta Parekh, Myong-Jin Kim; Ms. Margaret Kober and Mr. John Kim.

We acknowledge that the background information for this meeting was provided with your meeting request.

If you have any questions, call me at (301) 796-0932.

Sincerely,

{See appended electronic signature page}

John C. Kim, R.Ph., J.D.
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

John C. Kim

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7/18/06



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-864

Wyeth Pharmaceuticals
Attention: Robert DiGregorio, D.O., F.A.C.O.O.G.
Director I, WWRA (WHC)
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. DiGregorio:

Please refer to your May 27, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lybrel™ (levonorgestrel and ethinyl estradiol).

We also refer to your July 10, 2006, correspondence, received July 11, 2006, requesting an end of review teleconference to discuss the June 27, 2006, approvable letter for Lybrel™.

Based on the statement of purpose, objectives, and proposed agenda, we consider the teleconference a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The teleconference is scheduled for:

Date: July 31, 2006
Time: 1 pm – 2 pm
Call-in number: 1-866-643-3861
Passcode: 5383492

CDER Participants: Drs. Daniel Shames, Scott Monroe, Shelley R. Slaughter, Phill Price, Donna Christner, Leslie McKinney, Ameeta Parekh, Myong-Jin Kim, Mahboob Sobhan; Ms. Margaret Kober and Mr. John Kim.

We acknowledge that the background information for this meeting was provided with your meeting request.

If you have any questions, call me at (301) 796-0932.

Sincerely,

{See appended electronic signature page}

John C. Kim, R.Ph., J.D.
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

John C. Kim

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MEMORANDUM OF TELECONFERENCE

DATE: May 4, 2006

APPLICATION NUMBER: NDA 21-864

DRUG NAME: Lybrel™ (levonorgestrel and ethinyl estradiol)

PHONE NUMBER: 1-888-895-4286 Passcode # 829598

BETWEEN:

Wyeth Pharmaceuticals Inc.

Ferdinando Aspesi – Senior Vice President, Global Regulatory Conformance, CMC, Compliance Audit

Joseph De Vito, Ph.D. – Vice President, Women’s Health Quality

Parimal Desai, Ph.D. – Vice President, Pre-Clinical Development

Marijo Doedée, Ph.D. – Associate Director, Worldwide Regulatory Affairs, CMC

Nirdosh Jagota, Ph.D. – Assistant Vice President, Worldwide Regulatory Affairs, CMC

Phil Mayer, Ph.D. – Assistant Vice President, Clinical Pharmacology

Richard Saunders, Ph.D. – Assistant Vice President, Pharmaceutical Development

Dominic Ventura, Ph.D. – Vice President, Global Technical Services

Henrietta Ukwu, M.D. – Vice President, Worldwide Regulatory Affairs

AND:

FDA

Elaine Morefield, Ph.D. – Director, Division of Pre-Marketing Assessment II (DPMA II), Office of New Drug Quality Assessment (ONDQA)

Donna Christner, Ph.D. – Chemistry Reviewer, DPMA II, ONDQA

Ameeta Parekh, Ph.D. - Team Leader, Office of Clinical Pharmacology, OCP

Julie Bullock, Pharm.D. - Clinical Pharmacology Reviewer, OCP

Jayabharathi Vaidyanathan, Ph.D. - Clinical Pharmacology Reviewer, OCP

Leslie McKinney, Ph.D - Pharmacology/Toxicology Reviewer, DRUP

Margaret Kober, R.Ph., M.P.A. - Chief, Project Management Staff, DRUP

John Kim, R.Ph., J.D. - Regulatory Health Project Manager, DRUP

SUBJECT:

To discuss the denial of the biowaiver requested by Wyeth on March 23, 2006, and to discuss Wyeth’s proposal to revert to the _____ manufacturing process.

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DISCUSSION:

Biopharmaceutics Classification System (BCS) Response

- For Lybrel to be classified as a BCS class I, it must meet three criteria: high permeability, high solubility, and rapid dissolution as described in the Guidance entitled, "Waiver of *In-vivo* Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System." FDA explained that Lybrel cannot be classified as a BCS class I product based on following:

1) Criteria # 1: Permeability

As per Guidance:

"In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered to be *highly permeable* when the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose."

Conclusion: Levonorgestrel: Highly permeable
Ethinyl Estradiol: *Not* highly permeable

Rationale:

- The key concern for EE is its chemical instability in gastric pH.
- The absolute bioavailability (BA) is low (40-60%).
- Mass balance data shows >90% is recovery of total radioactivity. Because this molecule degrades in acidic medium, it is likely that there may be more than one radiolabeled species in the gastrointestinal (GI) lumen before or during permeation across the membrane and therefore what we see in the urine cannot be attributed to the permeation of the parent moiety.
- In vitro permeability data shows that it is highly permeable but raises doubts, since it shows pH dependency. (done at pH 6 and 7.4, therefore did not evaluate the potential effect of GI instability)

2) Criteria #2: Solubility - *Acceptable* for both components.

3) Criteria # 3: Dissolution

As per Guidance:

"An immediate release drug product is considered rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves within 30 minutes, using U.S. Pharmacopeia (USP) Apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 900 ml or less in each of the following media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes."

Conclusion: Product *not* rapidly dissolving

Rationale: The dissolution medium for both drugs contains _____ and also that EE degrades in HCl makes the product ineligible to be classified as rapidly dissolving.

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- In summary, high permeability had not been demonstrated for ethinyl estradiol and the Lybrel tablet could not be considered rapidly dissolving.
- The Sponsor requested a written assessment for the review of the biowaiver request

Proposal to Revert to Direct Compression

- The Sponsor proposed to revert to the _____ manufacturing process, including minor process improvements and PAT, and the associated USP dissolution method. The Sponsor explained that the following information will be provide to the FDA on May 22, 2006:
 - 1) Certificates of analysis for three (3) batches to be manufactured using the improved _____ manufacturing process;
 - 2) Up to 36 months supportive stability data on clinical batch A22646 packaged in _____ blisters; and
 - 3) Updated CTD sections to reflect the change in the manufacturing process and equipment, as appropriate, including updated composition, specifications, and stability sections.

In addition, the Sponsor will provide one-month stability data on the three batches above packaged in the Single Unit Dispensers proposed for the to-be-marketed product by June 22, 2006, which is five days prior to the goal date of June 27, 2006.

- FDA indicated that Sponsor's proposal for improved _____ process, including incorporation of PAT, seemed to be acceptable Level 2 changes under SUPAC-IR changes. However, FDA could not agree to Sponsor's proposal to revert to the USP dissolution method because currently proposed pH _____ buffer dissolution is more discriminating and has been used to monitor manufacturing changes. FDA requested that the Sponsor provide justification for changing the dissolution method for review.
- FDA suggested that a link to Sponsor's currently marketed product manufactured by a _____ process would be supportive information that should be included in the May 22, 2006, amendment.
- FDA explained that there were three possible scenarios when major amendments are receive within 90 days of the goal date: 1) review submissions within the time frame, 2) extend the clock, and 3) defer review of submissions until the next cycle. FDA further explained that an extension of the review clock was not possible because an extension has already been granted.

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ACTION ITEM:

- Will provide a written assessment for the denial of BCS Class 1 designation for ethinyl estradiol. *A written assessment was faxed to the Sponsor on May 5, 2006.*
- Sponsor will submit justification for using USP dissolution method for consideration. *Justification was submitted via email on May 9, 2006, and was submitted officially as part of May 22, 2006, amendment.*
- The teleconference minutes will be conveyed to the Sponsor within 30 days.

John C. Kim, R.Ph., J.D.
Regulatory Project Manager

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John C. Kim
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-864

Wyeth Pharmaceuticals
Attention: Robert DiGregorio, D.O., F.A.C.O.O.G.
Director I, WWRA (WHC)
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. DiGregorio:

Please refer to your May 27, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lybrel™ (levonorgestrel and ethinyl estradiol).

We also refer to the meeting between representatives of your firm and the FDA on March 8, 2006. The purpose of the meeting was to discuss the Discipline Review Letters dated February 23, 2006 and March 1, 2006.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0932.

Sincerely,

{See appended electronic signature page}

John C. Kim, R.Ph., J.D.
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 8, 2006 **TIME:** 1 pm – 2:30 pm

LOCATION: Food and Drug Administration
White Oak Building 22, Room 1417
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

APPLICATIONS: NDA 21-864

DRUG NAME: Lybrel™ (levonorgestrel and ethinyl estradiol)

SPONSOR: Wyeth Pharmaceuticals

TYPE OF MEETING: Type C, Guidance

MEETING RECORDER: John Kim, R.Ph., J.D.

FDA PARTICIPANTS:

Daniel Shames, M.D. – Director, Division of Reproductive & Urologic Products (DRUP)
Scott Monroe, M.D. – Deputy Director, DRUP
Shelley R. Slaughter, M.D., Ph.D. – Medical Team Leader, DRUP
Phill Price, M.D. – Medical Officer, DRUP
Barbara Wesley, M.D. – Medical Officer, DRUP
Ameeta Parekh, Ph.D. – Team Leader, Office of Clinical Pharmacology (OCP)
John Hunt – Acting Division Director DCP III, OCP
Julie Bullock, Pharm.D. – Clinical Pharmacology Reviewer, OCP
Elaine Morefield, Ph.D. – Director, Pre-Marketing Assessment Division II (PMAD II),
Office of New Drug Quality Assessment (ONDQA)
Moo Jhong Rhee, Ph.D. – Branch Chief, PMAD II, ONDQA
Donna Christner, Ph.D. – Chemistry Reviewer, PMAD II, ONDQA
Mahbood Sobhan, Ph.D. – Statistician, Division of Biometrics II
Margaret Kober, R.Ph., M.P.A. – Chief, Project Management Staff, DRUP
Ayoub Suliman, Pharm.D. – Regulatory Health Project Manager, DRUP
John Kim, R.Ph., J.D. – Regulatory Health Project Manager, DRUP

WYETH PARTICIPANTS:

Bruce Burlington, M.D. – Executive Vice President, Regulatory Compliance
Henrietta Ukwu, M.D. – Vice President, Worldwide Regulatory Affairs
Ginger Constantine, M.D. – Vice President, Clinical Research and Development
Gary Grubb, M.D., M.P.H. – Senior Director, Clinical Research and Development
Robert DiGregorio, D.O. – Director, Worldwide Regulatory Affairs
Sebastian Mirkin, M.D. – Director, Clinical Research and Development
Sheila Ronkin, M.D. – Director, Clinical Research and Development
Lynne Smith – Senior Biostatistician, Clinical Biostatistics
Joseph De Vito, Ph.D., Vice President, Women's Health Quality

Parimal Desai, Ph.D. – Vice President, Pre-Clinical Development
Marijo Doedée, Ph.D. – Associate Director, Worldwide Regulatory Affairs, CMC
Frederick A. (Simon) Golec Jr., Ph.D. – Director II, Worldwide Regulatory Affairs, CMC
Nirdosh Jagota, Ph.D. – Assistant Vice President, Worldwide Regulatory Affairs, CMC
Allan Kutz, Ph.D. – Assistant Vice President, Analytical and Quality Sciences
Phil Mayer, Ph.D. – Assistant Vice President, Clinical Pharmacology
Anvinder Nagi, Ph.D. – Senior Director, Pharmaceutical Development
Richard Saunders, Ph.D. – Vice President, Pharmaceutical Development
Domenic Ventura, Ph.D. – Vice President, Global Technical Services

BACKGROUND:

The Sponsor requested this meeting during the NDA review of Lybrel™ in response to the Discipline Review Letter dated February 23, 2006 and teleconference of February 23, 2006 for clinical issues, and Discipline Review Letter dated March 1, 2006 for CMC issues. The clinical review expressed concerns regarding a high Pearl Index. The clinical review team is concerned that the Sponsor-reported Pearl Index in the application is high at 1.93 and 2.38, respectively for the total population and the efficacy population of women less than or equal to 35 at the start of the study. Further, the identification of eight additional pregnancies, which the reviewers believe may have occurred during the “on treatment” time frame, leads to an even higher Pearl Index. Adding to the Division’s concern regarding this product, which was intended to provide contraception and sustained amenorrhea, is the high discontinuation rate of 56.8% in the primary efficacy trial, which is substantially greater than any discontinuation rate seen in previous trials for prevention of pregnancy, and the high percentage (40%) of subjects in this trial who were still bleeding and or spotting at 1 year.

The CMC review letter requested that bioequivalence should be addressed because the manufacturing change from _____ that support the NDA has been determined to be a Level 3 change.

DISCUSSION POINTS:

The Sponsor presented PowerPoint presentation, which are attached. The discussions that follow were generated in response the Discipline Review Letters dated February 23, 2006 and March 1, 2006.

CLINICAL

1. Additional Pregnancies

In the Clinical Discipline Review Letter dated February 23, 2006, the Sponsor was informed that:

1. We have determined that in Study 0858A2-313NA some additional pregnancies, beyond those pregnancies counted by you, should be considered as having occurred during the period of time identified as “On-Treatment” (medicine stop date + 14 days). These include two pregnancies (for subjects 313-067-5924 and 313-091-8347), identified by you as pre-treatment pregnancies, for which no documentation of return of test article was made. Without the return of test article, no verification can be made that the subject

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did not take the contraceptive drug product and did not conceive while using said medication. Another pregnancy (for subject 313-074-6604) was included because the stop date of the medication was ambiguous and thus the "On-treatment" time period was ambiguous. Finally, we have included four pregnancies (for subjects 313-034-2607, 313-001-8578, 313-011-0323, and 313-052-4421) for which serum beta hCG testing and ultrasound evaluation puts the probable date of conception within the "On-Treatment" time period. The resultant re-calculated (with the additional 7 pregnancies) Pearl Index of 2.89 and failure rate (from life table analysis) of 4.2% are unacceptably high.

In the teleconference of February 23, 2006, the Sponsor was informed regarding additional pregnancy that the Division felt to be problematic.

Wyeth Discussion:

- The Pearl Index is 1.33 based on a pooled analysis of data from 313-NA and 315-EU studies for the total population studied and including only those pregnancies which occurred between the start of the study drug and stop of study.
- The time period for consideration of pregnancies as occurring on treatment should be between the start of the study drug and stop of study drug because this is the way it was done in the past (prior to 1999).
- The original plan was to calculate the Pearl Index for subjects who had a pregnancy on therapy not including those pregnancies that occurred from the time the study drug was stopped up to 14 days post treatment.
- Although the 313-NA Statistical Analysis Plan (SAP,) dated 8 November 2004, refers to "include 14 days" for efficacy assessment, this SAP was submitted erroneously.

DRUDP Discussion:

- Although no pre-NDA meeting was held with the sponsor to discuss the submission, the study report for Study 313-NA clearly states that the primary efficacy variable was the number of on-therapy pregnancies.
- Further with respect to efficacy, the study report states that pregnancies were classified as on-therapy when the EDC occurred between the start of study drug and 14 days after stopping study drug.

Wyeth Discussion:

- We acknowledge that the primary efficacy variable as written in the study report includes the on-therapy time period as the period between the start of study drug and 14 days after stopping the study drug.
- Data from the ovulation suppression study 0858A2-208 support the premise that no ovulations occur before 8 days after discontinuing the test article. The report presented in figure 9.4.2.2-1 of the 208 CSR does not reflect ovulation, but rather the maximum follicle size.
- ——— Wyeth's consultant, stated that he did not believe that ovulation occurring within 14 days post the stop of the study drug should be attributed to *method failure*.
- We believes that Lybrel™ is comparable to other approved products based on the presented a comparison table of the Pearl Index calculations (see attachment).

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- Wyeth always intended to pool the data from both 313-NA and European 315-EU studies.

DRUP Discussion:

- The clinical team believes that any ovulation (and thus pregnancy) that occurs before 14 days post-stop of the study drug is likely due to weak suppression and the initiation of follicular development while on study drug; we would have to review the data on study 208 CSR but the Sponsor's report of the findings are not inconsistent with the preceding premise.
- We would like to ask _____ why he believes there are so many method failures with this drug product.

Wyeth Discussion – _____

- I do not have an explanation; the dose (LNG 90 mcg) should be high enough to be efficacious.

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DRUP Discussion:

- The clinical team's understanding is that only 313-NA study was intended to support registration in the US; therefore only 313-NA is being considered for efficacy assessment and;
- we request that the Sponsor provide the Division with the location of the citations that explicitly states Wyeth's intent to pool study 313-NA and 315-EU for purposes of registering the drug product in the United States. The Sponsor agreed.

Wyeth Discussion:

- We agree to provide the documentation.
- We will discuss the following eight questionable pregnancies including information previously presented to the Agency and *new* source data that the Agency has not seen
 - 313-029-2118 – this subject was never pregnant and the site erred by confusing this subject with subject 313-029-2127.
 - 313-067-5924 and 313-091-8347 were identified as pre-treatment pregnancies; these subjects never took the study drug and provided information to support this.
 - 313-074-6604 – Subject received 3 pill cycles on 9 March 2004 but did not return diaries or TA; new source documents support that subject stopped on 31 May 2004 and became pregnant _____ after discontinuation.
 - 313-034-2607 – New source document data support conception at _____ after last dose.
 - 313-001-8578 – New source document data support conception at _____ after last dose.
 - 313-011-0323 – This was a protocol violation because subject missed 2 doses in the last cycle and new source document data support conception at _____ after last dose.
 - 313-052-4421 – New source document data support conception at _____ after last dose.

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DRUP Discussion:

- Were subjects informed to return unused study drug and do you have documentation that you asked them to return the study drug?
- We request that you formally submit all new source document data and we will review.

Wyeth Discussion:

- Subjects were informed to return TA but never returned for their follow-up visit.

2. Discontinuation Rate

The following concern was conveyed Clinical Discipline Review Letter dated February 23, 2006:

2. As reported by you, the discontinuation rate of subjects from the primary "proof of efficacy" trial, Study 0858A2-313NA is 56.8%. This rate of discontinuation is the highest rate that we have seen for a trial of oral contraceptives. The usual rate of discontinuation in the "proof of efficacy" studies for 28-day regimen (21-day active combination drug product) oral contraceptives ranges between 20 – 35%. The discontinuation rate for the only approved drug product with an extended, 91-day cycle regimen was 40.6%. We find the rate of discontinuation from the "proof-of-efficacy trial for Lybrel™ to be very concerning.

Wyeth Discussion:

- The discontinuation rate cited by the FDA (56.8%) was not accurate; when both studies (313NA and 315EU) are combined, the discontinuation rate is calculated as 49.6%, which is comparable to Nordette® 52.6%, Mircette® 47%, and Alesse® 48.6% at one year.
- We will provide the bases for these discontinuation rates.

Time did not allow for further discussion.

3. Bleeding Rates

The following concern was also conveyed Clinical Discipline Review Letter dated February 23, 2006:

3. The cycle control, in the form of sustained amenorrhea, for this continuous use oral contraceptive is considered to be poor. Forty percent of subjects still had unanticipated bleeding in the form of bleeding or spotting at the end of one year of use. This apparently poor cycle control in a continuously administered oral contraceptive, which was developed to minimize cyclical bleeding, is concerning.

Time did not allow for further discussion.

CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)

In the CMC Discipline Review Letter dated on March 1, 2006, the Sponsor was informed that:

We have determined that the manufacturing change for Lybrel™ that is covered in your NDA (_____) has been determined to be a Level 3 change in accordance with the Agency's guidance entitled, "Guidance for Industry – Immediate Release Solid Oral Dosage Forms

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– Scale-Up and Postapproval Changes; Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and Documentation,” [see Section VI. (MANUFACTURING), Part B (Process), Item 3 (Level 3 Changes)]. As such, appropriate Test Documentation (Item 3. b. iii.) related to bioequivalence needs to be addressed.

The Sponsor indicated that data submitted on March 6, 2006 (Sequence No. 0013) to demonstrate that levonorgestrel/ethinyl estradiol produced by the _____ manufacturing processes are similar. The Sponsor made the following claims in their presentation:

- levonorgestrel and ethinyl estradiol are Biopharmaceutics Classification System (BCS) Class 1 drug substances (FDA stated data needs to be submitted to support this claim)
- no changes to the drug substances have been made when changing from _____
- similar tablet composition is used for both manufacturing processes
- similar particle size distributions of the blends is obtained from both manufacturing processes (FDA stated the particle size distribution has changed which is the purpose of using a _____ method)
- similar porosity and disintegration times are observed for tablets manufactured by both processes
- similar *in vitro* dissolution multi-media profiles are obtained for tablets manufactured by both processes

FDA expressed that a major concern is the solubility of levonorgestrel, which is not very soluble. More data is need. FDA requested that the Sponsor provide data to support the Biopharmaceutics Classification of levonorgestrel and ethinyl estradiol as BCS Class 1 (high solubility/high permeability/rapid dissolution) in accordance *Guidance for Industry – Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System*. This data must be reviewed by the Biopharmaceutics Classification System Coordination Committee for a BCS Class 1 designation for this combination product.

ACTION:

- The Sponsor is to provide the location of the statement supporting the intent to combine both studies for purposes of US registration.
- The Sponsor is to formally submit all new source data to the NDA for review by the Agency.
- The sponsor will submit data for review by the Biopharmaceutics Classification System Coordination Committee for a BCS Class 1 designation for this combination product. *Data for BCS Class 1 determination was submitted on March 24, 2006.*
- Project Manager to convey meeting minutes within 30 days.

ATTACHMENT: Slide Presentation

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 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-_____

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/s/

John C. Kim

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MEMORANDUM OF TELECONFERENCE

DATE: January 31, 2006

APPLICATION NUMBER: NDA 21-864

DRUG NAME: Lybrel™ (levonorgestrel and ethinyl estradiol)

PHONE NUMBER: 1-888-895-4286 Passcode # 829598

BETWEEN:

Wyeth Pharmaceuticals Inc.

Luis Collazo - Oral Contraceptives Primary Processing Unit, Technology Leader
 Joseph De Vito, Ph.D. - Vice President, Women's Health Quality
 Marijo Doedée, Ph.D. - Associate Director, Worldwide Regulatory Affairs, CMC
 Frederick A. (Simon) Golec, Ph.D. - Director II, Worldwide Regulatory Affairs, CMC
 Nirdosh Jagota, Ph.D. - Assistant Vice President, Worldwide Regulatory Affairs, CMC
 Allan Kutz, Ph.D. - Assistant Vice President, Analytical and Quality Sciences
 Phil Mayer, Ph.D. - Assistant Vice President, Clinical Pharmacology
 Arwinder Nagi, Ph.D. - Senior Director, Pharmaceutical Development
 Richard Saunders, Ph.D. - Assistant Vice President, Pharmaceutical Development
 Dominic Ventura, Ph.D. - Vice President, Global Technical Services
 Robert DiGregorio, O.D. - Director I, Worldwide Regulatory Affairs, WHC
 Henrietta Ukwu, M.D. - Vice President, Worldwide Regulatory Affairs

AND:

FDA

Moo-Jhong Rhee, Ph.D. - Branch Chief, Pre-Marketing Assessment Division II (PMAD II),
 Office of New Drug Quality Assessment (ONDQA)
 Donna Christner, Ph.D. - Pharmaceutical Assessment Lead, PMAD II, ONDQA
 Shelley R. Slaughter, M.D., Ph.D. - Medical Team Leader, Division of Reproductive and
 Urologic Products (DRUP)
 Ameeta Parekh, Ph.D. - Team Leader, Office of Clinical Pharmacology (OCP)
 Julie Bullock, Pharm.D. - Pharmacokinetics Reviewer, OCP
 John Kim, R.Ph., J.D. - Regulatory Health Project Manager, DRUP

SUBJECT:

To discuss recent amendments submitted to demonstrate the similarity of commercial manufacturing process validation batches and the primary stability batches, as well as a proposal to change the dissolution specification for method _____ submitted in amendments dated November 28, 2005 and December 21, 2005.

b(4)

DISCUSSION:

FDA expressed concerns over the dissolution data that were submitted. Comparison of dissolution profiles after 3 months at room temperature and 3 months accelerated dissolution showed significant changes that raise a question of whether the marketed product would be therapeutically equivalent to the clinical batch. FDA could not agree to Sponsor's proposal to set new specifications without reviewing additional data.

FDA proposed two options to Sponsor:

1.) Revert to the _____ manufacturing process used for the primary registration stability batches and the NDA review could continue based on those data. **b(4)**

2.) To remain with the _____ manufacturing process, Sponsor must provide acceptable similarity factor comparisons on the September 2005 validation batches at the time of release and after storage at room temperature and accelerated conditions. This information needs to be provided to FDA in an expedited manner and, depending upon the information and timing of this amendment, FDA will make a determination of categorizing this as a minor amendment without affecting the review clock or a major amendment which may affect the review clock. **b(4)**

An amendment dated February 8, 2006 confirmed Sponsor's agreement to revert to the manufacturing process used to manufacture clinical and primary registration batches.

Moo-Jhong Rhee, Ph.D.
Meeting Chair

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Moo-Jhong Rhee
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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-864

DISCIPLINE REVIEW LETTER

Wyeth Pharmaceuticals
Attention: Frederick A. (Simon) Golec, Jr., Ph.D.
Director, Worldwide Regulatory Affairs, CMC
401 North Middletown Road
Pearl River, NY 10965

Dear Dr. Golec:

Please refer to your May 27, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lybrel™ (levonorgestrel and ethinyl estradiol).

We also refer to your submissions dated November 28, December 21, 2005 and February 8, 2006.

The chemistry review of your application is ongoing. At this point in our review, we have identified the following area of concern:

1. We have determined that the manufacturing change for Lybrel™ that is covered in your NDA _____ has been determined to be a Level 3 change in accordance with the Agency's guidance entitled, "*Guidance for Industry - Immediate Release Solid Oral Dosage Forms - Scale-Up and Postapproval Changes; Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and Documentation*," [see Section VI. (MANUFACTURING), Part B (Process), Item 3 (Level 3 Changes)]. As such, appropriate Test Documentation (Item 3. b. iii.) related to bioequivalence needs to be addressed.

b(4)

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 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 John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, at 301-796-0932.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D., F.A.C.S.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-864

DISCIPLINE REVIEW LETTER

Wyeth Pharmaceuticals
Attention: Robert DiGregorio D.O., F.A.C.O.O.G.
Director I, WWRA (WHC)
P.O. Box. 8299
Philadelphia, PA 19101-8299

Dear Dr. DiGregorio:

Please refer to your May 27, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lybrel™ (levonorgestrel and ethinyl estradiol).

We also refer to your submissions dated February 7 and 21, 2006.

The review of your application is ongoing. At this point in our review, we have identified the following areas of concerns:

1. We have determined that in Study 0858A2-313NA some additional pregnancies, beyond those pregnancies counted by you, should be considered as having occurred during the period of time identified as "On-Treatment" (medicine stop date + 14 days). These include two pregnancies (for subjects 313-067-5924 and 313-091-8347), identified by you as pre-treatment pregnancies, for which no documentation of return of test article was made. Without the return of test article, no verification can be made that the subject did not take the contraceptive drug product and did not conceive while using said medication. Another pregnancy (for subject 313-074-6604) was included because the stop date of the medication was ambiguous and thus the "On-treatment" time period was ambiguous. Finally, we have included four pregnancies (for subjects 313-034-2607, 313-001-8578, 313-011-0323, and 313-052-4421) for which serum beta hCG testing and ultrasound evaluation puts the probable date of conception within the "On-Treatment" time period. The resultant re-calculated (with the additional 7 pregnancies) Pearl Index of 2.89 and failure rate (from life table analysis) of 4.2% are unacceptably high.
2. As reported by you, the discontinuation rate of subjects from the primary "proof of efficacy" trial, Study 0858A2-313NA is 56.8%. This rate of discontinuation is the highest rate that we have seen for a trial of oral contraceptives. The usual rate of discontinuation in the "proof of efficacy" studies for 28-day regimen (21-day active combination drug product) oral contraceptives ranges between 20 – 35%. The discontinuation rate for the only approved drug product with an extended, 91-day,

cycle regimen was 40.6%. We find the rate of discontinuation from the "proof-of-efficacy trial for Lybrel™ to be very concerning.

3. The cycle control, in the form of sustained amenorrhea, for this continuous use oral contraceptive is considered to be poor. Forty percent of subjects still had unanticipated bleeding in the form of bleeding or spotting at the end of one year of use. This apparently poor cycle control in a continuously administered oral contraceptive, which was developed to minimize cyclical bleeding, is concerning.

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 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 John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, at 301-796-0932.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D., F.A.C.S.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-864

Wyeth Pharmaceuticals Inc.
Attention: Frederick A. Golec, Jr., Ph.D.
Director, Worldwide Regulatory Affairs, CMC
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Golec:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lybrel™ (levonorgestrel and ethinyl estradiol) Tablets.

We also refer to your December 21, 2005, correspondence, received December 22, 2005, requesting a teleconference to discuss recent amendments that demonstrate the similarity of commercial manufacturing process validation batches and the primary stability batches, as well as a proposal to change the dissolution specification for method

b(4)

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The teleconference is scheduled for:

- Date: January 31, 2006
- Time: 2 pm – 3 pm
- Phone Arrangements: Call-in number and passcode to be arranged.

CDER Participants: Drs. Moo Jhong Rhee, Donna Christner, Phill Price, Leslie McKinney, and Julie Bullock; Ms. Margaret Kober and Mr. John Kim.

If you have any questions, call John Kim, R.Ph., J.D., Regulatory Project Manager, at (301) 796-0932.

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 Kober
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Chief, Project Management Staff

12/14/04



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65,693

Wyeth Pharmaceuticals, Inc.
Attention: Shirley Speers
Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Speers:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levonorgestrel and Ethinyl Estradiol Tablets.

We also refer to the meeting between representatives of your firm and the FDA by telephone on December 7, 2004 to discuss chemistry questions concerning the Chemistry, Manufacturing and Controls information that will be included in the NDA submission and as an amendment to the application.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Karen Kirchberg, N.P., Regulatory Project Manager, at (301) 827-4254.

Sincerely, ...

{See appended electronic signature page}

Suong Tran, Ph.D.
Division of New Drug Chemistry II
(DNDC II) @ Division of Reproductive and
Urologic Drug Products (HFD-580)
Center for Drug Evaluation and Research

Enclosure

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MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 7, 2004
TIME: 2:00 – 3:00 PM
LOCATION: Telephone conference
SPONSOR: Wyeth Pharmaceuticals, Inc.
APPLICATION: IND 65,693
DRUG NAME: Levonorgestrel and Ethinyl Estradiol Tablets
TYPE OF MEETING: CMC Pre-NDA

MEETING CHAIR: Suong Tran, Ph.D. – Chemist, Division of New Drug Chemistry II (DNDC II) @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

MEETING RECORDER: Karen Kirchberg, N.P. – Regulatory Project Manager, DRUDP (HFD-580)

FDA ATTENDEES:

Suong Tran, Ph.D. – Chemist, DNDC II @ DRUDP (HFD-580)
Karen Kirchberg, N.P. – Regulatory Project Manager, DRUDP (HFD-580)

EXTERNAL CONSTITUENT ATTENDEES:

Frederick (Simon) Golec, Ph.D. – Director, Worldwide Regulatory Affairs (WWRA), Chemistry, Manufacturing and Controls (CMC)
Nirdosh Jagota, Ph.D. – Senior Director, WWRA, CMC
Shirley Speer – Senior Regulatory Specialist, WWRA, CMC
Joseph DeVito, Pharm.D. – Assistant Vice President, Women's Healthcare, Quality Operations
Marijo Doedée, Ph.D. – Associate Director, Chemical & Pharmaceutical Development
Pedro E. Hernandez Abad, Ph.D. – Senior Scientist II, Guayama, Puerto Rico
Luis Collazo – New Product Manager, Guayama, Puerto Rico

BACKGROUND: Discussion of the proposed CMC portion of the NDA submission.

DISCUSSION POINTS:

1. *Does FDA agree with Wyeth's approach to use a comparability protocol to address changes to a new wax or for the deletion of the current Montanic Ester Wax polish for LNG 90 µg/EE 20 µg, Alesse and/or Triphasil drug products?*

FDA's Response:

[The following response applies only to LNG 90 µg/EE 20 µg because the proposed comparability protocol applicable to Alesse® and Triphasil® should be submitted to each of those approved NDAs for further assessment.]

IND 65,693

Yes, we concur with your approach to use a comparability protocol to address changes to a new wax or for the deletion of the current Montanic Ester Wax polish for LNG 90 µg/EE 20 µg.

To summarize the proposal in the meeting package, the protocol to be submitted in the NDA would provide comparative dissolution data and statistical f2 comparison, long term and accelerated stability data, a scientific report and justification that the wax is a non-functional excipient and replacement or removal is unlikely to have any impact on formulation quality and performance. The protocol would request a reduction in the regulatory filing category from a prior approval supplement to a CBE-30. As described in the meeting package, the CBE-30 will include the following: revised qualitative/quantitative composition table and batch formula, excipient test methods, revised description of the manufacturing process and in-process controls, application/compendial release results and stability results, 1 batch with 3 months accelerated stability data in the CBE-30 and long term stability in annual reports, a commitment to place the first commercial lot into the market product stability program, dissolution (Case C) documentation, and revision to the labeling description section.

2. *Does FDA agree with Wyeth's strategy to submit a minor amendment to the NDA, in October 2005, 3 months prior to the PDUFA action date, to provide comparative dissolution data and f2 similarity factor comparisons between one batch of undebossed tablets, manufactured using the equipment used to manufacture the primary registration stability batches, and one validation/conformance batch of debossed tablets manufactured using the alternate equipment, and to provide an updated narrative description of the manufacturing process including any changes resulting from the use of the alternate equipment used for manufacturing process validation?*

FDA's Response:

This question is associated with Question 3, and both questions are answered together for Question 3.

3. *Does FDA agree with Wyeth's proposal to use a comparability protocol in the NDA for approval of equipment changes used to commercialize LNG 90 µg/EE 20 µg tablets based on demonstration of similarity the data specified and file the data in a minor amendment outlined in Section 3.2.2, Question 2 with a commitment to provide stability data to the NDA Annual Report?*

b(4)

FDA's Response:

Yes, we agree with your proposal to submit the minor amendment to the NDA, in October 2005, 3 months prior to the PDUFA action date.

As described in the meeting package, the amendment will include the following data:

- comparative dissolution data and f2 similarity factor comparisons between one batch of undebossed tablets, manufactured using the equipment used to manufacture the primary registration stability batches, and one validation/conformance batch of debossed tablets manufactured using the alternate equipment,
- updated narrative description of the manufacturing process including any changes resulting from the use of the alternate equipment used for manufacturing process validation

IND 65,693

- similarity (e.g., particle size and bulk density)
- similarity (e.g., tablet strength/hardness, weight, disintegration, thickness, potency, content uniformity)
- release testing results for three validation batches,
- 3-month accelerated stability data, and
- commitment to place the three validation batches on long term stability and provide data in annual reports.

b(4)

4. Does FDA agree with Wyeth's proposal to submit a comparability protocol in the NDA to reduce the post-approval filing category from a CBE-30 to a CBE-0 for approval of equipment changes used to commercialize LNG 90 µg/EE 20 µg tablets based if similarity is not demonstrated as outlined in Question 3?

b(4)

FDA's Response:

No, we do not agree with your proposal to submit a comparability protocol in the NDA for the submission of a post-approval supplement in the situation where similarity is not demonstrated when comparing the commercial equipment to the clinical-batch equipment. Such a situation should be reported to us as soon as possible (i.e., at least 3 months prior to the PDUFA action date) in order to us to consult with the Clinical and Clinical Pharmacology review teams in a timely manner. Of concern to us is the comparability between the commercial product and the clinical batches in this worse-case scenario where the commercial process equipment fails to demonstrate similarity (in attributes such as particle size distribution and bulk density) to the equipment that manufactured the clinical batches. This situation should be resolved as soon as possible during the NDA review cycle because it may affect the approvability of the NDA. Any supportive information (e.g., comparative dissolution, batch release data, accelerated stability data, pharmaceutical development reports) should be provided in justifying the acceptability of the commercial equipment.

5. Does FDA agree with the justification and proposal for the drug product method and specification for dissolution of levonorgestrel and ethinyl estradiol in coated LNG 90 µg/EE 20 µg tablets which is different than the USP 27, Supplement 2 specification for coated tablets?

FDA's Response:

Yes; we agree with your proposal to have the specification for dissolution of levonorgestrel and ethinyl estradiol in the drug product be different from the compendial specification. The final numerical acceptance criteria for dissolution will be based on batch release and stability data.

Additional FDA's comments:

- Confirm that the manufacturing process and equipment used to manufacture the primary stability batches are the same as those used to manufacture the clinical batches.

Wyeth's response: Yes, they are the same.

- Clarify the number of primary stability batches per container closure system.

IND 65,693

Wyeth's response: Three batches were manufactured, and each batch was packaged in all three container closure systems (blister, cycle pack, single-unit dispenser) for the stability study.

- Clarify whether the stability commitments on pages 15, 16, and 18 are for the same validation batches and specify the number of batches per container closure system. Of concern to us is the linkage between the primary stability batches in each container closure system and the validation batches in the matching container closure system. Therefore, the 3-month accelerated data to be provided in the NDA for the validation batches should include all three packaging systems.

Wyeth's response: Yes, they are the same. Three validation/conformance batches will be manufactured and each batch will be packaged in all three container closure systems (blister, cycle pack, single-unit dispenser) for the stability study.

ACTION ITEMS:

- Meeting minutes to the sponsor within 30 days.

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/s/

Suong Tran

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65,693

Wyeth Pharmaceuticals, Inc.
Attention: Kelvin Li
Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Mr. Li:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levonorgestrel and Ethinyl Estradiol Tablets.

We also refer to the meeting between representatives of your firm and the FDA by telephone on May 27, 2004 to discuss chemistry questions concerning the development of the packaging for your product.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Karen Kirchberg, N.P., Regulatory Project Manager, at (301) 827-4254.

Sincerely,

{See appended electronic signature page}

Suong Tran, Ph.D.
Division of New Drug Chemistry II
(DNDC II) @ Division of Reproductive and
Urologic Drug Products (HFD-580)
Center for Drug Evaluation and Research

Enclosure

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MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 27, 2004

TIME: 1:30 – 2:00 PM

LOCATION: 17B43

SPONSOR: Wyeth Pharmaceuticals, Inc.

APPLICATION: IND 65,693

DRUG NAME: Levonorgestrel and Ethinyl Estradiol Tablets

TYPE OF MEETING: Telephone conference / Guidance

MEETING CHAIR: Suong Tran, Ph.D. – Chemist, Division of New Drug Chemistry II (DNDC II) @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

MEETING RECORDER: Karen Kirchberg, N.P. – Regulatory Project Manager, DRUDP (HFD-580)

FDA ATTENDEES:

Suong Tran, Ph.D. – Chemist, DNDC II @ DRUDP (HFD-580)
Karen Kirchberg, N.P. – Regulatory Project Manager, DRUDP (HFD-580)

EXTERNAL CONSTITUENT ATTENDEES:

Luis Collazo – New Product Manager, Guayama, Puerto Rico
Jeff Cremi – Principal Packaging Engineer, Global Packaging Services, Collegeville, PA
Joseph DeVito, Pharm.D. – Assistant Vice President, Women's Healthcare, Quality Operations, Collegeville, PA
Marijo Doedée, Ph.D. – Associate Director, Chemical & Pharmaceutical Development (CPD), Pearl River, NY
Arwinder Nagi, PhD. – Senior Director, CPD, Pearl River, NY
Simon Golec, PH.D. – Director, Worldwide Regulatory Affairs (WWRA), Chemistry, Manufacturing and Controls (CMC), Collegeville, PA
Mike Martin – Global Technology Team Leader, Collegeville, PA
Kelvin Li, R.Ph. – Associate Director – WWRA, CMC, Collegeville, PA
Shirley Speer – Senior Coordinator, WWRA, CMC, Collegeville, PA

BACKGROUND:

A meeting to discuss the stability program and proposed packaging comparability protocol that will be used to support the NDA filling for Levonorgestrel/Ethinyl Estradiol – continuous use oral contraceptive product.

DISCUSSION POINTS:

1. *Does the Agency concur with Wyeth's plan to use comparative dissolution data between the undebossed and debossed tablets?*

Answer: Yes. Data should be multipoint profiles to capture the transition region. The proposed study of multiple pHs would provide additional, useful data.

2. *Does the Agency concur with Wyeth's proposed parameters in the Proposed Package Comparability Protocol comparing the blister packaging of tablets between a third party and the WPC commercial site?*

Answer: Yes. Include the technical details in the protocol comparing the equipment at the sites.

3. *Does the Agency concur with the minor variation from USP <671>?*

Answer: Yes.

4. *Does the Agency concur, that with the package comparability protocol in place, and an equipment validation protocol available for review at the time of the FDA Pre approval inspection, as well as a commitment to place the first three batches of WPC Packaged product on stability, post approval, that the FDA will agree to allow WPC to package product launch batches using the validated, automated equipment upon NDA approval? Wyeth commits to report the results of the comparability protocol study at the first annual report.*

Answer: The answer is yes with regard to the comparability protocol and the stability commitment. The sponsor should consult with the FDA field office on the issue of the equipment validation protocol. The comparability protocol should be approved as part of the NDA (there is no approval mechanism during the IND phases) and should state clearly that the protocol is for a one-time use for these specific packaging changes.

ACTION ITEMS:

- Meeting minutes to the sponsor within 30 days.

Meeting minutes prepared by: K. Kirchberg

Meeting minutes concurred by: S. Tran

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Moo-Jhong Rhee
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Suong Tran
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65,693

Wyeth Pharmaceuticals, Inc.
Attention: Shirley Speer, Senior Regulatory Specialist
Worldwide Regulatory Affairs, CMC
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Speer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Levonorgestrel/Ethinyl Estradiol – Continuous Use Tablets.

We also refer to your correspondence dated October 7, 2004, requesting a meeting, and to the Division responses faxed to you on October 19, 2004.

The meeting was requested to discuss the Agency's concurrence with Wyeth's approach to address an extractable issue in the Single Unit Dispenser packaging component and to obtain concurrence on the extractable qualification for a level of _____ leachable observed in the Cycle Pack packing component.

b(4)

You indicated that you accepted those responses as written and would not require the scheduled teleconference meeting. The enclosed responses are considered the official minutes of that meeting. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Karen Kirchberg, NP, Regulatory Health Project Manager, at (301) 827-4254.

Sincerely,
{See appended electronic signature page}
Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
Division of Urologic and Reproductive Drug
Products (HFD-580)
Division of New Drug Chemistry II
Center for Drug Evaluation and Research

Enclosure

The following are the finalized answers to your questions as well as comments and recommendations. This correspondence is in lieu of the teleconference meeting scheduled for October 20, 2004.

Single Unit Dispenser (SUD)

1. Does FDA concur with Wyeth's approach to support filing and approval for the replacement of the SUD made from the original _____ to the SUD made from the alternate _____ that shows no demonstrable extractable? b(4)

FDA's Response: Yes, we concur with your approach to provide 6 months of stability data for the original SUD at the time of the NDA submission with the addition of 3 months of stability data for the commercial SUD. We note your commitment to provide additional stability data for both SUDs as an amendment to the NDA during the review cycle. Additional comment: The stability data should include both long term and accelerated data. Confirm that the protective secondary packaging of the original and commercial SUDs is the same, the _____ blister _____ as indicated in the 29-APR-2004 IND amendment. b(4)

2. Does FDA concur with Wyeth's approach in addressing the extractable issue in the SUD componentry, intending to request a 24-month expiration dating period for the approval of Levonorgestrel 90µg/Ethinyl Estradiol 20µg tablets to be packaged in the SUD?

FDA's Response: Yes, we concur with your approach to provide the following amount of stability data on the original SUD and commercial SUD in support of the 24-month expiry: a total of 12 months of data for the original SUD and a total of 9 months for the commercial SUD. We note your commitment to provide these data during the NDA review cycle and prior to 3 months before the PDUFA action date. Additional comment: The stability data should include 6 months of accelerated data.

Cycle Pack

1. Does FDA concur with Wyeth based on ICH Q6A, and the Wyeth Drug Safety and Metabolism toxicology assessment that provides a justification for a level _____ that would be considered qualified, that is not necessary to establish a regulatory specification for the level of _____ leachable in Levonorgestrel 90µg/Ethinyl Estradiol 20µg tablets at release and on stability? b(4)

FDA's Response: Yes, we concur that a regulatory specification for the _____ leachable is not necessary because the maximum theoretical exposure is much less than the WHO tolerable daily intake for _____ in drinking water and the EPA oral reference dose. b(4)

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IND 65,693

2. Does FDA concur with Wyeth that testing and control _____ is not necessary and no additional testing of components beyond what is provided by the component supplier in conformance to 21 CFR 177.1640 is necessary?

b(4)

FDA's Response: Yes, we concur that testing for the _____ extractable in _____ is not necessary because the regulations already include the limit of _____ (by weight) for _____.

b(4)

Additional comment: In-use stability data should be provided in the NDA for the cycle pack and SUD (i.e., 28-day storage _____ respectively).

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NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-864 Supplement # 000 Efficacy Supplement Type SE- N/A

Trade Name: **Lybrel™**
Established Name: **levonorgestrel (LNG)/ ethinyl estradiol (EE)**
Strengths: **90 mcg / 20 mcg**

b(4)

Applicant: **Wyeth Pharmaceuticals, Inc.**
Agent for Applicant: **N/A**

Date of Application: **27-May-05**
Date of Receipt: **27-May-05**
Date clock started after UN: **N/A**
Date of Filing Meeting: **12-Jul-05**
Filing Date: **26-Jul-05**
Action Goal Date (optional): **27-Mar-06** User Fee Goal Date: **27-Mar-06**

Indication(s) requested: **continuous oral contraceptive**

Type of Original NDA: (b)(1) (b)(2)
OR
Type of Supplement: (b)(1) (b)(2)

NOTE:

- (1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.*
- (2) *If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:*

NDA is a (b)(1) application OR NDA is a (b)(2) application

Therapeutic Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 5
Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.*

Version: 12/15/2004
This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO
If yes, explain:
- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO
If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).
- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A YES NO
- Is it an electronic CTD (eCTD)? N/A YES NO
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, 3 Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y NO
- PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: IND 65,693
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 7-Dec-04 CMC only _____ NO
If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES NO
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO
- Risk Management Plan consulted to ODS/IO? N/A YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO
- Has DOTCDP been notified of the OTC switch application? N/A YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
N/A YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

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On Original

ATTACHMENT

MEMO OF FILING MEETING

DATE: 12-Jul-05

BACKGROUND: Sponsor is proposing an extended use method of a combined oral contraception. The proposed dosage is slightly lower than Sponsor's approved product Alesse® to be used continuously. This product utilizes 0.090 mg of levonorgestrel (LN) and 0.02 mg of ethinyl estradiol (EE) continuously compared to Alesse® which utilizes 0.10mg of levonorgestrel and 0.02mg of ethinyl estradiol over a 21- day treatment period. A more recently approved product, Seasonale®, is given for 84 days continuously of active drug followed by 7 days of withdrawal on placebo pills. The implied benefit of prolonged contraception is a reduction in the number of withdrawal bleeding periods that woman undergo while taking oral contraceptives.

ATTENDEES: Drs. Scott Monroe, Phill Price, Lynnda Reid, Leslie McKinney, Donna Christner, Julie Bullock, and John Kim.

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Phill Price
Secondary Medical:	Shelley Slaughter
Statistical:	Mahboob Sobhan
Pharmacology:	Leslie McKinney
Statistical Pharmacology:	N/A
Chemistry:	Donna Christner
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Julie Bullock
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	N/A
Regulatory Project Management:	John Kim
Other Consults:	

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE REFUSE TO FILE

- Clinical site inspection needed? YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A YES NO

CLINICAL MICROBIOLOGY	N/A <input checked="" type="checkbox"/>	FILE <input type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
STATISTICS	N/A <input checked="" type="checkbox"/>	FILE <input type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
BIOPHARMACEUTICS		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• Biopharm. inspection needed?		YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
PHARMACOLOGY	N/A <input type="checkbox"/>	FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• GLP inspection needed?		YES <input type="checkbox"/> NO <input checked="" type="checkbox"/>
CHEMISTRY		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• Establishment(s) ready for inspection?		YES <input checked="" type="checkbox"/> NO <input type="checkbox"/>
	• Microbiology		YES <input type="checkbox"/> NO <input type="checkbox"/>

ELECTRONIC SUBMISSION:
Any comments: eCTD format

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- No filing issues have been identified.
- Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

- If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
- If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
- Convey document filing issues/no filing issues to applicant by Day 74.

John C. Kim, R.Ph., J.D.
Regulatory Project Manager, HFD-580

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

/s/

John C. Kim
6/27/2006 12:14:53 PM
CSO

ACTION PACKAGE CHECKLIST

Application Information		
BLA # NDA # 21-864	BLA STN# NDA Supplement # 000	If NDA, Efficacy Supplement Type N/A
Proprietary Name: Lybrel™ Established Name: 90 mcg levonorgestrel/ 20 mcg ethinyl estradiol Dosage Form: Tablet		Applicant: Wyeth Pharmaceuticals, Inc.
RPM: John C. Kim, RPh, JD		Division: Reproductive & Urologic Products Phone # 301-796-0932
NDAs: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): N/A Provide a brief explanation of how this product is different from the listed drug. <input type="checkbox"/> If no listed drug, check here and explain: Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct. <input checked="" type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date: 20-MAY-2007	
❖ User Fee Goal Date ❖ Action Goal Date (if different)		22-MAY-2007
❖ Actions		
<ul style="list-style-type: none"> • Proposed action 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR	
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 	<input type="checkbox"/> None AE 27-JUN-2006	
❖ Advertising (<i>approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (<i>indicate dates of reviews</i>)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 5	
NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation	
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies
NDAs and NDA Supplements: <input type="checkbox"/> OTC drug	
Other:	
Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP <input checked="" type="checkbox"/> N/A
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other Information Alert

❖ Exclusivity	
<ul style="list-style-type: none"> • NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity? • NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> • NDAs: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> • NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> • NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires: <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires: <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
<ul style="list-style-type: none"> • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> • Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. • [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification <u>pertains expires</u> (but may be tentatively approved if it is otherwise ready for approval). 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified <input checked="" type="checkbox"/> N/A 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii) <input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> • [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p>	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified <input type="checkbox"/> Yes <input type="checkbox"/> No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	27-JUN-2006
NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval 	N/A
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies	<input type="checkbox"/> None
<ul style="list-style-type: none"> Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) 	Telecon 4-MAY-2007
<ul style="list-style-type: none"> Incoming submission documenting commitment 	11-MAY-2007
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	7-MAY-2007 4-MAY-2007 9-JAN-2007 30-NOV-2006 1-SEP-2006 (2) 30-AUG-2006 16-AUG-2006 28-JUL-2006 18-JUL-2006 27-JUN-2006 2-JUN-2006 7-APR-2006 15-MAR-2006 2-MAR-2006 1-MAR-2006 23-FEB-2006 5-JAN-2006
❖ Internal memoranda, telecons, email, etc.	26-OCT-2006 31-MAY-2006 15-MAR-2006
❖ Minutes of Meetings	
<ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) 	N/A
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date</i>) 	<input type="checkbox"/> No mtg 18-APR-2002
<ul style="list-style-type: none"> Other (e.g., EOP2a, CMC pilot programs) 	14-DEC-2004 PRE-NDA CMC 1-NOV-2004 2-JUN-2006
❖ Advisory Committee Meeting	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date of Meeting 	23/24-JAN-2007 General AC
<ul style="list-style-type: none"> 48-hour alert or minutes, if available 	General AC Meeting Minutes
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
CMC/Product Quality Information	
CMC/Product review(s) (<i>indicate date for each review</i>)	15-MAY-2007 6-JUN-2006 15-JUL-2005
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer	<input checked="" type="checkbox"/> None

<i>(indicate date for each review)</i>	
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
Environmental Assessment (check one) (original and supplemental applications)	
• <input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See CMC Review #1 page 68
• <input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	N/A
• <input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) <i>(indicate date of each review)</i>	N/A <input type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 16-JAN-2007 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents	N/A
• Facility review <i>(indicate date(s))</i>	<input type="checkbox"/> Requested
• Compliance Status Check (approvals only, both original and supplemental applications) <i>(indicate date completed, must be within 60 days prior to AP)</i>	<input type="checkbox"/> Accepted
	<input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed
	<input type="checkbox"/> Requested
	<input type="checkbox"/> Not yet requested
	<input checked="" type="checkbox"/> Not needed
	CMC Review #2 see page 33
	CMC Review #1 see pages 45-46

Nonclinical Information

❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	21-MAR-2007 20-NOV-2006 13-FEB-2006 13-JUL-2006
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	N/A
❖ Nonclinical inspection review Summary (DSI)	<input checked="" type="checkbox"/> None requested

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Clinical Information

❖ Clinical review(s) (indicate date for each review)	Medical Team Leader	19-MAY-2007 22-MAY-2006
	Medical Officer	17-MAY-2007 5-APR-2006 12-JUL-2005
❖ Financial Disclosure reviews(s) or location/date if addressed in another review		Clinical Review #1 see page 18
❖ Clinical consult reviews from other review disciplines/divisions/Centers (indicate date of each review)		<input checked="" type="checkbox"/> None
❖ Microbiology (efficacy) reviews(s) (indicate date of each review)		<input checked="" type="checkbox"/> Not needed
❖ Safety Update review(s) (indicate location/date if incorporated into another review)		Clinical Review #2 see pages 6-10 Clinical Review #1 see page 74
❖ Risk Management Plan review(s) (including those by OSE) (indicate location/date if incorporated into another review)		N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date of each review)		<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) (include copies of DSI letters to investigators)		<input type="checkbox"/> None requested
• Clinical Studies		12-OCT-2006 6-OCT-2006 5-OCT-2006 12-SEP-2006
• Bioequivalence Studies		N/A
• Clin Pharm Studies		N/A
❖ Statistical Review(s) (indicate date for each review)		17-MAY-2007 23-JUN-2006
Clinical Pharmacology review(s) (indicate date for each review)		20-MAR-2007 9-MAR-2006 18-JUL-2005

Appears This Way
On Original

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

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

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

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

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

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

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

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

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.