CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-864

CHEMISTRY REVIEW(S)

Addendum to CMC Review #2 of NDA 21-864

From: **Donna F. Christner, Ph.D.**
To: **NDA 21-864**
Date: **18-May-2007**
Subject: **CMC evaluation of DMETS labeling comments dated 18-May-2007**

Background

DMETS has submitted a final labeling review. Comments are evaluated as follows.

Recommendation and Conclusions on Approvability:

No action is indicated on DMETS comments. From a CMC standpoint, the NDA can be APPROVED. DMETS comments are reproduced below, followed by CMC evaluation.

DMETS comment 1:

1. Ensure that the established name is one-half the size of the proprietary name. See 21 CFR 201.10(g)(2).

CMC Evaluation: This issue was addressed in CMC review # 1, dated 17-May-2006. Sponsor replied and it was determined that the size of the established name as compared to the proprietary name is adequate. See CMC Review # 1.

DMETS Comment 2:

2. Revise the established name and product strength on all labels and labeling to read:

b(4)

CMC Evaluation: Sponsor has been advised in April 2007 to change the µg to mcg. Sponsor agreed in Amendment 048, dated 04-May-2007 to change all future labels after use of the first batch and report this change in the Annual Report. This is acceptable. See CMC Review # 2, dated 08-May-2007.

DMETS Comment 3:

3. Throughout the labels and labeling, delete ____ graphic art (as indicated by the arrow below) following the proprietary name as it distracts attention away from important statements such as the proprietary name, established name, and product strength.

b(4)

CMC Evaluation: The graphic does not interfere with the readability of the proprietary name, established name or strength, therefore, CMC does not have a comment on the graphic. Any decision or negotiation on the graphic will be a decision for the clinical division.

DMETS comment 4:

I. ClickCase Single Unit Dispenser

DMETS has identified the following potential safety concern regarding the Single Unit Dispenser. After a preliminary overview of the device, DMETS has concerns about the potential for damage to the device, spring, or casing of this item (e.g. misalignment of the spring and subsequent inability to dispense the medication, cracking and breaking of the plastic case). DMETS questions the durability of the device under routine handling, and how the patient would dispense the medication if the device is damaged or becomes non-operational at any time. Additionally, has any usability testing been performed on the device? Please forward our concerns to the CDRH reviewer.

This issue was addressed in CMC review # 1. Wyeth responded favorably to the request. The following evaluation is taken from CMC Review #1, dated 17-May-2006.

b(4)

Wyeth response: *The is known for its strength and impact resistance. Testing as per 16CFR Part 1501, Choking Aspiration and Ingestion Hazard was performed on the dispenser and passed. Quality Assurance process controls are in place to ensure that the spring is present and oriented properly, the pill ring is oriented properly and the unit is functional. A camera vision system is used for this. In addition, if the unit is not functional, it can be returned to the pharmacist.*

Evaluation: *Acceptable.*

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

/s/

Donna Christner
5/18/2007 01:35:13 PM
CHEMIST

Addendum that you okayed

Moo-Jhong Rhee
5/18/2007 01:45:34 PM
CHEMIST
Chief, Branch III

NDA 21-864

Lybrel

Levonorgestrel and Ethinyl Estradiol Tablets

Wyeth Pharmaceuticals, Inc.

for
Division of Reproductive and Urologic Products

Donna F. Christner, Ph.D.

Office of New Drug Quality Assessment
Pre-Marketing Division II, Branch III

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-864

2. REVIEW #: 2

3. REVIEW DATE: 08-May-2007

4. REVIEWER: Donna F. Christner, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	27-May-2005
Amendment 003 (Withdrawn)	28-Nov-2005
Amendment 004 (Portions Withdrawn)	21-Dec-2005
Amendment 007	27-Jan-2006
Amendment 009	08-Feb-2006
Amendment 010 (Lybrel tradename)	10-Feb-2006
Amendment 013 (Meeting request/Level 3 change)	06-Mar-2006
Amendment 016 (Wyeth meeting minutes)	16-Mar-2006
Amendment 017 (Label icon)	21-Mar-2006
Amendment 019 (BCS Class 1 documentation)	24-Mar-2006
Amendment 022 (SUD/ClickCase Labeling)	29-Mar-2006
Amendment 023 (PI Labeling)	05-Apr-2006
Amendment 024 (Dial Pack Labeling)	20-Apr-2006
Amendment 026 (Reversion [redacted])	02-May-2006 b(4)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment 029 (Manufacturing change)	22-May-2006
Amendment 030 (Stability Data)	22-Jun-2006
Amendment 033 (Meeting Request)	18-Jul-2006
Amendment 037 (Complete Response to AE letter)	21-Aug-2006
Amendment 038 (Updated methods)	02-Oct-2006
Amendment 040 (Intent to Amend [redacted])	01-Nov-2006
Amendment 042 ([redacted])	22-Dec-2006
Amendment 043 (Removal of [redacted] Statement from wallet)	02-Feb-2007 b(4)
Amendment 044 (Updated eCTD links for final carton labels)	15-Mar-2007
Amendment 048 (Commitment to change µg to mcg on all **cartons after first batch utilized—Annual Reportable change)**	04-May-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Wyeth Pharmaceuticals, Inc
Address:	PO Box 8299 Philadelphia, PA 19101-8299
Representative:	Randall B. Bremmer Associate Director II
Telephone:	484-865-3792

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Lybrel
b) Non-Proprietary Name (USAN): Levonorgestral /Ethinyl estradiol
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Oral Contraceptive

11. DOSAGE FORM: Tablet (for continuous use)

12. STRENGTH/POTENCY: 90 µg Levonorgestrel (LNG)/
20 µg Ethinyl Estradiol (EE)

13. ROUTE OF ADMINISTRATION: Oral

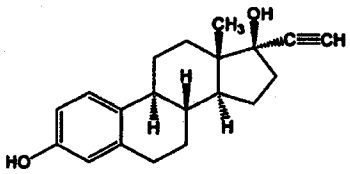
14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__x___Not a SPOTS product

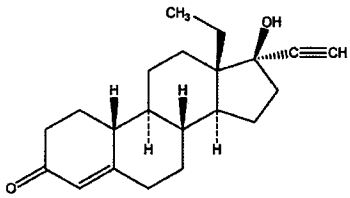
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Ethinyl estradiol



Compendial name:	Ethinyl Estradiol, USP
Chemical names:	19-Nor-17α-pregna-1,3,5(10)-triene-20-yne-3,17-diol (IUPAC) 19-Norpregna-1,3,5(10)-triene-20-yme-3,17-diol, (17α)- (CAS) 19-Ethynyl-estra-1,3,5(10)-triene-3,17β-diol (WHO) 17α-Ethynyl-1,3,5(10-stratriene-3,17-diol)
USAN:	Ethinyl Estradiol
INN:	Ethinylestradiol
Laboratory code:	AY-3877
CAS Registry No:	57-63-6
Molecular formula:	$C_{20}H_{24}O_2$
Molecular weight:	296.40

Levonorgestral



Compendial name:	Levonorgestrel, USP
Chemical names:	(-) 13β-Ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one (IUPAC) (-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one D-(-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one (WHO) 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-,(17α)-(-)- (CAS Index)
USAN:	Levonorgestrel
INN:	Levonorgestrel
Laboratory code:	WY-5104
CAS Registry No:	797-63-7
Molecular formula:	$C_{21}H_{28}O_2$
Molecular weight:	312.45

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
4178	II	Schering	Levonorgestrel	1	Adequate	07-Feb-2006	
1985	II	Schering	Ethinyl estradiol	3	Adequate	21-Nov-2005	Reviewed by R. Agarwal for NDA 21-871
	IV			1	Adequate	27-Jun-2005	
	III			3	Adequate	18-Nov-1996	Reviewed by R. Seevers for NDA 20-683
	III			1	Adequate	31-Jan-2006	
	III			4	N/A		complies with 21 CFR 175.300 (ONDC blister policy)
	III			1	Adequate	31-Jan-2006	
	III			1	Adequate	30-May-2003	Reviewed by L. Rocca for NDA 21-323

b(4)

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

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	**RECOMMENDATION**	**DATE**	**REVIEWER**
Biometrics	N/A		
EES	**Acceptable**	**16-Jan-2007**	**J. D'Ambrogio**
Pharm/Tox	Leachable limit ACCEPTABLE	22-Mar-2007	Leslie McKinney
Biopharm	BE study ACCEPTABLE	20-Mar-2007	Sandra Suarez-Sharp
LNC	N/A		
Methods Validation	Will be submitted		
DMETS	Tradename acceptable		L. Wisniewski
EA	Granted	31-Mar-2006	D. Christner
Microbiology	N/A		

The Chemistry Review for NDA 21-864

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA can be APPROVED from the CMC standpoint.

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

Not applicable.

II. Summary of Chemistry Assessments

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

Lybrel is an oral contraceptive that contains two drug substances: levonorgestrel and ethinyl estradiol. Levonorgestrel is contained in the drug product at 90 µg and ethinyl estradiol at 20µg.

The sponsor is Wyeth Pharmaceuticals. The drug substances are manufactured by Schering and information is provided in DMFs 4178 and 1985.

DRUG SUBSTANCES

Levonorgestrel

Complete information on levonor**gestrel is contained in Schering's DMF # 4178. The** DMF was reviewed for this NDA and found to be **adequate.**

General information, General Properties, and Batch Analysis of lots used to manufacuture the clinical batches are included in the original NDA submission.

Ethinyl estradiol

Complete information on ethinyl estradiol is **contained in Schering's DMF 1985. The most** recent review of the DMF was done by R. Agarwal (Review # 8, dated 21-Nov-2005) and found **adequate.**

General information, General Properties, and Batch Analysis of lots used to manufacture the clinical batches are included in the original NDA submission.

DRUG PRODUCT

The drug product is a continuous-use oral contraceptive (no pill-free period). The **formulation is based on the company's approved** product, Alesse, with a few changes. For the formulation, the amount of Levonorgestrel has been decreased from 100 µg to 90µg, . In the original application, the tablets were manufactured by a method. Due to inadequate bridging of the clinical supplies manufactured by a method to the to-be-marketed tablets manufactured via , and **the sponsor's reluctance to perform a BE** b(4) study for this change, the sponor opted to return to the manufacturing method late in the review cycle. It was agreed that the revision was allowed, but supporting data arrived too late for review, so the NDA received an AE action. In the complete response dated 21-Aug-2006, the sonsor submitted all required data for evaluation of the manufacturing method. On 22-Dec-2006, the sponsor submitted a major Amendment, changing the manufacturing method to method, submitting the required BE study to bridge tablets, and adequate stability data. Therefore, **the to-be-marketed tablets will be manufactured according to the method, which have been shown to be bioequivalent to the clinical supply tablets.**

The drug product is packaged in a Single Unit Dispenser which holds 28 active tablets containing 90µg levonorgestrel and 20µg ethinyl estradiol. The drug product is a yellow, biconvex, film-coated tablet **debossed with "W" on one side and "1117" on the other side.** Excipients in the tablet core include Microcrystalline Cellulose, Lactose monohydrate, b(4) Magnesium stearate), and Polacrilin potassium Hypromellose Titanium Dioxide, Polyethylene glycol 400, Iron Oxide , Polyethylene glycol 1450 and Montanic Ester Wax .

Regulatory specifications for the tablets include Appearance & Description, Identification A (HPLC) , Identification B (Melting range for LNG), Strength, Degradation products, Content Uniformity and Dissolution. Acceptance criteria are set based on the approved specifications for Alesse. The methods for Strength, Degradation Products and Dissolution have been modified since the first review cycle to allow routinue identification of potential packaging leachables .

The drug product is packaged in the Single Unit Dispenser (SUD). The sponsor has submitted 20 months of real-time stability data on tablets manufactured by the method, and has requested 24 months of expiry based on this submitted data. Based on analysis of the submitted data, 24 months of expiry can be granted. Tablets are to be stored at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F), .

The sponsor submitted two comparability protocols for post-approval changes in the original application and two additional comparability protocols in the 22-Dec-2006 Amendment:

- Comparability Protocol for Packaging of the Single Unit Dispenser
- Comparability Protocol for the Replacement or Deletion of Montanic Ester Wax
- Comparability Protocol for Foil-Based Component Interchangeability
- Comparability Protocol for Blister Films Interchangeability

The Montanic Ester Wax protocol requests a supplement category of CBE-30, while the packaging/packaging component protocols request a category of Annual Report. All four comparability protocols can be approved.

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

Lybrel is packaged in the Single Unit Dispenser. For the SUD, delivery of the pill is accomplished by squeezing the Dispenser to move the pill into an opening, where it is then dropped into the hand. Release of the Dispenser moves the next pill into place. No protective blister is in place during use. One pill is to be taken daily, in a continuous-use regimen (no pill-free day). Each package contains 28 active tablets. After one package is finished, the next package is started the following day.

C. Basis for Approvability or Not-Approval Recommendation

In the Complete Response, the sponsor provided all requested information on the manufacturing method and drug supplies for evaluation. Because of submission of the 22-Dec-2006 Amendment changing to the method and the adequate BE study comparing the and tablets, evaluation of the NDA was based on the data used to support the process. The sponsor has demonstrated that the manufacturing process is robust and the release specifications adequately control the quality of the drug product. Stability data supports granting of a 24 month expiry when stored at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F).

b(4)

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Donna F. Christner, Ph.D./Date: 18-Apr-2007
Moo-Jhong Rhee, Ph.D./Date
John Kim/Date

C. CC Block

40 Page(s) Withheld

6 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

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

/s/

Donna Christner
5/15/2007 01:17:43 PM
CHEMIST

As we discussed and per your request, made minor changes.

Moo-Jhong Rhee
5/15/2007 02:49:50 PM
CHEMIST
Chief, Branch III

NDA 21-864

Lybrel

Levonorgestrel and Ethinyl Estradiol Tablets

Wyeth Pharmaceuticals, Inc.

for
Division of Reproductive and Urologic Products

Donna F. Christner, Ph.D.

Office of New Drug Quality Assessment
Pre-Marketing Division II, Branch III

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-864

2. REVIEW #: 1

3. REVIEW DATE: 17-May-2006

4. REVIEWER: Donna F. Christner, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	27-May-2005
Amendment 003 (Withdrawn)	28-Nov-2005
Amendment 004 (Portions Withdrawn)	21-Dec-2005
Amendment 007	27-Jan-2006
Amendment 009	08-Feb-2006
Amendment 010 (Lybrel tradename)	10-Feb-2006
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Amendment 016 (Wyeth meeting minutes)	16-Mar-2006
Amendment 017 (Label icon)	21-Mar-2006
Amendment 019 (BCS Class 1 documentation)	24-Mar-2006
Amendment 022 (SUD/ClickCase Labeling)	29-Mar-2006
Amendment 023 (PI Labeling)	05-Apr-2006
Amendment 024 (Dial Pack Labeling)	20-Apr-2006
Amendment 026 (Reversion — Meeting Request)	02-May-2006

b(4)

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Wyeth Pharmaceuticals, Inc.
Address:	PO Box 8299 Philadelphia, PA 19101-8299
Representative:	Randall B. Bremmer Associate Director II
Telephone:	484-865-3792

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Lybrel
b) Non-Proprietary Name (USAN): Levonorgestral /Ethinyl estradiol
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 5
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Oral contraceptive

11. DOSAGE FORM: Tablet (for continuous use)

12. STRENGTH/POTENCY: 90 µg Levonorgestrel (LNG)/
20 µg Ethinyl Estradiol (EE)

13. ROUTE OF ADMINISTRATION: Oral

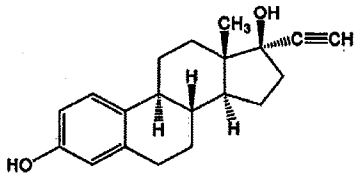
14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__x____Not a SPOTS product

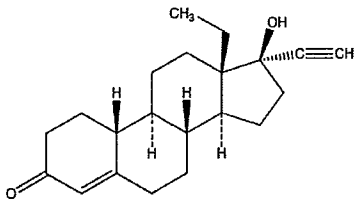
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Ethinyl estradiol



Compendial name:	Ethinyl Estradiol, USP
Chemical names:	19-Nor-17α-pregna-1,3,5(10)-triene-20-yne-3,17-diol (IUPAC) 19-Norpregna-1,3,5(10)-triene-20-yme-3,17-diol, (17α)- (CAS) 19-Ethynyl-estra-1,3,5(10)-triene-3,17β-diol (WHO) 17α-Ethynyl-1,3,5(10-stratriene-3,17-diol)
USAN:	Ethinyl Estradiol
INN:	Ethinylestradiol
Laboratory code:	AY-3877
CAS Registry No:	57-63-6
Molecular formula:	$C_{20}H_{24}O_2$
Molecular weight:	296.40

Levonorgestral



Compendial name:	Levonorgestrel, USP
Chemical names:	(-) 13β-Ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one (IUPAC) (-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one D-(-)-13-Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one (WHO) 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-,(17α)-(-)- (CAS Index)
USAN:	Levonorgestrel
INN:	Levonorgestrel
Laboratory code:	WY-5104
CAS Registry No:	797-63-7
Molecular formula:	$C_{21}H_{28}O_2$
Molecular weight:	312.45

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
4178	II	Schering	Levonorgestrel	1	Adequate	07-Feb-2006	
1985	II	Schering	Ethinyl estradiol	3	Adequate	21-Nov-2005	Reviewed by R. Agarwal for NDA 21-871
	IV			1	Adequate	27-Jun-2005	
	III			3	Adequate	18-Nov-1996	Reviewed by R. Seevers for NDA 20-683
	III			1	Adequate	31-Jan-2006	b(4)
	III			4	N/A		complies with 21 CFR 175.300 (ONDC blister policy)
	III			1	Adequate	31-Jan-2006	
	III			1	Adequate	30-May-2003	Reviewed by L. Rocca for NDA 21-323

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

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	11-Oct-2005	J. D'Ambrogio
Pharm/Tox	N/A		
Biopharm	Biowaiver not acceptable	28-Apr-2006	BSCS Committee
LNC	N/A		
Methods Validation	Will be submitted		
DMETS/DDMAC	Tradename acceptable	28-Sep-2005	L. Wisniewski
EA	Granted	31-Mar-2006	D. Christner
Microbiology	N/A		

The Chemistry Review for NDA 21-864

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is APPROVABLE from the CMC standpoint, pending review of data on manufacturing method and corresponding stability data. Complete data has not yet been submitted. Sponsor intends to submit data 5 days before PDUFA date. b(4)

The following information will be required for approval of the drug product:

- Information on the revised manufacturing method
- Release data on three drug product lots manufactured by the revised method
- Submission of the supportive stability data on the clinical trial supplies
- Justification for reversion to the USP dissolution method
- Supporting stability data on the approved product b(4)
- 3 months of real time and accelerated stability data on the 3 lots of drug product manufactured by the revised method.

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

Not applicable.

II. Summary of Chemistry Assessments

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

Lybrel is an oral contraceptive that contains two drug substances: levonorgestrel and ethinyl estradiol. Levonorgestrel is contained in the drug product at 90 µg and ethinyl estradiol at 20µg.

The sponsor is Wyeth Pharmaceuticals. The drug substances are manufactured by Schering and information is provided in DMFs 4178 and 1985.

DRUG SUBSTANCES

Levonorgestrel

Complete information on levonorgestrel is contained in Schering's DMF # 4178. The DMF was reviewed for this NDA and found to be **adequate.**

General information, General Properties, and Batch Analysis of lots used to manufacuture the clinical batches are included in the NDA submission.

Ethinyl estradiol

Complete information on ethinyl estradiol is contained in Schering's DMF 1985. The most recent review of the DMF was done by R. Agarwal (Review # 8, dated 21-Nov-2005) and found **adequate**.

General information, General Properties, and Batch Analysis of lots used to manufacture the clinical batches are included in the NDA submission.

DRUG PRODUCT

The drug product is a continuous-use oral contraceptive (no pill-free period). The formulation is based on the company's approved product, Alesse, with a few changes. For the formulation, the amount of Levonorgestrel has been decreased from 100 µg to 90µg, . The sponsor intended to manufacture the current drug product via a method as opposed to the method used for Alesse, although as of 02-May-2006 the sponsor plans to return to the method because of regulatory issues. b(4)

The drug product is packaged in two configurations: A Cycle Pack that is identical to that used for Alesse, and a Single Unit Dispenser. Each package holds 28 active tablets containing 90µg levonorgestrel and 20µg ethinyl estradiol. The drug product is a yellow, biconvex, film-coated tablet debossed with "W" on one side and "1117" on the other side. Excipients in the tablet core include Microcrystalline Cellulose, Lactose monohydrate, Magnesium stearate , and Polacrilin potassium. Hypromellose , Titanium Dioxide, Polyethylene glycol 400, Iron Oxide , Polyethylene glycol 1450 and Montanic Ester Wax (. b(4)

The pivotal Phase 3 clinical trials were performed using tablets manufactured via a method. Another smaller Phase 3 trial was performed using some tablets manufactured by the method, and these tablets were placed on stability for determination of expiry.

Late in the review cycle (Jan 2006), Clinical determined that the smaller Phase 3 trial would not be used for determination of efficacy. Therefore, there is no bridge to show that the tablets manufactured are similar, and the sponsor has no IVIVC. The sponsor initially planned to be the manufacturing process for the commercial tablets. b(4)

The change from a [redacted] method to [redacted] is a Level 3 change, which would require comparative dissolution, stability studies and a bioequivalence study. Comparative dissolution and stability studies have been provided, but Wyeth requested a biowaiver for the requirement for a BE study. This request was denied. Wyeth plans to revert to the [redacted] manufacturing method and submit data for review. In addition to the data, Wyeth also requests to return to the USP dissolution method for release and stability of the tablets and will provide justification for this. Wyeth plans to submit this data on 22-May-2006 and 22-Jun-2006, 5 days before the PDUFA date (27-Jun-2006). b(4)

In addition to the change from [redacted] during the Phase 3 trial, the sponsor had made plans to make additional changes in the manufacturing process during the NDA review and submit these changes in an Amendment at least 3 months prior to the PDUFA date. Negotiations were held prior to NDA submission concerning the type of information that should be submitted for this change, which were submitted in Amendments dated 28-Nov-2005 and 21-Dec-2005. Although the changes should not make a difference to the quality of the product, it was determined that the minor manufacturing changes had a marked affect on the dissolution profile of the drug product on stability, resulting [redacted] in the amount of levonorgestrel released, with an unknown effect on clinical efficacy. The sponsor requested a relaxation of the dissolution specification in response to this change in performance. This request was denied and the sponsor informed that expiry would be based only on the data for the batches manufactured by the original [redacted] process. The sponsor withdrew the new [redacted] manufacturing process and the resulting data. Therefore, expiry would be based on the submitted data for the batches manufactured by the original [redacted] process. Because of the subsequent reversion to the [redacted] method, determination of expiry and what to base it on is still pending. b(4)

Regulatory specifications for the tablets include Appearance & Description, Identification A (HPLC) , Identification B (Melting range for LNG), Strength, Degradation products, Content Uniformity and Dissolution. Acceptance criteria are set based on the approved specifications for Alesse.

The drug product is packaged in two different configurations, the Cycle Pack and the Single Unit Dispenser (SUD). A new [redacted] was used to manufacture the commercial SUD because there were [redacted] impurities leaching out of the original SUD [redacted] . The sponsor has provided 18 months of stability data for drug product packaged in the Cycle Pack, and 15 months of stability on drug product packaged in the Single Unit Dispenser manufactured using old [redacted] , and 12 months of data on drug product packaged in the SUD manufactured using the new [redacted] . The sponsor has requested 24 months of expiry based on this submitted data. **All submitted stability data is on tablets manufactured by the [redacted] method.** b(4)

Based on analysis of 18 months of real-time data in the Cycle Pack, and 15 months (old) and 12 months (new) in the SUD, along with accelerated, intermediate, and in-use stability data on tablets manufactured by the method, an expiry (could be granted in both packaging configurations. This decision will have to be reevaluated in light of the reversion back and the analysis of the to-be-submitted data. Tablets are to be stored at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F). b(4)

The sponsor had submitted two comparability protocols for post-approval changes:

- Comparability Protocol for Packaging of the Single Unit Dispenser
- Comparability Protocol for the Replacement or Deletion of Montanic Ester Wax

Both comparability protocols can be approved.

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

Lybrel is packaged in two different configurations: the Cycle Pack and the SUD. For the Cycle Pack, a plastic tab is removed to allow rotation of the pill-containing ring. The ring is rotated to move the opening over a pill, which is then dropped into the hand. No protective blister is in place when the pills are in use. For the SUD, release of the pill is accomplished by squeezing the Dispenser to move the pill into an opening, where it is then dropped into the hand. Release of the Dispenser moves the next pill into place. As for the Cycle Pack, no protective blister is in place during use. One pill is to be taken daily, in a continuous-use regimen (no pill-free day). Each package contains 28 active tablets. After one package is finished, the next package is started the following day.

C. Basis for Approvability or Not-Approval Recommendation

The following issues must be resolved for Approval from a CMC standpoint. The PDUFA date is 27-Jun-2006.

The sponsor plans to submit the following data on 22-May-2006.

- Reversion to the manufacturing method from the method. The method is used to manufacture the approved Alesse tablets, but the sponsor has made minor changes to the method. Although it is thought that these minor changes will have no adverse impact on the quality of the drug product, and will in fact make the process more robust, data will need to be submitted and reviewed before a final decision can be made. b(4)
- CoAs for three lots of drug product manufactured by the revised method.
- Analysis of the supporting stability data (36 months) on the clinical trial supplies manufactured but stored in conventional blisters which are not one of the to-be-marketed container closure systems.

- Justification to revert back to the USP dissolution method from the sponsor's proposed method in the original NDA submission.
- Supporting data on the aproved product Alesse.

The sponsor plans to submit the following data on 22-Jun-2006.

- One month of stability data on the tablets manufactured by the modified [redacted] method packaged in the to-be-marketed container closure system. b(4)

Once the above data is submitted and reviewed, expiry will be determined based on the stability data already submitted on tablets manufactured by the [redacted] method and stored in the to-be-marketed container closure system, the supporting data on [redacted] tablets stored in conventional blisters, and data on tablets manufactured by the modified [redacted] method and stored in the to-be-marketed container closure system. Supporting data on the approved Alesse product will also be taken into consideration. The sponsor has been informed in a teleconference held on 04-May-2006 that it is "highly unlikely" that the data submitted within 36 days of the PDUFA date will be reviewed during this review cycle (Clinical Division Decision). They were also informed during the teleconference that 3 months of accelerated stability data is normally required for a Level 3 manufacturing change, and that 1 month of accelerated stability data in the to-be-marketed container closure system (to be submitted on 22-Jun-2006) may not be adequate to determine expiry. b(4)

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Donna F. Christner, Ph.D./Date: 15-May-2006
Moo-Jhong Rhee, Ph.D./Date
John Kim/Date

C. CC Block

Appears This Way
On Original

59 Page(s) Withheld

8 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

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/s/
Donna Christner
6/5/2006 03:17:08 PM
CHEMIST

Changes made as requested

Moo-Jhong Rhee
6/6/2006 05:08:26 PM
CHEMIST
Chief, Branch III

NDA FILEABILITY CHECKLIST

NDA Number: 21-864 Applicant: Wyeth Pharmaceuticals, Inc. Stamp Date: 27-May-2005

Drug Name: Levonorgestrel(LNG)/Ethinyl Estradiol (EE) Continuous Use

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		Contained in reference DMFs and NDA 20-683
8	Does the section contain controls for the drug product?	X		
9	Has stability data and analysis been provided to support the requested expiration date?	X		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?	x		

If the NDA is not fileable from a manufacturing and controls perspective state why it is not.

Review Chemist: Donna F. Christner, Ph.D. Date: 27-Jun-2005

Team Leader: Moo-Jhong Rhee, Ph.D. Date: 27-Jun-2005

cc:
Original NDA 21-864
HFD-580/Division File
HFD-580/Chem/Dchristner/MJRhee
HFD-580/PM/JKim
HFD-580/DivDir/DShames

9 Page(s) Withheld

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/s/

Donna Christner
7/15/05 10:57:13 AM
CHEMIST

Filing review

Moo-Jhong Rhee
7/15/05 11:25:44 AM
CHEMIST
I concur