CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-355

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

13. PATENT INFORMATION

Pursuant to 21 CFR 314.50(i)(ii), the undersigned declares that there are no relevant patents that claim either Drospirenone or Estradiol, or the Drospirenone/Estradiol drug product on which the investigations described in NDA 21-355 for Angeliq™ [Drospirenone/Estradiol] Tablets were conducted, or that claim the method of use of Drospirenone and/or Estradiol for Hormone Replacement Therapy [HRT] in the manner described in NDA 21-355.

BERLEX LABORATORIES, INC.

Ted Ikeda

Ted Ikeda
General Counsel Intellectual Properties

Nov. 8, 2001

Date

14. PATENT CERTIFICATION

A patent certification pursuant to 21 U.S.C. 355(b)(2) or (j)(2)(A) is not applicable to the New Drug Application for Angeliq™ [Drospirenone/Estradiol] Tablets, NDA 21-355.

BERLEX LABORATORIES, INC.

Ted Ikeda

Ted Ikeda
General Counsel Intellectual Properties

Nov. 8, 2001
Date

Request for Three Years Marketing Exclusivity

Pursuant to 21 U.S.C. 21 U.S.C. 355(c)(3)(D)(iii) and 355(j)(4)(D)(iii), and with reference to 21 CFR 314.50(j)(1) and 314.108(b)(4)(iv), Berlex Laboratories, Inc. hereby requests a period of three years marketing exclusivity for Angeliq™ [Drospirenone/Estradiol] Tablets, the subject of NDA 21-355. This request for a three-year exclusivity period is based upon the following criteria:

1. The Food and Drug Administration has not previously approved the Drospirenone/Estradiol Tablets, the subject of NDA 21-355.

2. The results of the two new clinical investigations included in NDA 21-355 for Angeliq™ [Drospirenone/Estradiol] Tablets that support a finding of substantial evidence of effectiveness of Drospirenone/Estradiol Tablets for the treatment of moderate to severe vasomotor symptoms associated with menopause and vulvar and vaginal atrophy, in women with an intact uterus:

   A. Study 97071 entitled, "Study for the Evaluation of the Bioequivalence of 17β-Estradiol from a Tablet, Containing Drospirenone (2 mg) and 17β-Estradiol (1 mg), Relative to Estrace® (1 mg) Tablet, a Marketed 17β-Estradiol Product". Report B274 for Study 97071 can be found in N21-355/hpbio/bio/b274.pdf.

   B. Study 96097 entitled, "A Multicenter, Double-Blind, Randomized Comparison of Continuous Oral Estradiol-Drospirenone Combinations and Continuous Oral Estradiol, examining the effect on the Endometrium, Symptoms, and Bleeding Patterns in Postmenopausal Women". Report A02827 for Study 96097 can be found in N21-355/clin- stat/enodmetrialprotectionindication/a02827.pdf.

3. A determination that the two aforementioned clinical investigations are essential to the approval of Drospirenone/Estradiol Tablets, the subject of NDA 21-355, for the treatment of moderate to severe vasomotor symptoms associated with menopause and vulvar and vaginal atrophy, in women with an intact uterus. Berlex Laboratories, Inc. certifies that there are not sufficient published studies or publicly available reports of clinical investigations to support the approval of NDA 21-355, other than those clinical investigations sponsored by Berlex Laboratories, Inc. under IND 53,842.

4. Berlex Laboratories, Inc. submitted IND 53,842 for Drospirenone/Estradiol Tablets to the Food and Drug Administration on July 25, 1997 for review by the Division of Reproductive and Urologic Drug Products, HFD-580.

EXCLUSIVITY SUMMARY

NDA # 21-355 SUPPL # HFD # 580

Trade Name Angeliq

Generic Name Drospirenone/Estradiol

Applicant Name Berlex Laboratories, Inc.

Approval Date, If Known

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)(2)

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

YES ☒ NO ☐

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

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

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3

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

YES ☐ NO ☒

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

No

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# 21-098 Yasmin

NDA# Estrace

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:

Report # A02827
Report #B274

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"):

Report #A02827
Report B274

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 # 53,842	YES ☒	! NO ☐
		! Explain:
Investigation #2		!
		!
IND # 53,842	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: Kassandra Sherrod, R.Ph
Title: Project Manager
Date: September 30, 2005

Name of Office/Division Director signing form: Daniel Shames, M.D.
Title: Division Director

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
10/7/2005 02:23:50 PM

Request for a Waiver from the Requirement to Assess the Safety and Effectiveness of New Drugs in Pediatric Patients

Berlex Laboratories requests a full waiver from the requirement to submit data adequate to assess the safety and efficacy of the drug product in all relevant pediatric subpopulations in accordance with 21 CFR 314.55(c)(2)(ii). Additional reference is made to the November 27, 2000 "*Guidance for Industry Recommendations for Complying with the Pediatric Rule (21 CFR 314.55 (a) and 601.27* (a)" which categorizes *Symptoms of Menopause* as a *Disease-specific waiver indicated for the treatment of the condition in adults.*

NDA number: 21-355

Sponsor: c/o
Michael Doroshuk
Berlex Laboratories, Inc.
340 Changebridge Road
P.O. Box 1000
Montville, N.J. 07045-1000

Indications:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of vulvar and vaginal atrophy

Age ranges included in pediatric waiver:

Ages 0 to 16 years

Reason for waiving pediatric studies:

Disease-specific waiver indicated for the treatment of symptoms of menopause in adults.

Berlex hopes that the above satisfies the Division's request for the waiver for pediatric studies and that no further action is required on the part of Berlex.

NDA 21-355
Drug: Angeliq™ (drospirenone/17β-estradiol)

Pediatric Information

This new drug application is not being approved. No pediatric page is required.

PMR 10/15/02

16. DEBARMENT CERTIFICATION

Certification Under Section 306(k)(1) of the FD & C Act

Berlex Laboratories, Inc., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with NDA 21-355 for Drospirenone/Estradiol Tablets.

BERLEX LABORATORIES, INC.

Joan Mutascio
Associate, Regulatory Submissions
& Information

Nov 5, 2001
Date

19. OTHER

FINANCIAL CERTIFICATION

Pursuant to 21 CFR 54, Berlex Laboratories, Inc. is providing certification for the investigators who participated in the four following covered clinical studies, concluded after the February 2, 1999 rule.

One U.S. study identified as Report No. A02827 (Study 96097A – Phase 3) "A Multicenter, Double-Blind, Randomized Comparison of Continuous Oral Estradiol-Drospirenone Combinations and Continuous Oral Estradiol, Examining the Effect on the Endometrium, Symptoms, and Bleeding Patterns in Postmenopausal Women" (Form FDA 3454 – Attachment 1)

One foreign study identified as Report No. B682 (Study 303063 – Phase 1) "Open-label study to assess the effect of 3 mg drospirenone (DRSP) on serum potassium and to evaluate the pharmacokinetics of DRSP in female volunteers with impaired or normal renal function after repeated oral administration over 14 days" (Form FDA 3454 – Attachment 2)

Two foreign studies identified as Report No A00824 (Study 304181 - Phase 1) "Open-label, randomized, crossover study to evaluate the potential of SH T 641 DA (combination preparation containing 1 mg estradiol and 3 mg drospirenone) to cause hyperkalemia after repeated oral administration for 17 days when coadministered with 75 mg indomethacin in healthy postmenopausal volunteers", and Report No. BD09 (Study 303741 – Phase 1) "Open-label, randomized, crossover study to assess the potential of drospirenone (DRSP) to inhibit Cytochrome P450 3A4 by evaluating the metabolic interaction between DRSP and simvastatin as model substrate in healthy postmenopausal volunteers" (Form FDA 3454 – Attachment 3)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

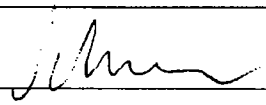
Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Dr. R. Schürmann	Head of Corporate Clinical Development FC/HT
FIRM/ORGANIZATION	
Schering AG	
SIGNATURE	**DATE**
	19 Nov 2001

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

Created by: PSC Media Arts (301) 443-2454 EF

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form approved: OMB No. 0910-0396
Expiration Date: 3/31/02

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if applicable)) submitted in support of this application, I certify to one of the statement below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

x (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator has a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Marie L. Foegh, MD, D. Sc.	Medical Director, Female Health Care, Clinical Research

FIRM / ORGANIZATION
Berlex Laboratories, Inc
PO Box 1000
Montville, New Jersey 07045-1000

SIGNATURE

DATE 4/5/01

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	
[illegible]	[illegible]

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
DR. ROLF SCHÜRMANN	INTERNATIONAL STUDY MANAGER, FEMALE HEALTHCARE
FIRM/ORGANIZATION: SCHERING AG	
SIGNATURE: [signature]	DATE: 03/03/2000

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

MEMORANDUM

To: Kassandra Sherrod, R.Ph.
Div. of Reproductive and Urologic Drugs

From: Iris Masucci, PharmD, BCPS
Christine Smith, PharmD
DDMAC

Date: September 16, 2005

Re: Comments on draft labeling for Angeliq (drospirenone/estradiol)
NDA 21-355

We have reviewed the proposed label for Angeliq dated March 31, 2005 and offer the following comments.

PI

Pharmacokinetics – Figure 1 and Table 2

Pharmacokinetics – Co-Administration with Drugs that Have the Potential to Increase Serum Potassium

Clinical Studies – Effects on Endometrium

2 Page(s) Withheld

_____ Trade Secret / Confidential

_X_ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 1A

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

/s/

Corrinne Kulick
9/19/2005 03:41:07 PM
DDMAC REVIEWER
Signed for Christine Smith, PharmD

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: July 1, 2005 **DOCUMENT DATE:** March 31, 2005	**DESIRED COMPLETION DATE:** September 1, 2005 **PDUFA DATE:** October 1, 2005	**ODS CONSULT #:** 02-0023-2

TO: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Kassandra Sherrod, R.Ph.
Project Manager
HFD-580

PRODUCT NAME: **Angeliq™** (Drospirenone/Estradiol Tablets) 0.5 mg/1 mg **NDA #:** 21-355	**SPONSOR:** Berlex, Inc.

SAFETY EVALUATOR: Todd D. Bridges, R.Ph.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Angeliq™, provided Angeliq™ is approved prior to the tradename ***. DMETS considers this a final review. However, if approval of the application is delayed beyond 90 days from the signature date of this review then the name and its labels and labeling must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the container labels, carton labeling, and package insert labeling revisions outlined in the Section III of this review in order to minimize user error.

3. DDMAC does not recommend approval of the proposed trade name "Angeliq" [redacted]

Denise P. Toyer, Pharm.D.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Carol Holquist, R.Ph.
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 18, 2005

NDA #: 21-355

NAME OF DRUG: **Angeliq™**
(Drospirenone/Estradiol Tablets)
0.5 mg/1 mg

NDA SPONSOR: Berlex, Inc.

NOTE: This review contains proprietary and confidential information that should not be released to the public.

I. INTRODUCTION

This consult was written in response to a March 31, 2005, request from your Division for a re-review of the proprietary name, Angeliq™. The proposed proprietary name, Angeliq™, was found acceptable by DMETS in ODS Consult 02-0023 dated July 9, 2002 and ODS Consult # 02-0023-1 dated June 25, 2004. However, the Division of Drug Marketing, Advertising and Communications (DDMAC) objected to the proposed proprietary name, Angeliq™, [redacted] Despite DDMAC's concerns, the Division of Reproductive and Urologic Drug Products made the decision to accept the tradename, Angeliq™.

PRODUCT INFORMATION

Angeliq™ is the proposed proprietary name for the combination hormone drug product containing drospirenone and estradiol. Drospirenone, a spironolactone analogue, is a progestogen with antimineralocorticoid activity. Angeliq™ is indicated, in women with an intact uterus, for the treatment of moderate to severe vasomotor symptoms and vulvar as well as vaginal atrophy associated with the menopause. The dispenser contains twenty-eight tablets, each tablet contains 0.5 mg of drospirenone and 1 mg of estradiol. The recommended dose is one tablet daily.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[i,ii] as well as several FDA databases[iii] for existing drug names which sound-alike or look-alike to Angeliq to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[iv] and the data provided by Thomson & Thomson's SAEGIS™ Online Service[v] were also conducted. An Expert Panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Angeliq. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. [redacted]

   [21 U.S.C. 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i); (e)(6)(i)].

2. The Expert Panel identified one additional proprietary name that was thought to have the potential for confusion with Angeliq. This product is listed in Table 1 (see page 4), along with the dosage form available and usual dosage.

---

[i] MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[ii] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[iii] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 1998-2005, and the electronic online version of the FDA Orange Book.

[iv] WWW location http://www.uspto.gov.

[v] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

NOTE: This review contains proprietary and confidential information that should not be released to the public.

Table 1: Potential Sound-Alike Name Identified for Angeliq

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Angeliq	Drospirenone and Estradiol 0.5 mg/1 mg tablets	One tablet daily	N/A
Agilect***	Rasagiline 0.5 mg, 1 mg tablets	One tablet daily	SA

*Frequently used, not all-inclusive.
**LA (look-alike), SA (sound-alike)
NOTE: This review contains proprietary and confidential information that should not be released to the public.

B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs though the phonetic algorithm. The phonetic search modules return a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Angeliq were discussed by the Expert Panel (EPD).

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, Angeliq, the primary concerns identified related to sound-alike confusion with Agilect***.

Angeliq may sound similar to Agilect*** when spoken. Agilect*** is currently under review at the Agency and the proprietary name has been reviewed by DMETS (ODS consult # 03-0142 and 03-0142-1, NDA # 21-641). DMETS did not have any objections to the use of the proprietary name, Agilect***, provided Agilect*** is approved prior to the tradename Angeliq. NDA # 21-641 received an approvable action on August 4, 2005. The phonetic similarities route from a shared three syllable count. Additionally, the names have some phonetic similarities when the name Angeliq is pronounced as (An-gel-ick) and the name.Agilect is pronounced as (A-gil-eck). The letter 't' at the end of Agilect may be silent, such as in "duct tape" and may not help to differentiate the names phonetically. Therefore, the two names may have similar sounding endings with '-ick vs. -eck', which are hard, palatal, oral stop sounds that sound like the letter 'k' when spoken. Additionally, the middle syllables of each name '-gil- vs. –gel-' are virtually indistinguishable phonetically since both have the soft letter 'g' sound. However, the first syllable in each name after the letter 'A' contributes to a different sounding prefix 'Ag- vs. Ang-'. However, the subtle sound of the letter 'n' may not always be noticeable to the listener. Furthermore, there are some product characteristics which may increase the potential for confusion between the two names. Overlapping product characteristics include route of administration (oral), dosage form (tablet), dosing frequency (once daily), dosage unit (mg), and storage area (pharmacy shelves). Angeliq is a combination tablet where the individual components strength (e.g., drospirenone 0.5 mg and estradiol 1 mg) overlap with the strengths of Agilect (0.5 mg and 1 mg). Usually combination products are ordered without a strength, but they also may be prescribed using only one of the strengths. Thus, an Angeliq prescription could be ordered as Angeliq 0.5 mg or Angeliq 1 mg and would be filled with the

combination product. The potential for Angeliq to be ordered with a strength increases the opportunity for confusion with Agilect. The potential overlapping strengths (i.e., 0.5 mg and 1 mg vs. 0.5 mg/1 mg), dosing intervals, route of administration, and phonetic similarities increases the potential for confusion between these two products. Therefore, DMETS does not feel that both the tradenames Angeliq and Angilect should co-exist in the marketplace. At this time, DMETS has no objections to the use of the proprietary name, Angeliq, provided that Angeliq is approved prior to the tradename Agilect***. However, should Agilect*** be approved prior to Angeliq, DMETS does not recommend use of the name Angeliq due to safety concerns with similarities between the two products.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In review of the revised labels and labeling for Angeliq, DMETS has focused on safety issues to prevent possible medication errors. Additionally, DMETS notes that none of the container label, carton and insert labeling recommendations made in ODS Consult 02-0023-1, dated June 25, 2004, have been addressed in this submission of the container label, carton and insert labeling. Thus, those recommendations are restated below. We have identified the following areas of improvement, in the interest of minimizing potential user error and patient safety.

A. GENERAL COMMENTS

1. The dosage form should be listed in conjunction with the established name and located below the proprietary name. Therefore, we suggest the following presentation:

   Angeliq
   (Drospirenone and Estradiol Tablets)
   0.5 mg/1 mg

2. Increase the font size of the established name, so that it is at least ½ the size of the proprietary name.

3. 

4. 

5. 

6. 

1 Page(s) Withheld

____ Trade Secret / Confidential

X Draft Labeling

____ Deliberative Process

Withheld Track Number: Administrative-1

D. PACKAGE INSERT LABELING

1. See General Comment A1.

2. Delete trailing zeros throughout labeling. DMETS notes that the Joint Commission for Accreditation of Hospitals (JCAHO), 2005 Hospitals National Patient Safety Goals includes the goal: Improve the effectiveness of communication among caregivers. A requirement to meet this goal is that each hospital must 'Standardize a list of abbreviations, acronyms and symbols that are not to be used throughout the organization. The use of trailing zeroes is specifically listed as a dangerous abbreviation, acronym, or symbol. Other healthcare organizations, such as ISMP have also published similar lists containing symbols that can lead to medication errors.

3. [redacted]

4. CLINICAL PHARMACOLOGY, PHARMACOKINETICS, DRUG INTERACTIONS

   Following the first use of any acronym, define the acronym (e.g., ACEI {angiotensin converting enzyme inhibitor}).

5. PRECAUTIONS

   Revise subsection heading "Patient Information" to read [redacted]

6. PRECAUTIONS, INFORMATION FOR PATIENTS

   List pertinent information physicians are to convey to patients for whom they prescribe Angeliq.

7. [redacted]

E. PATIENT INFORMATION LABELING

1. See General Comment A1 and Comment D7.

2. Include the statement [redacted]

3. Revise statement "Do not store above 86F (30C)." to read " [redacted]

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name, Angeliq™, provided Angeliq™ is approved prior to the tradename Agilect***. DMETS considers this a final review. However, if approval of the application is delayed beyond 90 days from the signature date of this review then the name and its labels and labeling must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

B. DMETS recommends implementation of the container labels, carton labeling, and package insert labeling revisions outlined in the Section III of this review in order to minimize user error.

C. DDMAC does not recommend approval of the proposed trade name "Angeliq"

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Diane Smith at 301-827-1998.

Todd D. Bridges, R.Ph.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Linda Kim-Jung, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

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/s/

Todd Bridges
9/7/2005 01:48:28 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
9/8/2005 02:19:51 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
9/8/2005 04:16:22 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
9/8/2005 04:19:51 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-355

Berlex Laboratories, Inc.
Attention: Michael Doroshuk
Manager, Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

Dear Mr. Doroshuk:

Please refer to your new drug application (NDA) dated October 14, 2001, received December 17, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Angeliq™ (drospirenone/17β-estradiol) ——— Tablets.

We acknowledge receipt of your submissions dated December 14, 2001, January 10, 14, 16, 21, February 1, 8, 15, March 7, 13, April 1, 11, May 1, 8, 13, June 10, 14, 19, July 3, 10, 11, 16, 17, 22, 26, August 8, 13, 15, 19, September 5, 10, 16, 30, and October 8, 16, 2002.

We completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

1. Post-marketing data on the oral contraceptive Yasmin® which contains drospirenone (3mg) suggests that users of Yasmin® have a higher reporting rate of thromboembolic events than that seen for users of other oral contraceptives. This raises serious concerns for an even greater risk of thrombogenic events in postmenopausal women, the population for which Angeliq™ is intended. Unlike the contraceptive population, the postmenopausal population is already at greater risk for cardiovascular disease and events. Study A02827 did not enroll sufficient numbers of at-risk subjects to adequately assess the effect of Angeliq™ on the incidence of thromboembolic events in this population.

2. There is insufficient safety data on the effects of Angeliq™ on serum potassium levels in postmenopausal women because Study A02827 did not enroll sufficient numbers of subjects with co-morbid conditions or those taking concomitant medications to adequately assess the effect of Angeliq™ on serum potassium levels in this population. Furthermore, this trial assessed potassium levels infrequently. In addition, the criteria for excluding blood samples collected for potassium measurement could have introduced bias against detection of hyperkalemia.

3. Our analysis of Study A02827 demonstrates an unacceptable endometrial safety profile because there was a high proportion of atypical endometrial hyperplasia in Angeliq™ subjects. Furthermore, upon review of the methods and conduct of the pathology readings, we are concerned that the efficacy readings cannot be relied upon to support endometrial protection. On several

occasions, there was disparity between the efficacy and safety readings of the same study slides, often by the same pathologist, rendering Study A02827 unreliable to support endometrial protection.

The following is needed to address these deficiencies:

1. The safety issues with respect to the risk of hyperkalemia and thromboembolic events should be addressed by a large clinical trial of postmenopausal subjects, including those on multiple medications with co-morbidity states associated with increased risk for hyperkalemia and thromboembolic events. The trial must provide a sufficiently precise risk estimate for hyperkalemia and thromboembolic events. To be approved, the benefits of Angeliq™ must clearly outweigh these risks.

2. The endometrial safety issue should be addressed by an additional clinical trial that demonstrates adequate endometrial protection.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application(s), notify us of your intent to file (an) amendment(s), or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application(s) under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Archana Reddy, M.P.H., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Division Director
Division of Reproductive and Urologic Drug Products
HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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
10/17/02 03:49:07 PM

MEMORANDUM

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

DATE: October 15, 2002

TO: Daniel Shames, M.D., Director
Division of Reproductive and Urologic Drug Products
HFD-580

VIA: Archana Reddy, M.P.H., Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products
HFD-580

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Anne Trontell, M.D., M.P.H., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for Angeliq® (drospirenone and estradiol), NDA 21-355

The patient labeling which follows represents the revised risk communication materials Angeliq® (drospirenone and estradiol), NDA 21-355, and has been reviewed by our office and by DDMAC. We have simplified wording, made it consistent with the PI, removed promotional language and other unnecessary information, and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

Outstanding questions or comments for the review division appear in the text and are bolded, italicized, and underlined. Please let us know if you have any questions.

5 Page(s) Withheld

_____ Trade Secret / Confidential

X
_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 2

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/s/

Jeanine Best
10/15/02 02:06:58 PM
CSO

Anne Trontell
10/15/02 03:59:46 PM
MEDICAL OFFICER

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA: 21-355	Efficacy Supplement Type SE-	Supplement Number: N/A
Drug: Angeliq™ (drospirenone/17β-estradiol)		Applicant: Berlex Laboratories, Inc.
RPM: Archana Reddy, M.P.H.	HFD- 580	Phone #: 7-5424
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name): IND 53,842 C —) NDA 21-098	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	Standard
• Other (e.g., orphan, OTC)	4s
❖ User Fee Goal Dates	October 17, 2002
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
Exclusivity Summary (approvals only)	N/A (Not approvable action)
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	X

General Information	
❖ Actions	
• Proposed action	( ) AP ( ) TA ( ) AE (X) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A (Not approvable action; no labeling review done)
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Yasmin C —)
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	X
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	* NIA
• Pre-NDA meeting (indicate date)	X JANUARY 24, 2007
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other (Status Meetings)	X
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	X
❖ Clinical review(s) *(indicate date for each review)*	X
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	X
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	N/A (Not approvable action)
❖ Statistical review(s) *(indicate date for each review)*	X
❖ Biopharmaceutical review(s) *(indicate date for each review)*	X
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	X
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	X (October 8, 2002)
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: **(X)** Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested **(X)** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	X
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	X
❖ CAC/ECAC report	N/A

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: October 2, 2002

To: Michael Doroshuk Manager, Drug Regulatory Affairs	**From:** Archana Reddy, M.P.H. Project Manager
Company: Berlex Laboratories, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 973-487-2016	**Fax number:** 301-827-4267
Phone number: 973-487-2184	**Phone number:** 301-827-4260

Subject: Clinical Comments

Total no. of pages including cover: 2

Comments:

Mike,

Clinical comments for Angeliq. Please provide a response as soon as possible.

Thanks,

Archana Reddy

PM, DRUDP

Document to be mailed: ☐ YES ☑ NO

1. Among women who seek therapy for menopausal symptoms, can you estimate the proportion who are taking drugs known to be associated with hyperkalemia? Please use the pool of women screened for your endometrial hyperplasia study, not the women who were eligible.

2. For the endometrial hyperplasia study, please provide the number of women who were screened and found ineligible based on each of the following abnormal screening labs hyperkalemia, abnormal liver function tests, and abnormal kidney function tests.

3. Please provide the same information for the ACE inhibitor study, the indomethacin study, the renal impairment study, and the liver impairment study.

BERLEX

UPS OVERNIGHT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

October 8, 2002

Daniel Shames, M.D, Director
Food and Drug Administration
Center for Drug Evaluation and Research
CDR (Central Document Room)
12229 Wilkins Ave
Rockville, Maryland 20852

Dear Dr. Shames:

Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
OTHER: Response to October 2, 2002 Request for Information – Clinical Comments to Sponsor

Reference is made to NDA 21-355 submitted on December 14, 2001 for ANGELIQ™ drospirenone and 17β-estradiol tablets, a hormone replacement therapy. Further reference is made to Safety Update Reports to NDA 21-355, submitted on April 11 and August 12, 2002.

This submission is in response to a TELEFAX received, October 2, 2002, from your representative, Archana Reddy. The FDA Clinical requests are bolded followed by a response from the sponsor.

1. **Among women who seek therapy for menopausal symptoms, can you estimate the proportion who are taking drugs known to be associated with hyperkalemia? Please use the pool of women screened for your endometrial hyperplasia study, not the women who were eligible.**

2. **For the endometrial hyperplasia study, please provide the number of women who were screened and found ineligible based on each of the following abnormal screening labs: hyperkalemia, abnormal liver function tests, and abnormal kidney function tests.**

For clinical requests 1 and 2, the attached TABLE 1 outlines, from the pool of subjects screened for the endometrial hyperplasia study, those subjects who were taking drugs known to be associated with hyperkalemia. This includes subjects exposed to short-term and/or long-term use of drugs known to be associated with hyperkalemia. A comprehensive list of drugs known to be associated with hyperkalemia

is provided. **(ATTACHMENT 1).** This list contains NSAIDS and ACE inhibitors provided in the integrated summary of safety in NDA 21-355 (Section 8.2.22), This list includes additional drugs (not previously submitted to the NDA) commonly associated with hyperkalemia (including angiotensin receptor antagonists, diuretics, potassium supplements, and digoxin).

This table also lists those subjects determined to be ineligible based on the following abnormal screening labs: hyperkalemia, abnormal liver function tests, and abnormal kidney function tests. Hyperkalemia was determined by individual study investigators and ranged from 5.5 to 6.0 mEq/L. There were no subjects in the pool of screened subjects that had a potassium level above 6.0 mEq/L. **(TABLE 1)**

3. Please provide the same information for the ACE inhibitor study, the indomethacin study, the renal impairment study, and the liver impairment study.

Berlex has confirmed by telephone on October 3, 2002, with your representative, Archana Reddy, that the above request "please provide the same information requested for the ACE inhibitor study, the indomethacin study, the renal impairment study, and the liver impairment study" refers to abnormal screening labs only, as defined in request number 2.

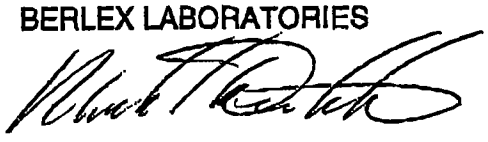
For request number 3, the attached TABLE 2 outlines the number of subjects in the above Phase 1 studies who were found ineligible based upon abnormal screening labs. Unless dictated by study protocol, hyperkalemia was determined by the individual study investigator. **(TABLE 2)**

NDA 21-355 is a fully electronic submission; therefore, we are also submitting this request for additional information in electronic format. This information is provided on one (1) diskette. Berlex Laboratories, Inc. certifies that the diskette has been scanned for viruses and is virus free using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54

Berlex trusts that today's submission satisfactorily addresses the clinical requests of October 2, 2002. Should you have any questions regarding this submission, please contact the undersigned at (973) 487-2184. The facsimile number is (973) 487-2016.

Sincerely,

BERLEX LABORATORIES



Michael Doroshuk
Manager
Drug Regulatory Affairs

Desk Copy: Archana Reddy

Table 1: Proportion of patients taking drugs known to be associated with hyperkalemia and number of women found ineligible based on abnormal screening labs in DRSP/E2 Study 96097

Study/Report #	N (screened)	Patients on medication associated with hyperkalemia N (%)*	Abnormal liver function tests N (%)**	Abnormal kidney function tests	Hyperkalemia (≥ 5.5 mEq/L) N (%)	Hyperkalemia (> 6.0 mEq/L)
96097/A02827 (Endometrium protection)	1825	670 (36.7)	42 (2.3)	none	1 (0.05)	none

* Included short-term and/or long-term medication, for *List of Drugs Known to be Associated with Hyperkalemia* please see Attachment 1

** as determined by individual study investigator

Table 2: Number of women found ineligible based on abnormal screening labs in DRSP/E2 Phase I studies

Study/Report #	N (screened)	Abnormal liver function tests N (%)	Abnormal kidney function tests N (%)	Elevated potassium - outside of the study specified reference range N (%)	Hyperkalemia (≥ 6.0 mEq/L)
98106/B990 (ACE inhibitor)	55	none	none	1 (1.8)**	none
ME304181/A00824 (Indomethacin)	81	5 (6.1)	none	4 (4.9)***	none
303063/B682 (Renal impairment)	38	none	1 (2.6)*	none	none
304666/A03161 (Hepatic impairment)	27	none	none	none	none

* in healthy control group
** reference range 3.5 - 4.5 mmol/l
*** reference range 3.4 - 4.4 mmol/l

List of Drugs known to be associated with hyperkalemia:

ACE Inhibitors and Combinations

- Accupril
- Accuretic
- Aceon
- Altace
- Benazepril
- Capoten
- Captopril
- Enalapril
- Fosinopril
- Lexxel
- Lisinopril
- Lotensin
- Lotrel
- Mavik
- Moexipril
- Monopril
- Perindopril
- Prinivil
- Prinzide
- Ramipril
- Quinapril
- Tarka
- Trandolupril
- Uniretic
- Univasc
- Vaseretic
- Vasotec
- Zestoretic
- Zestril

Angiotensin II Receptor Antagonists and Combinations

- Atacand
- Atacand HCT
- Avalide
- Avapro
- Cozaar
- Diovan
- Diovan HCT
- Hyzaar
- Micardis
- Micardis HCT
- Teveten

1

NSAIDs

- Advil
- Aleve
- Anaprox
- Apazone
- Arthrotec
- Cataflam
- Celebrex
- Celecoxib
- Clinoril
- Daypro
- Diclofenac
- Diflunisal
- Disalcid
- Dolobid
- Ecotrin
- Etodolac
- Feldene
- Fenoprofen
- Flurbiprofen
- Ibuprofen
- Indocin
- Indomethacin
- Ketoprofen
- Ketorolac
- Lodine
- Meclofenamate
- Mefenamic
- Meloxicam
- Motrin
- Nabumetone
- Nalfon
- Naprosyn
- Naprelan
- Naproxen
- Nuprin
- Orudis
- Orudis KT
- Oruvail
- Oxaprozin
- Piroxicam
- Ponstel
- Relafen
- Rofecoxib
- Salflex

- Salsalate
- Sulindac
- Tolmetin
- Tolectin
- Toradol
- Trilisate
- Vioxx
- Voltaren

ASPIRIN

- Alka Seltzer
- Alka-Seltzer
- ASA
- Aspirin
- Bayer Aspirin
- BC Powder
- Bufferin
- Butalbital
- Carisopradol and Aspirin
- Easprin
- Ecotrin
- Endodan
- Equagesic
- Excedrin
- Excederin
- Extra Strength Bayer
- Fiortal and Aspirin
- Goody
- Methoxycarbamol and Aspirin
- Norgesic
- Percodan
- Robaxisal
- Soma and Aspirin
- Salicylate

Diuretics, Potassium-sparing, and Hydrochlorothiazide (Systemic) :some commonly used brand names in the U.S. are:

- Aldactazide
- Amiloride
- Dyazide
- Dyrenium
- Maxzide
- Midamor
- Moduretic
- Spirozide
- Spironolactone
- Triamterene

Potassium Supplements: some commonly used brand names in the U.S. are:

- Cena-K
- Effer-K
- Gen-K
- Glu-K
- K-8
- K+ 10
- Kaochlor 10%
- Kaochlor S-F 10%
- Kaon
- Kaon-Cl
- Kaon-Cl-10
- Kaon-Cl 20% Liquid
- Kato
- Kay Ciel
- Kaylixir
- K+ Care
- K+ Care ET
- K-Dur
- K-Electrolyte
- K-G Elixir
- K-Ide
- K-Lease
- K-Lor
- Klor-Con 8
- Klor-Con 10
- Klor-Con/EF
- Klor-Con Powder
- Klor-Con/25 Powder
- Klorvess
- Klorvess Effervescent Granules
- Klorvess 10% Liquid
- Klotrix
- K-Lyte
- K-Lyte/Cl
- K-Lyte/Cl 50
- K-Lyte/Cl Powder
- K-Lyte DS
- K-Norm
- Kolyum
- K-Sol
- K-Tab
- K-Vescent
- Micro-K

- Micro-K 10
- Micro-K LS
- Potasalan
- Rum-K
- Slow-K
- Ten-K
- Tri-K
- Twin-K

Heparin (Systemic): Brand Names in the U.S.:

- Calciparine
- Heparin
- Liquaemin

Digoxin: Brand Names in the U.S.:

- Digitek
- Digoxin
- Lanoxin
- Lanoxicaps

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: September 30, 2002

To: Michael Doroshuk Manager, Drug Regulatory Affairs	**From:** Archana Reddy, M.P.H. Project Manager
Company: Berlex Laboratories, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 973-487-2016	**Fax number:** 301-827-4267
Phone number: 973-487-2184	**Phone number:** 301-827-4260

Subject: CMC Teleconference minutes of 7/16/02

Total no. of pages including cover: 4

Comments:

Mike,

Please find the teleconference minutes from the 7/16/02 minutes.

Thanks,

Archana Reddy

PM, DRUDP

Document to be mailed: ☐ YES ☑ NO

Meeting Minutes

Date: July 17, 2002 **Time:** 11:00 – 11:20 PM **Location:** 17B-43

NDA: 21-355 **Drug:** Angeliq™ (drospirenone/17-β estradiol)

Indication: ——— moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Seven-month Status Meeting

Meeting Chair: Shelley Slaughter, M.D., Ph.D.

Meeting Recorder: Archana Reddy, M.P.H.

FDA Attendees:
Shelley Slaughter, M.D., Ph.D., Reproductive Medical Team Leader, Division of Reproductive and Urologic Drug Products, (DRUDP; HFD-580)
Lesley Furlong, M.D., Medical Officer, DRUDP (HFD-580)
Archana Reddy, M.P.H., Regulatory Project Manager, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Su Tran, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)
Krishan Raheja, Ph.D., D.V.M., Pharmacology Reviewer, DRUDP (HFD-580)
Venkat Jarugula, Ph.D., Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

Meeting Objective: Seven-month status meeting

Background:
Angeliq™ (drospirenone/17-β estradiol) is a type 4 NDA (new combination) submitted by Berlex Laboratories, Inc. on December 14, 2001 and received on December 17, 2001 for hormone replacement therapy. The drug product is ——— tablet available in ——— Drospirenone (DRSP) is a novel progestin, a derivative of 17α-spironolactone, and similar to progesterone with progestogenic and aldosterone-antagonistic properties. DRSP is currently marketed as the progestin component in the oral contraceptive product Yasmin® (NDA 21-098). The User Fee goal date is October 17, 2002.

Discussion:

Chemistry:
- Negotiating dissolution specifications with sponsor; teleconference held on July 16th
- Recommend approval

Pharmacology/Toxicology:
- no safety concerns; review entered into DFS

Biopharmaceutics:
- Review is underway
- Elevated potassium levels found in the hepatic impairment study; in subjects with moderate hepatic impairment patients, a 3-fold increase in exposure was observed

Statistics:
- review is complete

Clinical
- nonapprovable based upon safety issues
- One case of hyperkalemia seen in a patient with hepatic impairment given a single dose of 3 mg formulation
- possibility that drospirenone is a thrombogenic progestin raised by postmarketing reports for Yasmin
- applicant's analysis of endometrial protection (including some histological FDA diagnoses is questionable but FDA analysis utilizing the safety diagnoses, still yield acceptable rates of hyperplasia
- at this stage of the review, there appears to be no clear benefit of this drug product over other existing HRT drug products
- the Medical Officer will address what the sponsor needs to do to overcome the deficiencies in the review

Decisions made:
- final reviews are due to the team leader by September 14, 2002
- the action package will be ready for circulation one month before the goal date

Minutes Preparer: Archana Reddy, M.P.H.

Concurrence: Meeting Chair
Shelley Slaughter, M.D.

Cc:
Original NDA 21-322
HFD-580/Division File
HFD-580/PM/Reddy
HFD-580/Slaughter/Shamesd/Furlong/Raheja/Jarugula/Tran/Rhee/Parekh/
HFD-715/Castillos

Drafted by: ar/July 17, 2002
Concurrence: ss/July 23, 2002, mjr/July 19, 2002, st/July 23, 2002, kr/July 18, 2002, lf/July 18, 2002
Finalized: ar/August 23, 2002

MEETING MINUTES

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

/s/

Shelley Slaughter
8/27/02 12:14:47 PM
I concur.

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

/s/

Archana Reddy
10/1/02 02:16:30 PM
CSO

BERLEX

UPS OVERNIGHT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

September 30, 2002

Daniel Shames, M.D
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention:CDR (Central Document Room)
12229 Wilkins Avenue
Rockville, Maryland 20852

Dear Dr. Shames:

Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
OTHER: Response Request for Information – Additional Biopharmaceutics Comments

Reference is made to NDA 21-355 submitted on December 14, 2001 for ANGELIQ™ drospirenone and 17β-estradiol tablets, a hormone replacement therapy. Reference is also made to a TELEFAX received August 30, 2002 from your representative Archana Reddy, which relayed specific questions from the biopharmaceutics reviewer regarding dissolution report A01500.

Additional reference is made to our submission of September 5, 2002 which contained our responses to the Division biopharmaceutics reviewer comments on dissolution report A01500. Reference is also made to a TELEFAX received September 23, 2002 from your representative Archana Reddy, which relayed additional questions from the biopharmaceutics reviewer. The FDA questions are bolded followed by a response from the sponsor.

1. **In your amendment dated September 2, 2002, you stated that the profile for SH T00641C is lower than the profile for formulation SH T00641D and it was mistakenly reported in dissolution report A01500. However, report A01499 for SH T00641C does not show that it's dissolution for DRSP is lower compared to SH T00641D In report A01500. Please explain the discrepancy between your statement and the results reported in the original submission.**

Formulation SH T00641C has a nominal content of 2 mg drospirenone, whereas formulation SH T00641D has a nominal content of 3 mg. Therefore the absolute values (in µg) obtained from dissolution testing are necessarily lower for the C formulation. To illustrate this point, please refer to Table 1 below:

Table 1

Dissolution in buffered solution with pH 6.5 30 minute withdrawal time for Drospirenone (n=12)			
Formulation SH T 00641C - Batch # 80301 (Reference: Report No. A01499, Section 3.3, Table 5)		**Formulation SH T00641D - Batch # 80301 (Reference: Report No. A01500, Section 3.3, Table 5)**	
Amount Released* (µg)	% Released	Amount Released* (µg)	% Released

* Corrected for Volume Withdrawn [as referenced from the ——— (German) column in reports A01499 and A01500].

To obtain the % released value, the amount released* in µg is divided by the ——— , in µg (2000 µg for SH T00641C and 3000 µg for SH T00641D) and multiplied by —

Therefore, when SH T00641C tablets were erroneously used for the 6.5 buffer dissolution test instead of the to-be-investigated formulation SH T00641D, as stated in the September 5, 2002 amendment, a lower dissolution profile was seen. The amount released for formulation SH T00641C (approaching 2000 µg) was compared against the label claim of SH T00641D (3000 µg), and maximum % released results of approximately 66% were observed in the dissolution profile.

The statement made in the September 5, 2002 amendment regarding a lower dissolution profile for formulation SH T00641C was made in reference to the lower amounts of drospirenone released in µg, compared to formulation SH T00641D.

2. **The batch numbers reported in the Dissolution summary section for pilot batches (#80301, 80302 and 80303) don't agree with the batch numbers reported in the individual reports (#80301 for all strengths). Please explain the discrepancy.**

In section 6.8.4 of NDA 21-355 (located in the Bioavailability/Bioequivalence Summary), the dissolution comparison between pilot and scale-up batches is discussed (this section corresponds to the Dissolution summary section referenced in the question above).

Dissolution was performed in five different media to link the pilot batches and the scale-up batches (scale-up batches = production scale intended for marketing). The batch numbers manufactured from the pilot and scale-up batches are identified in Table 2 below:

Table 2

Pilot Scale Batches (manufactured by Schering AG at Berlin, Germany site)		Scale-Up Batches (manufactured by Schering AG at Weimar, Germany site)	
Formulation	**Batch #**	**Formulation**	**Batch #'s**
SH T 641 BA	6421	SH T 641 B	80301, 80302, 80303
SH T 641 CA	AC007	SH T 641 C	80301, 80302, 80303
SH T 641 DA	AC008	SH T 641 D	80301, 80302, 80303

NOTE: In FDA's bolded question above, batches # 80301, 80302, and 80303 are wrongly referenced as pilot batches. Batches # 80301, 80302, and 80303 are the scale-up batches, as noted in the table.

For the scale-up batches, 3 lots of each formulation were manufactured (a total of 9 batches). Although the batch numbers are identical (these batch numbers are used by Schering AG to identify production scale validation batches), three separate batches of drug product were manufactured for each formulation.

Section 6.8.4 of NDA 21-355 specifies the following:

> Dissolution for one batch from each of the three formulations manufactured at Weimar, Germany [scaleup Batch No. 80301 (SH T 641 B), 80302 (SH T 641 C), 80303 (SH T 641 D)] and one batch for each of the three formulations manufactured at Berlin, Germany [Pilot batch No. 6421 (SH T 641 BA), AC007 (SH T 641 CA), AC008 (SH T 641 DA)] was performed.

Dissolution for one batch from each of the three formulations manufactured at Weimar, Germany was conducted, as specified in NDA 21-355. However, scale-up batch 80301 for each of the three formulations was tested, instead of scale-up batches 80302 (for formulation SH T 641 C) and 80303 (for formulation SH T 641 D). Berlex recognizes that the text identified above, found in section 6.8.4 of NDA 21-355, is ambiguous and confusing. The text should read:

> Dissolution for one batch from each of the three formulations manufactured at Weimar, Germany [scaleup Batch No. 80301 (SH T 641 B), 80301 (SH T 641 C), 80301 (SH T 641 D)] and one batch for each of the three formulations manufactured at Berlin, Germany [Pilot batch No. 6421 (SH T 641 BA), AC007 (SH T 641 CA), AC008 (SH T 641 DA)] was performed.

The ambiguous text of section 6.8.4 is the cause of the discrepancy noted by FDA. This administrative discrepancy has no effect on the results or conclusions drawn in Report Nos. A01498, A01499, and A01500. The correct pilot and scale-up formulations were used for the dissolution comparison.

NDA 21-355 is a fully electronic submission; therefore, we are submitting this request for additional information in electronic format. This information is provided on one (1) diskette. Berlex Laboratories, Inc. certifies that the diskette has been scanned for viruses and is virus free using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54.

Berlex trusts that this submission adequately addresses the September 23, 2002 request and serves to clarify this issue. Should you have any questions regarding this submission, please contact the undersigned at (973) 487-2184. The fax number is (973) 487-2016.

Sincerely,

BERLEX LABORATORIES

Michael Doroshuk
Manager - Drug Regulatory Affairs

Desk Copy: Archana Reddy

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: September 30, 2002

To: Michael Doroshuk Manager, Drug Regulatory Affairs	**From:** Archana Reddy, M.P.H. Project Manager
Company: Berlex Laboratories, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 973-487-2016	**Fax number:** 301-827-4267
Phone number: 973-487-2184	**Phone number:** 301-827-4260

Subject: CMC Teleconference minutes of 7/16/02

Total no. of pages including cover: 4

Comments:

Mike,

Please find the teleconference minutes from the 7/16/02 minutes.

Thanks,

Archana Reddy

PM, DRUDP

Document to be mailed: ☐ YES ☑ NO

Teleconference Minutes

Date: July 16, 2002 **Time:** 11:00 – 11:20 PM **Location:** PKLN 17B-45

NDA: 21-355 **Drug:** Angeliq™ (drospirenone/17-β estradiol)

Sponsor: Berlex Laboratories, Inc.

Meeting Chair: Moo-Jhong Rhee, Ph.D.

Type of Meeting: Chemistry (Guidance)

External Participant Lead: Michael Doroshuk

Meeting Recorder: Archana Reddy, M.P.H.

Indication: [redacted] of moderate to severe vasomotor symptoms and vulvar and vaginal atrophy in post menopausal women

External Participants:
Michael Doroshuk, Manager, Drug Regulatory Affairs
Shawn Hoskins, Senior CMC Representative

FDA Participants:
Archana Reddy, M.P.H., Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580
Suong Tran, Ph.D., Chemistry Reviewer, DRUDP, HFD-580
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, DRUDP (HFD-580)
Venkat Jarugula, Ph.D., Biopharmaceutics/Clinical Pharmacology Reviewer, DRUDP (HFD-580)

Background:
Angeliq™ (drospirenone/17-β estradiol) is a type 4 NDA (new combination) submitted by Berlex Laboratories, Inc. on December 14, 2001, and received on December 17, 2001, for hormone replacement therapy. The sponsor proposed the dissolution specifications, which are deemed too wide to discern changes in the quality of the drug product.

Meeting Objectives:
To discuss the dissolution specifications for Angeliq™.

Discussion:

Question:
Berlex proposes that the current dissolution specification (E2 Q=[redacted] DRSP Q=[redacted] remains in place. What is the rationale behind the Division's suggested changes for these dissolution specifications for the Angeliq™ drug product?

DRUDP comments

- the rationale for changing the [redacted] minute withdrawal time to [redacted] minutes; based on the dissolution profiles of the clinical batches which support E2 Q=[redacted] DRSP Q=[redacted] minutes
- if stability batches have difficulty in meeting the dissolution specifications; then expiration date may have to be adjusted accordingly
- if Berlex wants to change Q value at [redacted] minutes; the Q value should be set so that some discriminatory power can be exhibited; ideally DRUDP would recommend [redacted] minutes, but acknowledges that this is impractical so [redacted] minutes is recommended
- Sponsor argued that Q = [redacted] % for DRSP and Q = [redacted] % for E2 at [redacted] minutes may be difficult to meet; sponsor noted that the USP 25 for Estradiol tablets is a 60 minute sampling time compared to USP 25; Berlex's proposal is a more discriminatory acceptance criterion for E2; DRUDP clarified that the USP is a minimum requirement and that the sampling time should be based on historical data of the specific product
- Sponsor agrees to the [redacted]; for the withdrawal time (Q value); E2 = [redacted] %; DRSP = [redacted] %

Decision reached:
Berlex has agreed to submit an amendment to the NDA to change the current dissolution specifications for both drug substances (from estradiol Q=[redacted] % at [redacted] minutes and drospirenone Q=[redacted] % at [redacted] minutes) to Q=[redacted] % for E2 and Q=[redacted] % for DRSP at [redacted] minutes as recommened by DRUDP.

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

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader

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

/s/

Moo-Jhong Rhee
10/1/02 01:21:06 PM

UPS OVERNIGHT

ORIGINAL

BERLEX

ORIG AMENDMENT

N-000-15L

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

September 30, 2002

Daniel Shames, M.D
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention:CDR (Central Document Room)
12229 Wilkins Avenue
Rockville, Maryland 20852

RECEIVED
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CDR/CDER

RECEIVED
OCT 0 3 2002
FDR/CDER

Dear Dr. Shames:

Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
OTHER: Response to Requests for Information – Chemistry comments regarding container labels dated 10 September-2002

Reference is made to NDA 21-355 submitted on December 14, 2001 for ANGELIQ™ (drospirenone and 17β-estradiol tablets), a hormone replacement therapy. Reference is also made to revised container/carton label mock-ups for the above drug product submitted on September 10, 2002. Further reference is made to telephone conversations between the undersigned and the reviewing chemist, Dr. Su Tran and a follow-up conversation between Division Chemistry team Leader, Dr. Moo-Jhong Rhee and representatives of Berlex Laboratories.

On September 26, 2002, Dr. Tran telephoned the undersigned regarding the carton and container label for Angeliq. Dr. Tran's concern was that Berlex did not adhere to 21 CFR 201.10(g)(2) which provides for the established name to be printed in letters that are at least half as large as the letters comprising the proprietary name. During this telephone conversation and again during a follow-up conversation with Dr. Tran on September 27, 2002, the undersigned cited 21 CFR 201.10(h)(1), which, in the case of prescription drug products containing two or more active ingredients, allows for the prominence of the quantitative ingredient information to bear a reasonable relationship to the prominence of the proprietary name. Angeliq clearly has two active ingredients and should therefore be permitted the allowance of "reasonable relationship to the prominence of the proprietary name" set forth in 21 CFR 201.10(h)(1). The undersigned also made reference to several Berlex prescription drug products, approved by this Division, that contain two active ingredients and, for that reason, were not subject to the height

requirement set forth in 21 CFR 201.10 (g)(2). On September 27, 2002, Division Chemistry Leader Dr. Moo-Jhong Rhee telephoned the undersigned to discuss this issue and seek adherence to the height requirement for the quantitative ingredients in the Angeliq carton/container label as set forth in 21 CFR 201.10(g)(2). June Bray, Vice President of Drug Regulatory Affairs, Berlex Laboratories, joined this conversation with Dr. Rhee and a negotiated agreement was reached wherein Berlex would attempt to increase the font size of the quantitative ingredient information in carton/container labeling for Angeliq by 10% if possible and a representative sample of that change would be sent to the reviewing chemist as soon as possible.

Berlex has complied with the agreement to increase font size and is herewith submitting the requested change to carton/container labeling for Angeliq. For the reviewer's convenience, this submission contains a side-by-side comparison between the previously submitted carton/container labels and the revised labels with the 10% increase in font size. Berlex trusts that today's submission satisfactorily addresses the issue regarding the height and prominence of the quantitative ingredient information in the Angeliq carton/container labeling.

NDA 21-355 is a fully electronic submission; therefore, we are submitting this request for additional information in electronic format. This information is provided on one (1) diskette. Berlex Laboratories, Inc. certifies that the diskette has been scanned for viruses and is virus free using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54.

Should you have any questions regarding this submission, please contact the undersigned at (973) 487-2184. The fax number is (973) 487-2016.

Sincerely,

BERLEX LABORATORIES

Michael Doroshuk
Manager - Drug Regulatory Affairs

Desk Copy: Archana Reddy

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: September 23, 2002

To: Michael Doroshuk Manager, Drug Regulatory Affairs	**From:** Archana Reddy, M.P.H. Project Manager
Company: Berlex Laboratories, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 973-487-2016	**Fax number:** 301-827-4267
Phone number: 973-487-2184	**Phone number:** 301-827-4260

Subject: Request for clinical pharmacology information

Total no. of pages including cover: 2

Comments:

Mike,

Please find attached clinical pharmacology comments for Angeliq™ (NDA 21-355). Provide a written response as soon as possible.

Thanks,

Archana Reddy

PM, DRUDP

Document to be mailed: ☐ YES ☑ NO

NDA: 21-355
Drug: Angeliq™
Sponsor: Berlex Laboratories

1. In your amendment dated September 2, 2002, you have stated that the profile for SH T00641C is lower than the profile for formulation SH T00641D and it was mistakenly reported in dissolution report A01500. However, report A01499 for SH T00641C does not show that its dissolution for DRSP is lower compared to SH T00641D in report A01500. Please explain the discrepancy between your statement and the results reported in the original submission.

2. The batch numbers reported in the Dissolution summary section for pilot batches (#80301, 80302 and 80303) don't agree with the batch numbers reported in the individual reports(#80301 for all strengths). Please explain the discrepancy.

UPS OVERNIGHT

ORIGINAL

BERLEX

N 0000 BL
ORIG AMENDMENT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

September 16, 2002

RECEIVED
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SEP 17 2002
CDR/CDER

Daniel Shames, M.D, Director
Food and Drug Administration
Center for Drug Evaluation and Research
CDR (Central Document Room)
12229 Wilkins Ave.
Rockville, Maryland 20852

Dear Dr. Shames:

Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
OTHER: Response to September 12, 2002 Request for Information – Final Draft labeling

Reference is made to NDA 21-355 submitted on December 14, 2001 for ANGELIQ™ drospirenone and 17β-estradiol tablets, a hormone replacement therapy.

Further reference is made to a telephone conversation on September 12, 2002 with your representative, Archana Reddy, requesting the final draft labeling for ANGELIQ. During this conversation, the undersigned asked if the Division could offer any advice on inclusion of results, or reference to, the Women's Health Initiative study in the labeling. Ms. Reddy informed the undersigned not to include anything about the Women's Health Initiative as this was still under discussion.

Attached please find an electronic copy of the revised Physician prescribing information consisting of 19 pages and dated September 13, 2002. This document was also sent via telefax to the Division Project Manager, Archana Reddy on September 13, 2002, as per Ms. Reddy's request. This document incorporates changes from the original Physician prescribing information submitted with NDA 21-355 on December 14, 2001. Today's submission includes a clean (unmarked) copy of the labeling and a marked copy, indicating changes from the original December 14, 2001 version. Revisions in this final draft labeling contain the following changes requested by the Division during the NDA review have been incorporated into the final draft labeling.

1. Information regarding the safety and pharmacokinetics of ANGELIQ in women with moderate hepatic impairment submitted May 8, 2002.

2. Removal of [redacted] indications for ANGELIQ, as instructed in a February 19, 2002 teleconference with Division representatives Diane Moore and Archana Reddy.

3. Revision of HOW SUPPLIED section as requested by the Chemistry Reviewer in a telefax dated August 26, 2002.

NDA 21-355 is a fully electronic submission; therefore, we are submitting this request for additional information in electronic format. This information is provided on one (1) diskette. Berlex Laboratories, Inc. certifies that the diskette has been scanned for viruses and is virus free using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54.

Berlex trusts that today's submission addresses the September 12, 2002 request for final draft labeling. Should you have any questions regarding this submission, please contact the undersigned at (973) 487-2184.

Sincerely,

BERLEX LABORATORIES

Michael Doroshuk
Manager
Drug Regulatory Affairs

Desk Copy: Archana Reddy
(letter and labeling via telefax)

Meeting Minutes

Date: September 12, 2002 **Time:** 2:30 – 3:00 PM **Location:** 17B-43

NDA: 21-355 **Drug:** Angeliq™ (drospirenone/17-β estradiol)

Indication: [redacted] moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Nine-month Status Meeting

Meeting Chair: Lesley Furlong, M.D.

Meeting Recorder: Archana Reddy, M.P.H.

FDA Attendees:
Lesley Furlong, M.D., Medical Officer, DRUDP (HFD-580)
Archana Reddy, M.P.H., Regulatory Project Manager, DRUDP (HFD-580)
Su Tran, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)
Krishan Raheja, Ph.D., D.V.M., Pharmacology Reviewer, DRUDP (HFD-580)

Meeting Objective: Nine-month status meeting

Background:
Angeliq™ (drospirenone/17-β estradiol) is a type 4 NDA (new combination) submitted by Berlex Laboratories, Inc. on December 14, 2001 and received on December 17, 2001 for hormone replacement therapy. The drug product is [redacted] drospirenone and 1 mg estradiol per tablet). Drospirenone (DRSP) is a novel progestin, a derivative of 17α-spironolactone, and similar to progesterone with progestogenic and aldosterone-antagonistic properties. DRSP is currently marketed as the progestin component in the oral contraceptive product Yasmin® (NDA 21-098). The User Fee goal date is October 17, 2002.

Discussion:

Chemistry:
- Chemistry Review # 1 is complete and signed-off in DFS by Chemistry Team Leader
- All chemistry issues have been satisfactorily resolved with the exception of labeling; additional draft labeling received on September 16, 2002 and will be reviewed in Chemistry Review # 2

Pharmacology/Toxicology:
- no safety concerns; review entered into DFS on April 29, 2002

Biopharmaceutics/Clinical Pharmacology

- Review is complete; labeling revisions are pending; OCPB briefing scheduled for September 30, 2002
- DSI report on BE study is acceptable

Statistics:

- Review submitted to Team Leader and will be signed off in DFS by the end of the week

Clinical

- nonapprovable based upon safety issues
- Medical Primary Reviewer has submitted a draft review to the Medical Team Leader

Decisions made:

- final reviews are due to the team leader by September 14, 2002
- the action package will be ready for circulation one month before the goal date

Regulatory:

- Tradename review is complete; tradename is acceptable
- DSI inspections are complete; report complete
- Bioequivalence report is complete; site inspected is acceptable

Minutes Preparer: Archana Reddy, M.P.H.

Concurrence: Meeting Chair
Lesley Furlong, M.D.

Cc:
Original NDA 21-322
HFD-580/Division File
HFD-580/PM/Reddy
HFD-580/Slaughter/Shamesd/Furlong/Raheja/Jarugula/Tran/Rhee/Parekh/
HFD-715/Castillos

Drafted by: ar/September 18, 2002
Concurrence: st/September 17, 2002, kr/September 17, 2002, lf/September 17, 2002, vj/September 17, 2002
Finalized: ar/September 27, 2002

MEETING MINUTES

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

/s/

Leslie Ann Furlong
10/4/02 10:56:53 AM

ORIGINAL

BERLEX

UPS OVERNIGHT

RECEIVED
SEP 13 2002
FDR/CDER

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

September 10, 2002

RECEIVED
SEP 11 2002
CDR/CDER

Daniel Shames, M.D
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention:CDR (Central Document Room)
12229 Wilkins Avenue
Rockville, Maryland 20852

ORIG AMENDMENT
N-000-BL

Dear Dr. Shames:

Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
OTHER: Response to Requests for Information – Chemistry comments regarding container labels dated 15-Aug-2002 and chemistry comments to the Physician's Insert dated 14-Dec-2001

Reference is made to NDA 21-355 submitted on December 14, 2001 for ANGELIQ™ drospirenone and 17β-estradiol tablets, a hormone replacement therapy. Reference is also made to a TELEFAX received August 26, 2002 from your representative, Archana Reddy which relayed specific questions from the chemistry reviewer regarding carton/container labels and Physician's insert for ANGELIQ™ tablets. The FDA questions are bolded followed by a response from the sponsor.

Regarding the container labels dated 15-AUG-2002:

1 Replace "Angeliq" with "Angeliq Tablets".

Berlex has added the word "tablets" to the container and carton label.

2 **Change the height of the text of the established name to be at least half the height of "A" in "Angeliq" and change the color of the text to a darker color, such as black, to make the text more legible.**

In compliance with § CFR 201.10(h)(1) which, in the case of a prescription drug containing two or more active ingredients, allows for the prominence of the quantitative ingredient information to bear a reasonable relationship to the prominence of the proprietary name. Berlex has made efforts to display the quantitative ingredient information in a reasonable relationship to the prominence of the proprietary name. Berlex has also placed the quantitative ingredient information directly under the proprietary name (white lettering in the dark field) which provides distinct recognition of the quantitative ingredient information.

3 **Change the color of the highlight for [redacted] to a brighter shade of [redacted]**

Berlex has incorporated the dose information as part of the logo therefore, making them more prominent.

4

5

6

Comments regarding the Physician's Insert dated 14-DEC-2001:

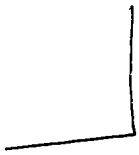
Berlex has revised the Physician's Insert to reflect the following presentation. This presentation has been incorporated into the current Draft Physician's Insert. Because we anticipate numerous changes to the Physician's Insert prior to the Action Date of October 17, 2002, Berlex will submit the following changes along with future revisions in labeling prior to the action date.

Revised title of the Physician's Insert:

ANGELIQ TABLETS
(drospirenone and estradiol)

Revised How Supplied section of the Physician's Insert:
HOW SUPPLIED

ANGELIQ TABLETS (drospirenone and estradiol) ~~~ are available as round, ~~ pink, film-coated tablets embossed with ~~ inside a hexagon, and supplied in the following packaging:



NDA 21-355 is a fully electronic submission; therefore, we are submitting this request for additional information in electronic format. This information is provided on one (1) compact disk (CD). Berlex Laboratories, Inc. certifies that the CD has been scanned for viruses and is virus free using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54. In addition, Berlex is providing one (1) matchprint of the labels to more accurately represent the true label color.

Berlex trusts that this submission adequately addresses the August 26, 2002 request. Should you have any questions regarding this submission, please contact the undersigned at (973) 487-2184. The fax number is (973) 487-2016.

Sincerely,

BERLEX LABORATORIES

Michael Doroshuk
Manager - Drug Regulatory Affairs

Desk Copy: Archana Reddy
cmd/101

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: August 30, 2002

To: Michael Doroshuk Manager, Drug Regulatory Affairs	**From:** Archana Reddy, M.P.H. Project Manager
Company: Berlex Laboratories, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 973-487-2016	**Fax number:** 301-827-4267
Phone number: 973-487-2184	**Phone number:** 301-827-4260

Subject: Request for clinical pharmacology information

Total no. of pages including cover: 2

Comments:

Mike,

Please find attached clinical pharmacology comments for Angeliq™ (NDA 21-355). Provide a written response as soon as possible.

Thanks,

Archana Reddy

PM, DRUDP

Document to be mailed: ☐ YES ☑ NO

- In Dissolution Report A01500, the reported F2 values don't agree with actual dissolution profiles. Specifically, the release profiles of drospirenone at pH 6.5 are different between pilot and scale up batches. But the reported F2 value is high. Please explain this discrepancy.
- Please explain why the dissolution profile of drospirenone at pH 6.5 is different between pilot and scale up batches.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: August 26, 2002

To: Michael Doroshuk Manager, Drug Regulatory Affairs	**From:** Archana Reddy, M.P.H. Project Manager
Company: Berlex Laboratories, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 973-487-2016	**Fax number:** 301-827-4267
Phone number: 973-487-2184	**Phone number:** 301-827-4260

Subject: Chemistry comments (Labeling)

Total no. of pages including cover: 2

Comments:

Mike,

Please find attached chemistry comments for Angeliq™ (NDA 21-355). Provide a written response as soon as possible.

Thanks,

Archana Reddy

PM, DRUDP

Document to be mailed: ☐ YES ☑ NO

Comments regarding the container labels dated 15-AUG-2002:

1. Replace "Angeliq" with "Angeliq Tablets".
2. Change the height of the text of the established name to be at least half the height of "A" in "Angeliq" and change the color of the text to a darker color, such as black, to make the text more legible.
3.
4.
5.
6.

Comments regarding the Physician's Insert dated 14-DEC-2001:

Revised title of the Physician's Insert:

ANGELIQ TABLETS
(drospirenone and estradiol)

Revised How Supplied section of the Physician's Insert:

HOW SUPPLIED
ANGELIQ TABLETS (drospirenone and estradiol) are available as round, pink, film-coated tablets embossed with inside a hexagon, and supplied in the following packaging:

Store at 25° C (77° F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].
REFERENCES FURNISHED UPON REQUEST

Reddy

MEMORANDUM

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

DATE: August 20, 2002

FROM: Martin K. Yau, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. MFbelly for 8/20/02
Associate Director, Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 21-355
Angeliq® (Drospirenone/17ß-Estradiol) Tablets
Sponsored by Berlex Laboratories

TO: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products (HFD-580)

At the request of HFD-580, the Division of Scientific Investigations conducted an audit of the following bioequivalence study:

> **Protocol 97071**: Study for the Evaluation of the Bioequivalence of 17ß-Estradiol from a Tablet, Containing Drospirenone (2 mg) and 17ß-Estradiol (1 mg), Relative to Estrace® (1 mg) Tablet, a Marketed 17ß-Estradiol Product.

The clinical portion of the study was conducted by [redacted] The analytical portion of the study was conducted by [redacted]

Following the inspection of the clinical site (6/10-14/02) and the analytical site (5/13-15/2002), Form 483 was issued at each site. The objectionable items and our evaluation of the findings are as follow:

Clinical Site: [redacted]

1. **The screening ECG for subjects 027 and 028 were annotated to indicate that the sponsor was notified of abnormal findings and approved their inclusion in the study. However, there is no documented evidence showing that the sponsor approved the enrollment of these subjects.**

2. **ECG for subject 19 at discharge showed premature ventricular contractions not present at screening ECG. Both ECGs were reported as normal to the sponsor on the case report form.**

The site should correct the above objectionable observations that involved safety of study subjects. The above observations, however, should not have a significant impact on the study outcomes. [Note: Item 2 was discussed in the EIR but not listed on the Form FDA-483]

Analytical Site: [redacted]

5. **An [redacted] was used for the quantitation of estrone [redacted] and estrone sulfate [redacted]. The [redacted] used is a theoretical value and is not confirmed by experiment. Limited experimental data was generated during the inspection to confirm the theoretical [redacted].**

   In the written 483 response, the site provided additional experimental data to confirm the theoretical [redacted] (see Attachment 1). These additional data were reviewed by DSI and found to be adequate.

Conclusion:

The Division of Scientific Investigations recommends that Angeliq® Study 97071 be accepted for Agency review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Martin K. Yau 8/20/02

Martin K. Yau, Ph.D.

Attachment

Final Classification:

VAI

VAI

cc:
HFA-224
HFD-45/Rhoads
HFD-48/Yau/O Shaughnessy(2)/cf
HFD-580/Reddy
HFD-870/Jarugula/Parekh
HFR-CE2545/Cortes
HFR-CE250/Salisbury
HFR-SE2575/Collado
HFR-SE250/Torres
Draft: MKY 8/20/02
Edit: MFS 8/20/02
File:5418 O:\BE\eircover\21355Ber.est.doc

FACTS 287647

Attachment 1

5 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 3

Meeting Minutes

Date: August 20, 2002 **Time:** 11:00 – 11:20 PM **Location:** 17B-43

NDA: 21-355 **Drug:** Angeliq™ (drospirenone/17-β estradiol)

Indication: ——— moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Eight-month Status Meeting

Meeting Chair: Lesley Furlong, M.D.

Meeting Recorder: Archana Reddy, M.P.H.

FDA Attendees:
Lesley Furlong, M.D., Medical Officer, DRUDP (HFD-580)
Archana Reddy, M.P.H., Regulatory Project Manager, DRUDP (HFD-580)
Su Tran, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)
Krishan Raheja, Ph.D., D.V.M., Pharmacology Reviewer, DRUDP (HFD-580)

Meeting Objective: Eight-month status meeting

Background:
Angeliq™ (drospirenone/17-β estradiol) is a type 4 NDA (new combination) submitted by Berlex Laboratories, Inc. on December 14, 2001 and received on December 17, 2001 for hormone replacement therapy. The drug product is an ———

drospirenone and 1 mg estradiol per tablet). Drospirenone (DRSP) is a novel progestin, a derivative of 17α-spironolactone, and similar to progesterone with progestogenic and aldosterone-antagonistic properties. DRSP is currently marketed as the progestin component in the oral contraceptive product Yasmin® (NDA 21-098). The User Fee goal date is October 17, 2002.

Discussion:

Chemistry:
- Recommend approvable for ——— dosage form pending labeling
- Review is complete and signed-off in DFS by Chemistry Team Leader

Pharmacology/Toxicology:
- no safety concerns; review entered into DFS

Biopharmaceutics/Clinical Pharmacology

- Review to be complete by the end of September
- Increased exposure of DRSP in hepatic impairment subjects; in the past this issue has been addressed by means of labeling (Class labeling for HRT products contraindicates for liver dysfunction)
- DSI report on BE study is acceptable

Statistics:

- review is complete

Clinical

- nonapprovable based upon safety issues
- Medical Team Leader has a draft of the clinical review

Decisions made:

- final reviews are due to the team leader by September 14, 2002
- the action package will be ready for circulation one month before the goal date

Regulatory:

- Tradename review is complete; tradename is acceptable
- DSI inspections are complete; report complete
- Bioequivalence report is complete; site inspected is acceptable

Minutes Preparer: Archana Reddy, M.P.H.

Concurrence: Meeting Chair
Lesley Furlong, M.D.

Cc:
Original NDA 21-322
HFD-580/Division File
HFD-580/PM/Reddy
HFD-580/Slaughter/Shamesd/Furlong/Raheja/Jarugula/Tran/Rhee/Parekh/
HFD-715/Castillos

Drafted by: ar/August 20, 2002
Concurrence: st/August 29, 2002, kr/September 5, 2002, lf/September 5, 2002, vj/August 20, 2002
Finalized: ar/September 17, 2002

MEETING MINUTES

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

/s/

Leslie Ann Furlong
9/17/02 02:21:40 PM

BERLEX

UPS OVERNIGHT

August 19, 2002

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

Daniel Shames, MD, Director
Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-580, Room 17B-45
Rockville, Maryland 20857-1706

Dear Dr. Shames:

Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
AMENDMENT TO PENDING APPLICATION:
Chemistry, Manufacturing and Controls Amendment
to Drug Master File No. —

Reference is made to NDA 21-355 submitted on December 14, 2001 for ANGELIQ™ drospirenone and 17β-estradiol tablets, a hormone replacement therapy. Reference is also made to Type II Drug Master File (DMF) No. 12138 for drospirenone drug substance.

DMF No. 12138 was amended on July 3, 2002, as described in the attached 4-page summary (DMF amendment cover letter followed by a 3-page summary of the changes). Immediately following this correspondence is a July 3, 2002 letter from the DMF holder, our parent company, Schering AG authorizing the FDA to reference DMF No. 12138 on behalf of Berlex.

Berlex is NDA 21-355 is a fully electronic submission; therefore, we are also submitting this Amendment to a Pending Application in electronic format. This Amendment is provided on one (1) diskette. Berlex Laboratories, Inc. certifies that the diskette has been scanned for viruses and is virus free using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54. The diskette is being sent under separate cover to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room 17B-20
5600 Fishers Lane
Rockville, Maryland 20857

Should you require any additional information or have any questions regarding today's submission, please contact the undersigned at (973) 487-2184. The fax number is (973) 487-2016.

Sincerely,

BERLEX LABORATORIES

Michael Doroshuk
Manager
Drug Regulatory Affairs

Desk Copy: Archana Reddy

CMD/letter/angeliq090

N-022 BL

UPS OVERNIGHT

ORIGINAL

BERLEX

August 15, 2002

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

Daniel Shames, MD, Director
Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-580, Room 17B-45
Rockville, Maryland 20857-1706

RECEIVED
AUG 16 2002
FDR/CDER

Dear Dr. Shames:

Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
OTHER: Carton/Container labeling Mock-ups

Reference is made to NDA 21-355 submitted on December 14, 2001 for ANGELIQ™ drospirenone and 17β-estradiol tablets, a hormone replacement therapy. Further reference is made to the March 21, 2002 telefax received from the Chemistry team leader, Dr. Moo Jong Rhee, requesting container labeling mock-ups be provided by August 16, 2002. Additional reference is made the August 1, 2002 email from your representative, Archana Reddy requesting changes to container labeling from the Office of Drug Safety.

Comments from the Office of Drug Safety regarding the labeling for Angeliq tablets are highlighted in bold, followed by the response from Berlex Laboratories.

[ ] [ ]

[ ] [ ]

The mock-ups of the container labels, incorporating the above changes requested by the Office of Drug Safety, including colors and graphics, are provided electronically with this submission. At

the request of the Regulatory Project Manager, Archana Reddy, a paper copy of the container label mock-up is being submitted as well.

NDA 21-355 is a fully electronic submission; therefore, we are therefore sending the mock-ups of the container labels in electronic format to be compatible with the NDA. This information is provided on one (1) compact disk (CD). Berlex Laboratories, Inc. certifies that the CD has been scanned for viruses and is virus free using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54. The CD is being sent under separate cover to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room17B-20
5600 Fishers Lane
Rockville, Maryland 20857

Berlex trusts that today's submission satisfies the request of March 21, 2002 from the Chemistry Team leader as well as the request of August 1, 2002 from the Office of Drug Safety.

Should you require any additional information or have any questions regarding this submission, please contact the undersigned at (973) 487-2184. The fax number is (973) 487-2016.

Sincerely,

BERLEX LABORATORIES

Michael Doroshuk
Manager
Drug Regulatory Affairs

Desk Copy Ms. Archana Reddy
(letter only)
md089

UPS OVERNIGHT

DUPLICATE

BERLEX

RECEIVED
AUG 14 2002
FDR/CDER

August 13, 2002

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

Daniel Shames, MD, Director
Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-580, Room 17B-45
Rockville, Maryland 20857-1706

REPORT

Dear Dr. Shames:

N-000-54

Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
OTHER: Safety Update Report

Reference is made to NDA 21-355 submitted on December 14, 2001 for ANGELIQ™ drospirenone and 17β-estradiol tablets, a hormone replacement therapy. Further reference is made to the initial Safety Update to NDA 21-355, submitted on April 11, 2002.

In accordance with 21 CFR 314.5(d)(5)(vi)(b), attached please find the second Safety Update Report submitted for NDA 21-355. This update is being submitted approximately 8 months after the initial NDA submission.

The reporting interval for this Safety Update is March 16, 2001 – July 31, 2002. These dates correspond to the cut-off date for inclusion of data into the initial Safety Update and the cut-off date established for inclusion of data into this update, respectively.

As described in the Guideline for the Format and Content of the Clinical and Statistical Sections of an Application (July 1988), this Safety Update refers only to new data obtained during the interval. These additional data are relatively few, therefore, only serious or potentially serious adverse events (AE), an unusually high frequency of a less serious event, subjects who died and subjects who failed to complete a clinical study due to an AE are described. Commercial marketing experience, foreign regulatory actions, nonclinical information, and the results of literature searches are also provided for your information.

NDA 21-355 is a fully electronic submission; therefore, we are therefore sending this SAFETY UPDATE REPORT in electronic format to be compatible with the NDA. This information is

provided on one (1) diskette. Berlex Laboratories, Inc. certifies that the diskette has been scanned for viruses and is virus free using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54. The diskette is being sent under separate cover to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room17B-20
5600 Fishers Lane
Rockville, Maryland 20857

Should you require any additional information or have any questions regarding this submission, please contact the undersigned at (973) 487-2184. The fax number is (973) 487-2016.

Sincerely,

BERLEX LABORATORIES

Michael Doroshuk
Manager
Drug Regulatory Affairs

Desk Copy Ms. Archana Reddy
(letter only)

md088

BERLEX

UPS OVERNIGHT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

August 8, 2002

DUPLICATE
N-000-BM

Daniel Shames, M.D, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Shames:

Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
OTHER: Response to July 16, 2002 Request for Information – Clinical Comments to Sponsor

Reference is made to NDA 21-355 submitted on December 14, 2001 for ANGELIQ™ drospirenone and 17β-estradiol tablets, a hormone replacement therapy. Further reference is made to the 4-Month Safety Update Report to NDA 21-355, submitted on April 11, 2002.

This submission is in response to a TELEFAX received, July 16, 2002, from your representative, Archana Reddy. The FDA Clinical requests are bolded followed by a response from the sponsor.

1. **Please provide a listing of women who had either no biopsy, or tissue insufficient for diagnosis (read by the safety reader) and endometrial thickness greater than 5 mm at their last data measurement. Please provide their clinical follow-up if available, with attention to bleeding history and further decision-making. If no clinical follow-up is available, please state.**

   Berlex is providing, in this submission, a listing (biopsy data) of women with either no biopsy or tissue insufficient for diagnosis by the safety reader and who had endometrial thickness greater than 5 mm at their last data measurement. Follow-up data for all but 4 of these women was available. Berlex is attempting to obtain the follow-up data for these 4 women, and will submit this data if and when it becomes available. A table (diary data) outlining bleeding history for these women is also provided. These data are provided in electronic format.

2. Please provide the case report forms for the two cases of superficial thrombophlebitis in the Integrated Summary of Safety database.

Berlex is providing, in this submission, the requested case report forms in electronic format.

NDA 21-355 is a fully electronic submission; therefore, we are also submitting this request for additional information in electronic format. This information is provided on one (1) compact disk (CD). Berlex Laboratories, Inc. certifies that the CD has been scanned for viruses and is virus free using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54. The CD is being sent under separate cover to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room 17B-20
5600 Fishers Lane
Rockville, Maryland 20857

Berlex trusts that today's submission satisfactorily addresses the clinical requests of July 16, 2002. Should you have any questions regarding this submission, please contact the undersigned at (973) 487-2184.

Sincerely,

BERLEX LABORATORIES

Michael Doroshuk
Manager
Drug Regulatory Affairs

Desk Copy: Archana Reddy

CMD/086

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: August 7, 2002

To: Michael Doroshuk Manager, Drug Regulatory Affairs	**From:** Archana Reddy, M.P.H. Project Manager
Company: Berlex Laboratories, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 973-487-2016	**Fax number:** 301-827-4267
Phone number: 973-487-2184	**Phone number:** 301-827-4260

Subject: Request for clinical information

Total no. of pages including cover: 4

Comments:

Mike,

Please find attached chemistry comments for Angeliq™ (NDA 21-355). Provide a written response as soon as possible.

Thanks,

Archana Reddy

PM, DRUDP

Document to be mailed: ☐ YES ☑ NO

3 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 4

Teleconference Minutes

Date: July 29, 2002 **Time:** 2:30 – 3:30 PM **Location:** PKLN 17B-45

NDA: NDA 21-355 **Drug:** Angeliq™ (drospirenone/17-β estradiol)

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Clinical/Statistics (Guidance)

Meeting Chair: Shelley Slaughter, M.D., Ph.D.

External Participant Lead: Michael Doroshuk

Meeting Recorder: Archana Reddy, M.P.H.

Indication: [redacted] moderate to severe vasomotor symptoms and vulvar and vaginal atrophy in post menopausal women

External Participants:
Michael Doroshuk, Manager, Drug Regulatory Affairs
Sharon Brown, Director, Drug Regulatory Affairs
Marie Foegh, Vice President of Clinical Development, Female Health Care
Vladimir Hanes, Core Clinician, Director of Clinical Development, Female Health Care
Minoo Niknian, Director, Statistics, Female Health Care
Adel Karara, Director, Clinical Pharmacology
Wolfgang Eder, International Project Manager
Ann-Mari Bresky, Regional Project Manager

FDA Participants:
Shelley Slaughter, M.D., Ph.D., Medical Team Leader, Division of Urologic and Reproductive Drug Products (HFD-580)
Lesley Furlong, M.D., Medical Officer, DRUDP (HFD-580)
Archana Reddy, M.P.H., Regulatory Project Manager, DRUDP, HFD-580

Background:
Angeliq™ (drospirenone/17-β estradiol) is a type 4 NDA (new combination) submitted by Berlex Laboratories, Inc. on December 14, 2001, and received on December 17, 2001, for hormone replacement therapy. The sponsor submitted a Type C meeting request on July 9, 2002 to discuss their interim analysis plan with the Division.

Meeting Objectives:
To discuss the sponsor's proposal for interim analysis of Protocol 305471, submitted on July 1, 2002.

Discussion:

Sponsor Questions

Question 1.

[redacted]

DRUDP Response: Labeling is a review issue. [redacted]

Question 2. Does the Division concur that these data can be used to better define patients where blood sampling for potassium is necessary?

DRUDP Response:
This is considered a review issue.

Question 3.

[redacted]

DRUDP Response:
No, interim analysis will not be considered as supportive of label changes. Interim analysis is not powered to draw any definitive conclusions and is dependent upon how compelling the data is. The study is not powered to show statisitical significance for any particular endpoint.

Decision reached:

- the sponsor agreed to not submit their interim analysis plan, since this would trigger a major amendment and inform the FDA of their decision regarding their pursuit of these indications

Action Items:

1) The PM will fax the minutes of the meeting to the sponsor.

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

Shelley Slaughter, M.D., Ph.D.
Medical Team Leader

Cc:
Arch NDA
HFD-580/Division Files
HFD-580/Reddy/Moore/Slaughter/Shames/Furlong/Tran/Jarugula/Parekh/Rhee/Raheja/Jordan
HFD-170/Castillos

Created by: Archana Reddy, , 2002
Concurrence: lf/, 2002, ss/2002
Finalized: ar/, 2002

Meeting Minutes

UPS OVERNIGHT

DUPLICATE

BERLEX

July 26, 2002

RECEIVED
JUL 29 2002
HFD-580/CDER

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

Daniel Shames, MD, Director
Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-580, Room 17B-45
Rockville, Maryland 20857-1706

BC
ORIG AMENDMENT

Dear Dr. Shames:

Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
AMENDMENT TO PENDING APPLICATION
CMC Amendment: Change in dissolution specifications

Reference is made to NDA 21-355 submitted on December 14, 2001 for ANGELIQ™ drospirenone and 17β-estradiol tablets, a hormone replacement therapy. Reference is also made to a telephone conversation on June 4, 2002, between the undersigned and the Division Chemistry Reviewer, Dr. Su Tran, wherein Dr. Tran proposed changes to the current dissolution specifications in the original application. Additional reference is made to a CMC teleconference on July 16, 2002 with Dr. Moo-Jhong Rhee (Division Chemistry Team Leader) wherein Berlex discussed dissolution specifications for estradiol and drospirenone. Further reference is made to a telephone conversation on July 24, 2002 between the undersigned and the Division Chemistry Reviewer, Dr. Su Tran.

Berlex Laboratories is submitting a Chemistry, Manufacturing and Controls amendment to NDA 21-355 which amends the current dissolution specifications for both drug substances (from estradiol Q= —% at / minutes and drospirenone Q= /% at / minutes) to the dissolution specifications proposed by the reviewing chemistry team on June 4, 2002 (estradiol: Q= /% at 30 minutes and drospirenone: Q= —% at \ minutes).

The adjusted specification is provided.

- Quality Specification No. RES01-185B
  Angeliq [redacted], film-coated tablet (for USA)
  dated July 25, 2002

- Quality Specification No. RES01-186B
  Angeliq [redacted], film-coated tablet (for USA)
  dated July 25, 2002

NDA 21-355 is a fully electronic submission; therefore, Berlex is also submitting this Amendment to a Pending Application in electronic format. This Amendment is provided on one (1) diskette. Berlex Laboratories, Inc. certifies that the diskette has been scanned for viruses and is virus free using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54. The diskette is being sent under separate cover to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room 17B-20
5600 Fishers Lane
Rockville, Maryland 20857

Should you require any additional information or have any questions regarding today's submission, please contact the undersigned at (973) 487-2184. The fax number is (973) 487-2016.

Sincerely,

BERLEX LABORATORIES

Michael Doroshuk
Manager
Drug Regulatory Affairs

Desk Copy: Archana Reddy

CMD/080

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 1/31/02	**DUE DATE:** 7/1902	**ODS CONSULT #:** 02-0023

TO:

Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH:

Archana Reddy
Project Manager, Division of Reproductive and Urologic Drug Products
HFD-580

PRODUCT NAME:	**NDA SPONSOR:** Berlex Laboratories
Angeliq (Drospirenone and Estradiol Tablets) **NDA #:** 21-355	

SAFETY EVALUATOR: Jennifer Fan, Pharm.D.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Angeliq" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:
DMETS has no objection to the use of the proprietary name, "Angeliq". This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document. In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

Carol Holquist, R.Ph.
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: July 9, 2002

NDA NUMBER: 21-355

NAME OF DRUG: Angeliq (Drospirenone and Estradiol Tablets)

NDA HOLDER: Berlex Laboratories

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) for assessment of the tradename "Angeliq", regarding potential name confusion with other proprietary/established drug names.

PRODUCT INFORMATION

"Angeliq" is the proposed proprietary name for the combination hormone drug product containing drospirenone and estradiol. Drospirenone, a spironolactone analogue, is a progestogen with antimineralocorticoid activity. "Angeliq" is indicated in women with an intact uterus for the treatment of moderate to severe vasomotor symptoms associated with the menopause, vulvar and vaginal atrophy, It is contraindicated in women who are known or suspected to be pregnant as well as women who have undiagnosed abnormal genital bleeding, known or suspected estrogen-dependent neoplasia, active thrombophlebitis or thromboembolic disorders, sensitivity to "Angeliq" or other estrogen and progestin containing products, renal insufficiency, hepatic dysfunction, and adrenal insufficiency. "Angeliq" is available as a drospirenone/ estradiol tablet The usual dosage is one tablet once a day;

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound alike or look alike to "Angeliq" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and

[1] MICROMEDEX Healthcare Intranet Series, 2001, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2001).
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

Trademark Office's Text and Image Database[4] and the data provided by Thomson & Thomson's SAEGIS™ Online Service[5] were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Angeliq". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The panel had some concern with *Actiq* and *Angelica* (herbal product). These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.

2. DDMAC did not have any objections to "Angeliq".

Table 1

Product Name	**Dosage form(s), Generic name**	**Usual adult dose***	**Other****
Angeliq	Drospirenone and Estradiol (Rx) Tablet: 1 mg/1 mg and 3 mg/1 mg	1 tablet daily.	
Actiq	Fentanyl Transmucosal System (Rx) Lozenge on a stick: 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg	Dosage is individualized depending on the status of the patient age, weight, medical status), the clinical environment, and the desired therapeutic effect. It is not recommended for adults to receive doses more than 5 mcg/kg (400 mcg).	*SA
Angelica atropurpurea *Angelica archangelica* *Angelica sinesis*	*Angelica sinesis* is also known as Dong Quai. (herbal product) Available as tablets, capsules, extract/tincture, dried root and rhizome, and seeds.	Doses depends on literature and the dosage form. Generally, it is given three times a day.	*SA/LA
*Frequently used, not all-inclusive. **SA (sound-alike), LA (look-alike)			

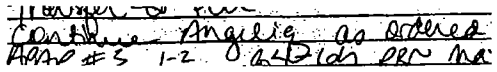
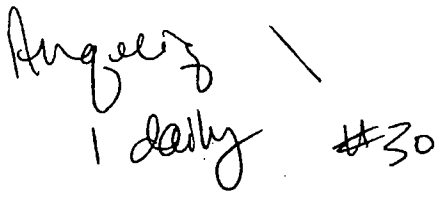
[4] WWW location http://www.uspto.gov.

[5] WWW location http://www.thomson-thomson.com.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

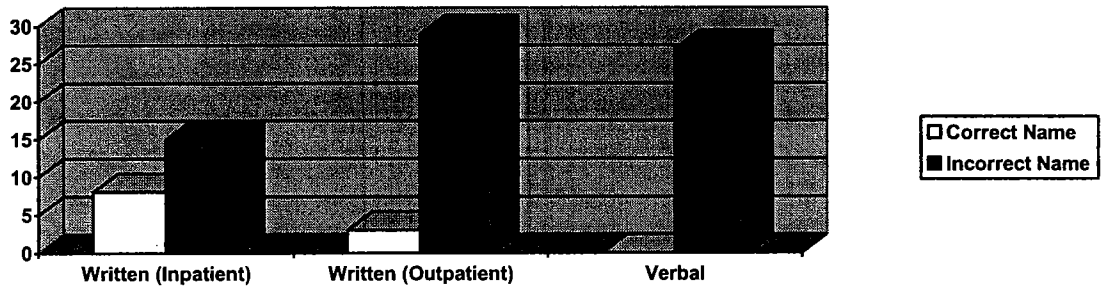
Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of "Angeliq" with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 112 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for "Angeliq" (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Inpatient Rx: 	*Outpatient Rx:* Angeliq — Take one daily. #30
Outpatient Rx: 	

2. Results:

Results of these exercises are summarized below:

Study	# of Participants	# of Responses (%)	Correctly Interpreted "Angeliq"	Incorrectly Interpreted
Written Inpatient	34	23 (68%)	8 (35%)	15 (65%)
Written Outpatient	40	32 (80%)	3 (9%)	29 (91%)
Verbal: Outpatient	38	27 (71%)	0 (0%)	27 (100%)
Total	112	82 (73%)	11 (13%)	71 (87%)



Among the written inpatient prescriptions, 15 (65%) out of 23 respondents interpreted "Angeliq" incorrectly. Interpretations included *Angelig* (17%), *Angelia* (13%), *Angilia* (9%), *Angilig* (9%), *Angesic* (4%), *Angiliq* (4%), *Angelis* (4%), and *Angelic* (4%).

Among the written outpatient prescriptions, 29 (91%) out of 32 respondents interpreted "Angeliq" incorrectly. Interpretations included *Anquiz* (9%), *Anquiq* (9%), *Auquez* (6%), *Auqueliz* (6%), *Anqeliz* (6%), *Angeliz* (6%), *Ange* (3%), *Anqurig* (3%), *Aqualenz* (3%), *Augurq* (3%), *Anquerig* (3%), *Anaquil* (3%), *Anquez* (3%), *Auqeliq* (3%), *Angelig* (3%), *Anquig* (3%), *Anqeeig* (3%), *Anqeez* (3%), *Anqurz* (3%), *Arqeriq* (3%), and *Anqueis* (3%).

Among the verbal outpatient prescriptions, 27 (100%) out of 27 respondents interpreted "Angeliq" incorrectly. Interpretations included *Angelique* (48%), *Angelic* (11%), *Anjelique* (7%), *Enjoleek* (4%), *Enjurique* (4%), *Enjureek* (4%), *Anjoleek* (4%), *Angeleek* (4%), *Anjoleek* (4%), *Anejliq* (4%), and *Angolic* (4%).

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Angeliq", the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. Such proprietary names include *Actiq* and *Angelica* (*atropurpurea, archangelica,* and *sinesis*).

Actiq is the proprietary name for oral transmucosal fentanyl citrate and is indicated only for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. *Actiq* is individually titrated to a dose that provides adequate analgesia and minimal side effects. It is available as a lozenge on a stick (200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg). *Actiq* sounds similar to "Angeliq" due to the "a" sound in the beginning and the "iq" ending. However, the pronunciation of "act" in *Actiq* and "ang" in "Angelic" are distinctively different. Also, "Angeliq" contains three syllables while *Actiq* only has two syllables. There are no overlapping strengths, [redacted] and different dosage forms (lozenge vs. tablet). Additionally, *Actiq* is a Schedule II narcotic that will be stored separately from other products. All these differences would decrease the potential risk of a medication error occurring between these two drug products.

Angelica atropurpurea, Angelica archangelica, and *Angelica sinesis* are herbal products that belong to the Umbelliferae family and are not sold in the United States as prescription products. Another name for *Angelica sinesis* is Dong Quai. The roots and rhizomes are usually used, and, according to various literature, these parts of the plant are used for alcoholism, amenorrhea, anemia, anorexia nervosa, bronchitis, common cold, cough, cystitis, dermatitis, flatulent colic,

gastritis, immunodeficiency, inappetence, indigestion, insomnia, peripheral vascular disease, pleurisy, psychogenic asthma, rheumatism, and tumor. The roots and rhizomes are available as dried products as well as tablets, capsules, extract/tincture, and seeds. Dosing is different depending upon the literature source, but generally, it is given three times a day. There is much similarity between the names "Angeliq" and *Angelica* as shown in the DMETS study where four respondents misinterpreted "Angeliq" as *Angelic*. Even though "Angeliq" and *Angelica* have an overlapping dosage form (tablet) and have similar names, they have different dosing schedules and are sold in different U.S. markets (herbal products vs. prescription products), which would decrease the potential risk of a medication error occurring between these products and "Angeliq".

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

A. CONTAINER LABEL (

1.

2.

3.

4.

B. INSERT LABELING (Package Insert and Patient Information Insert)

Package Insert

1.

2. Under the HOW SUPPLIED section, the terminal zero in "— mg" and "—mg" should be deleted since they could be misinterpreted as "—

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name "Angeliq".

This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

B. DMETS recommends the above labeling revisions that might lead to safer use of the product. We

would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

Jennifer Fan, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Denise Toyer, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Jennifer Fan
7/19/02 08:10:41 AM
PHARMACIST

Denise Toyer
7/19/02 08:29:17 AM
PHARMACIST

Carol Holquist
7/22/02 07:13:17 AM
PHARMACIST

UPS OVERNIGHT

ORIG AMENDMENT

BC

BERLEX

July 22, 2002

DUPLICATE

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

Daniel Shames, MD, Director
Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-580, Room 17B-45
Rockville, Maryland 20857-1706

Dear Dr. Shames:

Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
Other: Follow-up Question from July 16, CMC teleconference

Reference is made to NDA 21-355 submitted on December 14, 2001 for ANGELIQ™ drospirenone and 17β-estradiol tablets, a hormone replacement therapy. Additional reference is made to a telephone conversation on July 16, 2002 with Dr. Moo-Jhong Rhee (Division Chemistry Team Leader) wherein Berlex discussed dissolution specifications for estradiol and drospirenone.

Berlex would like to propose the following question for consideration, regarding the proposed drospirenone specification of Q=—% at ✓ minutes, prior to submitting an amendment:

Taking these points into consideration, does the Division concur that a Q value of —% for drospirenone is unnecessarily restrictive and a Q of —% is justified?

Berlex appreciates your consideration of the above question for drospirenone dissolution specification. Berlex will amend NDA 21-355 as appropriate, pending your response on this issue.

NDA 21-355 is a fully electronic submission; therefore, Berlex is also submitting this request for information in electronic format. This request is provided on one (1) diskette. Berlex Laboratories, Inc. certifies that the diskette has been scanned for viruses and is virus free using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54. The diskette is being sent under separate cover to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room 17B-20
5600 Fishers Lane
Rockville, Maryland 20857

Should you require any additional information or have any questions regarding today's submission, please contact the undersigned at (973) 487-2184. The fax number is (973) 487-2016.

Sincerely,

BERLEX LABORATORIES

Michael Doroshuk
Manager
Drug Regulatory Affairs

Desk Copy: Archana Reddy

CMD/078

DUPLICATE

BERLEX

UPS OVERNIGHT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

ORIG AMENDMENT

RECEIVED
JUL 1 8 2002
HFD-580/CDER

July 17, 2002

Daniel Shames, M.D, Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Shames:

Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
OTHER: Response to June 6, 2002 Request for Information – Clinical Comments to Sponsor

Reference is made to NDA 21-355 submitted on December 14, 2001 for ANGELIQ™ drospirenone and 17β-estradiol tablets, a hormone replacement therapy. Further reference is made to a telefax received from your representative on June 6, 2002, requesting names of safety readers matched to patient number for clinical study report A02827 (Protocol 96097A) and the names of the pathologists conducting specific biopsy readings. Berlex apologizes for any delay in providing this information that had to be retrieved from the contract laboratory. The clinical requests from the Division are bolded followed by a response from the sponsor.

1. **Provide a list of the names of the safety readers matched to patient number and biopsy date for study 96097A.**
   A table listing patient number, date of biopsy read and initials of the safety reader is provided (diskette). At the bottom of the table is a key identifying the safety readers by name.

2. **Provide the names of the pathologists who did the safety endometrial biopsy readings for Study Report A02827 for the following patients.**

   #52012, biopsy date 1/28/99
   #01015, biopsy date 9/30/99
   #20028, biopsy date 4/26/00

The names of the pathologists conducting the safety readings are as follows:

Subject	Biopsy Date	Pathologist
#52012	1/28/99	
#01015	9/30/99	
#20028	4/26/00	

NDA 21-355 is a fully electronic submission; therefore, we are also submitting this additional information in electronic format. This information is provided on one (1) diskette. Berlex Laboratories, Inc. certifies that the diskette has been scanned for viruses and is virus free using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54. The diskette is being sent under separate cover to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room 17B-20
5600 Fishers Lane
Rockville, Maryland 20857

Berlex trusts that today's submission adequately addresses the Division's request of June 6, 2002. Should you have any questions regarding this submission, please contact the undersigned at (973) 487-2184.

Sincerely,

BERLEX LABORATORIES

Michael Doroshuk
Manager
Drug Regulatory Affairs

Desk Copy: Archana Reddy

CMD/075

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: July 16, 2002

To: Michael Doroshuk Manager, Drug Regulatory Affairs	**From:** Archana Reddy, M.P.H. Project Manager
Company: Berlex Laboratories, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 973-487-2016	**Fax number:** 301-827-4267
Phone number: 973-487-2184	**Phone number:** 301-827-4260

Subject: Request for clinical information

Total no. of pages including cover: 2

Comments:

Mike,

Please find attached clinical comments for Angeliq™ (NDA 21-355). Provide a written response as soon as possible.

Thanks,

Archana Reddy

PM, DRUDP

Document to be mailed: ☐ YES ☑ NO

CLINICAL COMMENTS FOR THE SPONSOR

DRUG: Angeliq™ (drospirenone/17β-estradiol)
NDA: 21-355
SPONSOR: Berlex Laboratories, Inc.

(1) Please provide a listing of women who had either no biopsy, or tissue insufficient for diagnosis(read by the safety reader) and endometrial thickness greater than 5 mm at their last data measurement. Please provide their clinical follow-up if available, with attention to bleeding history and further decision-making. If no clinical follow-up is available, please state.

(2) Please provide the case report forms for the two cases of superficial thrombophlebitis in the Integrated Summary of Safety database.

ORIGINAL

BERLEX
Laboratories

Facsimile
Transmittal Sheet

FROM: Michael Doroshuk	TELEPHONE: (973) 487-2184
ADDRESS: ✘ 340 Changebridge Road, P. O. 1000, Montville, NJ 07045-1000 ❑ 300 Fairfield Road, Wayne, NJ 07470-4100	
FAX NUMBER: ✘ Drug Regulatory Affairs (973) 487-2016 ❑ Wayne Headquarters (973) 942-1610	
TO: Archana Reddy, Project Manager	TELEPHONE: 301-827-5424
SUBJECT: NDA 21-355 Angeliq (DRSP/E2) Tablets Request for CMC teleconference	FAX NUMBER: (301) 827-4267
	DATE: July 10, 2002
	TOTAL NUMBER OF PAGES (INCLUDING COVER SHEET): 2

ORIG AMENDMENT

RECEIVED
JUL 15 2002
HFD-580/CDER

MR

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

MEETING REQUEST

Product Name and application number:
Drospirenone/Estradiol (DRSP/E2) Tablets, NDA 21-355

The **PURPOSE** of the meeting is to discuss the changes in dissolution specifications for the drug product suggested by the Division Chemistry Reviewer.

The **OBJECTIVE** of the meeting is to obtain agreement with the Division Chemistry Reviewer on dissolution specifications for the drug product.

Proposed Agenda:

Introductions	5 minutes
Chemistry Discussion	30 minutes
Total meeting time	35 minutes

Questions:
Berlex proposes that the current dissolution specification (E2 Q= —, DRSP Q=—; @ ⁄ min) remains in place. What is the rationale behind the Division's suggested changes for these dissolution specifications for the Angeliq drug product?

Sponsor Participants:
Michael Doroshuk – Regulatory Affairs, Berlex Laboratories
Shawn Hoskin – Analytical Chemistry, Berlex Laboratories

Desired FDA Participants:
Dr. Su Tran – Chemistry Reviewer
Archana Reddy – Project Management.

Date and time of teleconference:
Berlex agrees to a brief teleconference with the Chemistry Reviewer on Tuesday July 16, 2002 at 11am, as proposed by the Division Project manager. Archana Reddy agreed to telephone undersigned at 1-973-487-2184.

Sincerely,

BERLEX LABORATORIES

Michael Doroshuk
Manager
Drug Regulatory Affairs

DUPLICATE

BERLEX

UPS OVERNIGHT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

July 11, 2002

ORIG AMENDMENT

BM1

Daniel Shames, M.D, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Shames:

Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
OTHER: Response to June 27, 2002 Request for Information – Clinical

Reference is made to NDA 21-355 submitted on December 14, 2001 for ANGELIQ™ drospirenone and 17β-estradiol tablets, a hormone replacement therapy. Further reference is made to a TELEFAX received, June 27, 2002, from your representative, Archana Reddy, requesting average number of exposure weeks for subjects in the Integrated Summary of Safety. The FDA Clinical request is bolded followed by the response from the sponsor.

1. **Please calculate the average number of weeks of exposure to (drospirenone plus estradiol) for the 1893 subjects in you Integrated Summary of Safety database. The average is referring to the arithmetic mean.**

The average number of exposure weeks for all doses of drospirenone + estradiol in the 1893 subjects described in the Integrated Summary of Safety 53.8 weeks. The following table provides a breakdown of mean exposure in weeks to any dose of DRSP by study phase.

Mean Exposure (Weeks) to Any Dose of DRSP by Study Phase

	Exposure (Weeks)				
Phase	n	Mean	Median	SD	Min Max
Phase I	134	2.2	2.4	1.37	0 4
Phase III	1759	57.7	52.0	34.38	0 112
Total	1893	53.8	52.0	36.08	0 112

NDA 21-355 is a fully electronic submission; therefore, we are also submitting this request for additional information in electronic format. This information is provided on one (1) diskette. Berlex Laboratories, Inc. certifies that the diskette has been scanned for viruses and is virus free using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54. The diskette is being sent under separate cover to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room 17B-20
5600 Fishers Lane
Rockville, Maryland 20857

Berlex trusts that today's submission addresses the June 27, 2002 question from the clinical reviewer. Should you have any questions regarding this submission, please contact the undersigned at (973) 487-2184.

Sincerely,

BERLEX LABORATORIES

Michael Doroshuk
Manager
Drug Regulatory Affairs

Desk Copy: Archana Reddy

CMD/071

DUPLICATE

BERLEX

UPS OVERNIGHT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

July 3, 2002

ORIG AMENDMENT RECEIVED

JUL 05 2002

HFD-580/CDER

N-000-BR

Daniel Shames, MD, Director
Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-580, Room 17B-45
Rockville, Maryland 20857-1706

Dear Dr. Shames:

Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
AMENDMENT TO PENDING APPLICATION: Drug Interaction Study BD09

Reference is made to NDA 21-355 submitted on December 14, 2001 for ANGELIQ™ drospirenone and 17β-estradiol tablets, a hormone replacement therapy.

Reference is also made to a telephone message on May 29, 2002 from your representative, Archana Reddy, wherein the clinical pharmacology reviewer requested a submission date for the drug interaction study (Study No. 303471).

Study No. 303741 (Report No. BD09) *"Open-label, randomized, crossover study to assess the potential of drospirenone (DRSP) to inhibit Cytochrome P450 3A4 by evaluating the metabolic interaction between DRSP and simvastatin as model substrate in healthy postmenopausal volunteers"* was intended to characterize the in vivo potential of DRSP to interact with drugs using metabolic pathways catalyzed by CYP3A4. Data listings for this study are provided in Item 11 as SAS datasets in compliance with Item 11.

The results of this study do not indicate a clinically relevant CYP3A4 inhibition by DRSP at steady-state after daily oral administration of 3 mg DRSP. However, no final conclusion can be drawn from these results, because the number of subjects enrolled into this study was too small to account for the high intra-subject variability of simvastatin pharmacokinetics. No clinically relevant drug-drug interactions between DRSP and CYP3A4 substrates are expected based on these data. Simvastatin was well tolerated alone and in combination with DRSP. The study data were carefully examined by two independent experts: [redacted] has extensive experience in the conduct and interpretation of simvastatin interaction studies. Both experts have concluded that drospirenone at the studied dose of 3 mg does not have a significant effect on CYP3A4 enzyme activity in humans.

Previous in vitro findings and results of another clinical drug-drug interaction study submitted with NDA 21-355 (Report B277) did not indicate a clinically relevant interaction of DRSP with CYP3A4. This information is consistent with the results obtained in the majority (83%) of subjects in the study reported in BD09. Only a small part of the study population (17%) showed contradictory data that did not show a clear trend. Berlex does not consider the results of the present study sufficient to conclude either the presence or the absence of CYP3A4 interaction by DRSP (see discussion section in Report BD09).

However, Berlex is committed to further characterize the potential of DRSP to interact with drugs utilizing metabolic pathways catalyzed by CYP3A4. Therefore, Berlex is proposing an additional clinical study to evaluate the effect of DRSP on the catalytic activity of CYP3A4 by investigating the pharmacokinetics of the model substrate midazolam after oral administration with and without co-administration of DRSP. An outline of the proposed study is included with this submission. Berlex is seeking a prompt review of the attached study outline by the Division as we intend to proceed with the study as soon as possible.

NDA 21-355 is a fully electronic submission; therefore, we are also submitting the present study report in electronic format compatible with the NDA. This information is provided on one (1) compact disk (CD). Berlex Laboratories, Inc. certifies that the CD has been scanned for viruses and is virus free using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54. The CD is being sent under separate cover to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room 17B-20
5600 Fishers Lane
Rockville, Maryland 20857

Berlex trusts today's submission along with the proposed additional study adequately addresses your request of May 29, 2002. Should you require any additional information or have any questions regarding this submission, please contact the undersigned at (973) 487-2184. The fax number is (973) 487-2016.

Sincerely,

BERLEX LABORATORIES

Michael Doroshuk
Manager
Drug Regulatory Affairs

Desk Copy (Letter only)
Ms. Archana Reddy

CMD/letter/angeliq062

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: June 27, 2002

To: Michael Doroshuk Manager, Drug Regulatory Affairs	**From:** Archana Reddy, M.P.H. Project Manager
Company: Berlex Laboratories, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 973-487-2016	**Fax number:** 301-827-4267
Phone number: 973-487-2184	**Phone number:** 301-827-4260

Subject: Request for clinical information

Total no. of pages including cover: 2

Comments:

Mike,

Please find attached clinical comments for Angeliq™ (NDA 21-355). Provide a written response as soon as possible.

Thanks,

Archana Reddy

PM, DRUDP

Document to be mailed: ☐ YES ☑ NO

CLINICAL COMMENTS FOR THE SPONSOR

DRUG: Angeliq™ (drospirenone/17β-estradiol)
NDA: 21-355
SPONSOR: Berlex Laboratories, Inc.

(1) Please calculate the average number of weeks of exposure to (drospirenone plus estradiol) for the 1893 subjects in your Integrated Summary of Safety database. The average is referring to the arithmetic mean.

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

/s/

Archana Reddy
6/27/02 09:52:09 AM
CSO

BERLEX

UPS OVERNIGHT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

June 19, 2002

Daniel Shames, MD, Acting Director
Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-580, Room 17B-45
Rockville, Maryland 20857-1706

Dear Dr. Shames:

Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
AMENDMENT TO PENDING APPLICATION: Drug Interaction Study BD09

Reference is made to NDA 21-355 submitted on December 14, 2001 for ANGELIQ™ drospirenone and 17β-estradiol tablets, a hormone replacement therapy.

Reference is also made to a telephone message on May 29, 2002 from your representative, Archana Reddy, wherein the clinical pharmacology reviewer requested a submission date for the drug interaction study (Study No. 303471).

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The results of this study do not indicate a clinically relevant CYP3A4 inhibition by DRSP at steady-state after daily oral administration of 3 mg DRSP. However, no final conclusion can be drawn from these results, because the number of subjects enrolled into this study was too small to account for the high intra-subject variability of simvastatin pharmacokinetics. No clinically relevant drug-drug interactions between DRSP and CYP3A4 substrates are expected based on

these data. Simvastatin was well tolerated alone and in combination with DRSP. The study data were carefully examined by two independent experts: [redacted] has extensive experience in the conduct and interpretation of simvastatin interaction studies. Both experts have concluded that drospirenone at the studied dose of 3 mg does not have a significant effect on CYP3A4 enzyme activity in humans.

Previous in vitro findings and results of another clinical drug-drug interaction study submitted with NDA 21-355 (Report B277) did not indicate a clinically relevant interaction of DRSP with CYP3A4. This information is consistent with the results obtained in the majority (83%) of subjects in the study reported in BD09. Only a small part of the study population (17%) showed contradictory data that did not show a clear trend. Berlex does not consider the results of the present study sufficient to conclude either the presence or the absence of CYP3A4 interaction by DRSP (see discussion section in Report BD09).

However, Berlex is committed to further characterize the potential of DRSP to interact with drugs utilizing metabolic pathways catalyzed by CYP3A4. Therefore, Berlex is proposing an additional clinical study to evaluate the effect of DRSP on the catalytic activity of CYP3A4 by investigating the pharmacokinetics of the model substrate midazolam after oral administration with and without co-administration of DRSP. An outline of the proposed study is included with this submission. Berlex is seeking a prompt review of the attached study outline by the Division as we intend to proceed with the study as soon as possible.

NDA 21-355 is a fully electronic submission; therefore, we are also submitting the present study report in electronic format compatible with the NDA. This information is provided on one (1) compact disk (CD). Berlex Laboratories, Inc. certifies that the CD has been scanned for viruses and is virus free using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54. The CD is being sent under separate cover to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room 17B-20
5600 Fishers Lane
Rockville, Maryland 20857

Berlex trusts today's submission along with the proposed additional study adequately addresses your request of May 29, 2002. Should you require any additional information or have any questions regarding this submission, please contact the undersigned at (973) 487-2184. The fax number is (973) 487-2016.

Sincerely,

BERLEX LABORATORIES

Michael Doroshuk
Manager
Drug Regulatory Affairs

Desk Copy (Letter only)
Ms. Archana Reddy

CMD/letter/angeliq062

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June 14, 2002

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

Daniel Shames, MD, Acting Director
Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-580, Room 17B-45
Rockville, Maryland 20857-1706

BC

ORIG AMENDMENT

Dear Dr. Shames:

Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
AMENDMENT TO A PENDING APPLICATION
CMC: 36-Month Stability Reports

Reference is made to NDA 21-355 submitted on December 14, 2001 for ANGELIQ™ drospirenone and 17β-estradiol tablets, a hormone replacement therapy.

Reference is also made to a telephone conversation on June 4, 2002 with Dr. Su Tran (Division Chemistry Reviewer) wherein Berlex informed Dr. Tran that the 36-month stability reports for Angeliq that were in progress at the time this application was submitted were being finalized.

With this amendment, Berlex is submitting ——— stability reports for both strengths of the drug product. Reports A06108, A06109 for the 1 mg estradiol/1 mg drospirenone tablets, and reports A06111, A06112 for the 1 mg estradiol/3 mg drospirenone tablets. Specifications referenced in these reports reflect the original specifications submitted with the NDA. However, the stability data were assessed against the proposed specifications (———) submitted in the Berlex CMC response to the March 21, 2002 request for information. Angeliq 1/1 and 1/3 meets the specifications after — months' storage, at 25°C/60% relative humidity and 30°C/70% relative humidity, when compared to the proposed specifications. Berlex seeks concurrence from the Division that these new stability reports justify a —-month expiry date for ANGELIQ™ tablets.

NDA 21-355 is a fully electronic submission; therefore, we are also submitting this CMC amendment to a pending application in electronic format compatible with the NDA. This information is provided on one (1) diskette. Berlex Laboratories, Inc. certifies that the diskette

has been scanned for viruses and is virus free using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54. The diskette is being sent under separate cover to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room 17B-20
5600 Fishers Lane
Rockville, Maryland 20857

Should you require any additional information or have any questions regarding this submission, please contact the undersigned at (973) 487-2184. The fax number is (973) 487-2016.

Sincerely,

BERLEX LABORATORIES

Michael Doroshuk
Manager
Drug Regulatory Affairs

Desk Copy (Letter only)
Ms. Archana Reddy
Dr. Su Tran

cmd/061

Meeting Minutes

Date: June 11, 2002 **Time:** 12:00 – 1:00 PM **Location:** 17B-43

NDA: 21-355 **Drug:** Angeliq™ (drospirenone/17-β estradiol)

Indication: ——— moderate-to-severe vasomotor symptoms and vulvar and vaginal atrophy

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Six-month Month Status Meeting

Meeting Chair: Shelley Slaughter, M.D., Ph.D.

Meeting Recorder: Archana Reddy, M.P.H.

FDA Attendees:
Shelley Slaughter, M.D., Ph.D., Reproductive Medical Team Leader, Division of Reproductive and Urologic Drug Products, (DRUDP; HFD-580)
Lesley Furlong, M.D., Medical Officer, DRUDP (HFD-580)
Archana Reddy, M.P.H., Regulatory Project Manager, DRUDP (HFD-580)
Su Tran, Ph.D., Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Krishan Raheja, Ph.D., D.V.M., Pharmacology Reviewer, DRUDP (HFD-580)
Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCBP) @ DRUDP (HFD-580)
Venkat Jarugula, Ph.D., Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
Sonia Castillo, Ph.D., Statistical Reviewer, Division of Biometrics II (DBII) @ Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170)

Meeting Objective: Six- month status meeting

Background:
Angeliq™ (drospirenone/17-β estradiol) is a type 4 NDA (new combination) submitted by Berlex Laboratories, Inc. on December 14, 2001 and received on December 17, 2001 for hormone replacement therapy. The drug product is ———— drospirenone and 1 mg estradiol per tablet. Drospirenone (DRSP) is a novel progestin, a derivative of 17α-spironolactone, and similar to progesterone with progestogenic and aldosterone-antagonistic properties. DRSP is currently marketed as the progestin component in the oral contraceptive product Yasmin® (NDA 21-098). The User Fee goal date is October 17, 2002.

Discussion:

Clinical:

- Bias detected in the endometrial hyperplasia trial; bias in reading of slides
- Two additional studies reviewed; indomethacin study and liver impairment study
- One case of significant hyperkalemia seen in a woman given a single dose of the formulation containing 3 mg drospirenone; the woman required hospitalization
- Multiple events of thrombosis reported; 3 deaths in Europe
- Clinical reviewer recommends a non-approvable action based upon safety concerns

Chemistry:

- Awaiting additional stability data from the sponsor
- EES is complete and acceptable
- ——— expiration for stability recommended to sponsor
- Recommend approval for both dosage forms

Pharmacology/Toxicology:

- no safety concerns; review will be entered into DFS

Biopharmaceutics:

- Review is underway
- Sponsor has submitted hepatic impairment study and drug interaction study with simvastatin expected by the end of the month

Statistics:

- at this time, review is complete; additional analyses requested by the medical reviewer may be added

Decisions made:

- final reviews are due to the team leader by September 14, 2002

Minutes Preparer: Archana Reddy, M.P.H.

Concurrence: Meeting Chair
Shelley Slaughter, M.D., Ph.D.

Cc:
Original NDA 21-322
HFD-580/Division File
HFD-580/PM/Reddy
HFD-580/Slaughter/Shamesd/Furlong/Raheja/Jarugula/Tran/Rhee/Parekh/
HFD-715/Castillos

Drafted by: ar/ /6monthstatusminutes.doc
Concurrence: sc/July 19, 2002, mjr/July 19, 2002, kr/July 18, 2002, st/July 23, 2002, ss/July 18, 2002, lf/July 18, 2002, vj/August 15, 2002
Finalized: ar/August 16, 2002

MEETING MINUTES

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

/s/

Shelley Slaughter
8/21/02 01:35:07 PM
I concur

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BERLEX

June 10, 2002

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JUN 11 2002
HFD-580/CDER

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

ORIG AMENDMENT

BC

Daniel Shames, MD, Acting Director
Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-580, Room 17B-45
Rockville, Maryland 20857-1706

Dear Dr. Shames:

Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
AMENDMENT TO PENDING APPLICATION:
Chemistry, Manufacturing and Controls Amendment to Drug Master File No. 12138

Reference is made to NDA 21-355 submitted on December 14, 2001 for ANGELIQ™ drospirenone and 17β-estradiol tablets, a hormone replacement therapy. Reference is also made to Type II Drug Master File (DMF) No. 12138 for drospirenone drug substance.

DMF No. 12138 was amended on April 24, 2002 as described in the attached 3-page summary (DMF amendment cover letter followed by a 2-page summary of the changes). Immediately following this correspondence is a May 23, 2002 letter from the DMF holder, our parent company, Schering AG authorizing the FDA to reference DMF No. 12138 on behalf of Berlex.

Berlex is NDA 21-355 is a fully electronic submission; therefore, we are also submitting this Amendment to a Pending Application in electronic format. This Amendment is provided on one (1) compact disk (CD). Berlex Laboratories, Inc. certifies that the CD has been scanned for viruses and is virus free using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54. The CD is being sent under separate cover to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room 17B-20
5600 Fishers Lane
Rockville, Maryland 20857

Should you require any additional information or have any questions regarding today's submission, please contact the undersigned at (973) 487-2184. The fax number is (973) 487-2016.

Sincerely,

BERLEX LABORATORIES

Michael Doroshuk
Manager
Drug Regulatory Affairs

Desk Copy: Archana Reddy

CMD/letter/angeliq061

3 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 5

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: June 6, 2002

To: Michael Doroshuk Manager, Drug Regulatory Affairs	**From:** Archana Reddy, M.P.H. Project Manager
Company: Berlex Laboratories, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 973-487-2016	**Fax number:** 301-827-4267
Phone number: 973-487-2184	**Phone number:** 301-827-4260

Subject: Request for clinical information

Total no. of pages including cover: 2

Comments:

Mike,

Please find attached clinical comments for Angeliq™ (NDA 21-355). Provide a written response as soon as possible.

Thanks,

Archana Reddy

PM, DRUDP

Document to be mailed: ☐ YES ☑ NO

CLINICAL COMMENTS FOR THE SPONSOR

DRUG: Angeliq™ (drospirenone/17β-estradiol)
NDA: 21-355
SPONSOR: Berlex Laboratories, Inc.

(1) Provide a list of the names of the safety readers matched to patient number and biopsy date for study 96097A.

(2) Provide the names of the pathologists who did the safety endometrial biopsy readings for Study Report A02827 for the following patients.

52012, biopsy date 1/28/99
#01015, biopsy date 9/30/99
#20028, biopsy date 4/26/00

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BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

May 13, 2002

RECEIVED
MAY 14 2002
HFD-580/CDER

BC
NDA ORIG AMENDMENT

Daniel Shames, M.D, Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Shames:

Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
OTHER: Response to March 21, 2002 Request for Information – CMC Comments to Sponsor

Reference is made to NDA 21-355 submitted on December 14, 2001 for ANGELIQ™ drospirenone and 17β-estradiol tablets, a hormone replacement therapy.

This submission is in response to a TELEFAX received March 21, 2002 from your representative, Archana Reddy. The FDA CMC requests are bolded followed by a response from the sponsor.

1. Please include the drug substance specifications in the NDA.

Drug substance specifications are referenced in Type II DMF No. 12138 for Drospirenone and Type II DMF No. —— for Estradiol. For the reviewers convenience the following specifications are included: **(Attachment 1)**

- Quality Specification No. ——
  Drospirenone (
  dated October 27, 2000

- Quality Specification No. ——
  Estradiol —— (EP and USP) ——
  dated September 2, 1998

5 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 6

Berlex will provide an amended protocol removing the statement regarding statistical analyses to support expiry extensions. The stability commitment is updated to include a statement that any extension of the expiry will be based on real-time data from three production batches and a full study design.

The adjusted stability protocol: **(Attachment 10)**

- Stability Commitment RSC-01-078B
  Drospirenone/Estradiol Tablets
  dated May 6, 2002

15. Provide container and carton labels for the ———

Berlex intends to comply with this request by August 16, 2002.

16. Provide mock-ups of all package labeling to include colors and graphics by August 16, 2002.

Berlex intends to comply with this request by August 16, 2002.

17. Revise the container and carton labels as follows: The same revisions should be applied to the labeling for the — ——————————— strength. The underlined test is to be added, and the crossed-out text is to be deleted.)

Berlex intends to comply with this request by August 16, 2002.

NDA 21-355 is a fully electronic submission; therefore, we are also submitting this request for additional information in electronic format. This information is provided on one (1) compact disk (CD). Berlex Laboratories, Inc. certifies that the CD has been scanned for viruses and is virus free using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54. The CD is being sent under separate cover to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room 17B-20
5600 Fishers Lane
Rockville, Maryland 20857

Berlex trusts that this submission adequately addresses your March 21, 2002 request. Should you have any questions regarding this submission, please contact the undersigned at (973) 487-2184. The fax number is (973) 487-2016.

Sincerely,

BERLEX LABORATORIES

Michael Doroshuk
Manager - Drug Regulatory Affairs

Desk Copy: Archana Reddy
cmd/052

BERLEX

UPS OVERNIGHT

DUPLICATE

May 13, 2002

ORIG AMENDMENT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

Daniel Shames, MD, Acting Director
Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-580, Room 17B-45
Rockville, Maryland 20857-1706

BS

Dear Dr. Shames:

Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
OTHER: Response to May 2, 2002 Request for Information: Question from Statistical reviewer

Reference is made to NDA 21-355 submitted on December 14, 2001 for ANGELIQ™ drospirenone and 17β-estradiol tablets, a hormone replacement therapy.

Reference is also made to a telephone message and a followup telefax received on May 2, 2002 from your representative, Archana Reddy who relayed a request from the Statistical Reviewer for a written response to the following question specific to protocol 96097A, the endometrial protection study:

1. **Please describe the discrepancy between the number of ITT patients in each group and the number of patients who entered the first time interval (days 0-60) in Table 19: Preliminary Life Table Analysis of Endometrial Hyperplasia and/or Cancer Over One Year Treatment Period.**

The ITT population was defined as all subjects randomized to the study and known to have taken at least 1 dose of study medication. The clinical database for the study identified 1142 subjects as ITT subjects. However, Table 19 was created from the biopsy records defined as all subjects who had any biopsy done for this study. There were data for 1108 subjects; these were subjects who had a biopsy at baseline, post baseline, or both.

The LIFE dataset for Table 19 was created by taking all the biopsy records and merging/sorting the data as needed to create one record per subject. A number of derived variables were then created which included DAYS (BIOPDT-FIRSTDAY), DAYEND (LASTDAY - FIRSTDAY), HYPER(Yes if biopsy codes reflect hyperplasia, No if not), INTERVAL(study intervals), TYPE (Withdrawal type), STATUS (Completed/Censored/Hyperplasia).

If the DAYEND field was = null/missing, the subject record was not included in the analysis. There were 8 subjects (9709019, 9718020, 9722007, 9724022, 9734013, 9741002, 9747006, and 9753022) that did not have a value for DAYEND in the LIFE dataset. Hence, the dataset for Table 19 consisted of 1100 (1108 – 8) subjects, the sum of the number of subjects who entered the first time interval (days 0-60) for various treatment groups.

NDA 21-355 is a fully electronic submission, therefore, we are sending this AMENDMENT TO A PENDING APPLICATION in electronic format be compatible with the NDA. This information is provided on one (1) compact disk (CD). Berlex Laboratories, Inc. certifies that the CD has been scanned for viruses and is virus free using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54. The CD is being sent under separate cover to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room17B-20
5600 Fishers Lane
Rockville, Maryland 20857

Berlex trusts this submission adequately addresses the statistical question received on May 2, 2002. Should you require any additional information or have any questions regarding this submission, please contact the undersigned at (973) 487-2184. The fax number is (973) 487-2016.

Sincerely,

BERLEX LABORATORIES

Michael Doroshuk
Manager
Drug Regulatory Affairs

Desk Copy:
Ms. Archana Reddy

cmd/051

BERLEX

UPS OVERNIGHT

May 8, 2002

~~DUPLICATE~~

ORIGINAL

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

Daniel Shames, MD, Acting Director
Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-580, Room 17B-45
Rockville, Maryland 20857-1706

BZ
NDA ORIG AMENDM
RECEIVED
MAY 0 9 2002
HFD-580/CDER

Dear Dr. Shames:

Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
OTHER: Response to FDA Request for Information: Submission of Phase 1 Clinical Report and Draft Labeling Changes

Reference is made to NDA 21-355 submitted on December 14, 2001 for ANGELIQ™ drospirenone and 17β-estradiol tablets, a hormone replacement therapy. Reference is also made to a telefax request for submission of the hepatic study received April 12, 2002. Additional reference is made to the Pre-NDA meeting which occurred on January 24, 2001, where the Division of Reproductive and Urologic Drug Products agreed to accept submission of the hepatic impairment study within 7 months of the NDA submission date.

Berlex is hereby submitting Study Number 304666 (Report No. A03161). "A study to evaluate the pharmacokinetics and safety of drospirenone (DRSP) after single oral administration of a film coated tablet (SH T 641 D) containing the combination product 3 mg DRSP and 1 mg 17β-estradiol (E2) in female volunteers with moderately impaired or normal liver function". Corresponding Case Report Tabulations are included as SAS datasets.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

In addition, Berlex is submitting changes to the proposed draft labeling for ANGELIQ submitted in the original application. These changes are highlighted (using the track changes mode in MS WORD) for the reviewer and reflect the following:

Special Populations:

- [redacted]
- [redacted]

CLINICAL STUDIES

- [redacted]

INDICATIONS AND USAGE

- [redacted]

CONTRAINDICATIONS

- Removal of " [redacted]

WARNINGS

- Removal of " [redacted]

NDA 21-355 is a fully electronic submission, therefore, we are sending this request for additional information in electronic format be compatible with the NDA. This information is provided on one (1) compact disk (CD). Berlex Laboratories, Inc. certifies that the CD has been scanned for viruses and is virus free using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54. The CD is being sent under separate cover to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room17B-20
5600 Fishers Lane
Rockville, Maryland 20857

Berlex trusts that this submission adequately addresses your April 12, 2002 request. Should you require any additional information or have any questions regarding today's submission, please contact the undersigned at (973) 487-2184. The fax number is (973) 487-2016.

Sincerely,

BERLEX LABORATORIES

Michael Doroshuk
Manager
Drug Regulatory Affairs

Desk Copy Ms. Archana Reddy

cmd/050

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: May 2, 2002

To: Michael Doroshuk Manager, Drug Regulatory Affairs	**From:** Archana Reddy, M.P.H. Project Manager
Company: Berlex Laboratories, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 973-487-2016	**Fax number:** 301-827-4267
Phone number: 973-487-2184	**Phone number:** 301-827-4260

Subject: Statistical comment for the sponsor

Total no. of pages including cover: 2

Comments:

Mike,

Please respond to the statistical comment that follows.

Thanks,

Archana Reddy

PM, DRUDP

Document to be mailed: ☐ YES ☑ NO

STATISTICAL COMMENT FOR THE SPONSOR

NDA: 21-355
Drug: Angeliq™ (drospirenone/17-β estradiol)
Sponsor: Berlex Laboratories, Inc.

Please provide a response to the following statistical comment.

(1) Please describe the discrepancy between the number of ITT patients in each group and the number of patients who entered the first time interval (days 0 - 60) in Table 19: Preliminary Life Table Analysis of Endometrial Hyperplasia and/or Cancer Over One Year Treatment Period.

UPS OVERNIGHT

BERLEX

RECEIVED
MAY 0 2 2002
HFD-580/CDER

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000
Telephone: (973) 487-2000

May 1, 2002

BM
NDA ORIG AMENDMENT

Daniel Shames, M.D, Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room (Room 17B20)
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Shames:

Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
OTHER: Response to April 12, 2002 Request for Information – Clinical Comments to Sponsor

Reference is made to NDA 21-355 submitted on December 14, 2001 for ANGELIQ™ drospirenone and 17β-estradiol tablets, a hormone replacement therapy. Further reference is made to the 4-Month Safety Update Report to NDA 21-355, submitted on April 11, 2002.

This submission is in response to a TELEFAX received, April 12, 2002, from your representative, Archana Reddy. The FDA Clinical requests are bolded followed by a response from the sponsor.

1. Please submit hepatic impairment study report and the four-month safety update (due April 14).

The four-month safety update report was submitted on April 11, 2002. The hepatic impairment study report is in quality review. We anticipate this report will be submitted during the week of May 6, 2002.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

2. For the Integrated Summary of Safety, Please provide the proportion of potassium samples that were rejected by [redacted] out of all potassium samples, by exposure group (for women exposed to drospirenone and, separately, for control women exposed to placebo or E2).

E2 1 mg	10 of 609 samples rejected
E2 1 mg + DRSP 0.5 mg	13 of 616 samples rejected
E2 1 mg + DRSP 1 mg	12 of 618 samples rejected
E2 1 mg + DRSP 2 mg	7 of 612 samples rejected
E2 1 mg + DRSP 3 mg	10 of 626 samples rejected.
Total	52 of 3,081 total samples rejected

3. Have you any theories regarding why so many hyperplasia diagnoses disappear in the drospirenone group when going from the safety reading to the efficacy reading, but so few disappear for the E2 group? There were 10 safety readings read as hyperplasia in women taking drospirenone. In all but one of these women, the efficacy reading resolved the hyperplasia diagnosis. However, there were 23 safety readings of hyperplasia in women taking E2 alone, and the efficacy reading resolved only 3 of them.

The quality of the safety readings can be expressed in terms of specificity and sensitivity. Taking the efficacy reading as the gold standard, the specificity of the safety reading (or the proportion of false positive results within all negative results, i.e. one minus the specificity) can be compared between E2 + DRSP and E2 subjects. Sensitivity cannot be compared reliably due to the small number of positive results (i.e. hyperplasia). Since four times as many subjects had an endometrial biopsy in E2 + DRSP groups compared to E2 alone, the ratio of the number of false positive results in both groups reflects the difference in treated subjects, leading to a comparable proportion and, thus, a comparable specificity. The different number of safety readings resolved by the efficacy reading in the two groups can therefore be explained by a different number of subjects.

In addition to the above mentioned, it is commonly seen in clinical studies investigating endometrial safety of HRT products that a safety reading read as simple hyperplasia can be resolved by the efficacy reading. The safety readings are done by any histopathologist, the efficacy readings, on the other hand, are done by expert histopathologists specialized in reading of endometrial biopsies in women on HRT. In this respect, it can be speculated that the effect of a combined HRT on endometrium which includes a wide spectrum of morphologic features, various combinations of weakly to intensely proliferative glands and/or secretory glands, with sub- and supranuclear vacuoles and luminal secretion, often surrounded by stromal edema, stromal hyperplasia, and decidual reaction[1] produces a histologic pattern that may appear rather confusing, and that is more difficult to read by a non-expert histopathologist.

4. Have there been any marketing applications for Angeliq that have been turned down?

No marketing applications for Angeliq have been turned down.

---

[1] Liane Deligdisch, M.D. Hormonal Pathology of the Endometrium. Mod Pathol 2000;13(3):285-294

5. Please provide a summary of ECG data for the Integrated Summary of Safety. Was there any evidence for Q-T interval prolongation in the electrocardiogram data?

As specified in the Integrated Summary of Safety (section 8.2.13.3) electrocardiogram measurements were only performed at screening and final visit during Phase 1 studies. These data were not entered into the electronic ISS database, but are available in the individual study reports. No electrocardiogram measurements were performed during Phase 3 studies. During a Guidance meeting (teleconference March 24, 2000) DRUDP commented that ECG data would be desirable in any patients with abnormal potassium and/or creatinine levels in future studies. Berlex agreed to capture ECG data in future studies. To date, Berlex has/is collecting ECG data in the following studies:

- NSAID interaction study Phase 1 (Protocol 304181, Report A00824) – included in NDA 21-355
- Hepatic impairment study Phase 1 (Protocol 304666, Report A03161) – being finalized
- Simvastatin study Phase 1 (Protocol 303741, Report BD09) - being finalized
- Mild hypertension study Phase 3 (Protocol 305140) – study ongoing
- High risk study Phase 3 (Protocol 305471) – study ongoing

NDA 21-355 is a fully electronic submission; therefore, we are also submitting this request for additional information in electronic format. This information is provided on one (1) compact disk (CD). Berlex Laboratories, Inc. certifies that the CD has been scanned for viruses and is virus free using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54. The CD is being sent under separate cover to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room 17B-20
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions regarding this submission, please contact the undersigned at (973) 487-2184.

Sincerely,

BERLEX LABORATORIES

Michael Doroshuk
Manager
Drug Regulatory Affairs

Desk Copy: Archana Reddy

CMD/047

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: August 23, 2002

TO: Archana Reddy, Regulatory Project Manager, HFD-580
Division of Reproductive and Urologic Drug Products, HFD-580

THROUGH: Khin Maung U, M.D.
Acting Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, Maryland 20855

FROM: Roy Blay, Ph.D.,
Director Regulatory Review Officer
Good Clinical Practice Branch 1, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-355

APPLICANT: Berlex Laboratories

DRUG: Angeliq™ (drospirenone/17β-estradiol)

THERAPEUTIC CLASSIFICATION: 4S

INDICATION: Hormone replacement therapy in postmenopausal, non-hysterectomized women

REVIEW DIVISION GOAL DATE: August 30, 2002
ACTION GOAL DATE (PDUFA Date): October 17, 2002

I. BACKGROUND:

Hormone replacement therapy (HRT) is used to reduce or eliminate the symptoms and pathologic conditions associated with menopause and the subsequent decline in the production of female sex hormones. HRT has been shown to reduce the number of hot flushes, improve urogenital symptoms, halt progression of postmenopausal osteoporosis, and possibly provide protection against cardiovascular disease. However, unopposed estrogen therapy is associated with increased risks of endometrial hyperplasia and carcinoma. This increased risk is minimized with the addition of progestin treatment. Drospirenone is a progestin under development for combination hormone therapy. The clinical pharmacology profile of drospirenone suggests that it will not antagonize the beneficial effects of estrogens upon the lipid profile and will have a good tolerance profile. These studies were designed to determine

the dose of drospirenone that will prevent the development of endometrial hyperplasia when used in continuous combination with 17β-estradiol and to demonstrate a dose-response relationship of metabolic effects and tolerance among the various dose combinations used.

The clinical sites of Drs. Corn and Wehle submitted data that were essential to the approval of this submission; thus, they were selected for inspection. The goals of inspection included validation of submitted data and compliance of study activities with Federal regulations and good clinical practices. Among the study elements reviewed for compliance were subject record accuracy, appropriate informed consent, appropriate use of inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of serious adverse events.

II. RESULTS (by site):

NAME	CITY, COUNTRY	ASSIGNED DATE	INSPECTION DATES	RECEIVED DATE	CLASSIFICATION/ FILE NUMBER
Lydia Corn, M.D.	Sarasota, FL	11 Mar 02	22-26 Jul 02	22 Aug 02	VAI
Susan Wehle, M.D.	Tampa, FL	11 Mar 02	29 Jul-1 Aug 02		NAI

Site #1 (protocol #96097A)
Lydia Corn, M.D.

a. 63 subjects were screened at this site, 47 were randomized, and 34 completed the study. The records of thirteen subjects were reviewed in depth which included but were not limited to source data, case report files, IRB correspondence, sponsor correspondence, drug accountability, and laboratory reports. Data reported in the source data was compared with that in the case report files and the data listings submitted with the inspection request.

b. There were no limitations on the inspection.

c. A Form 483 was issued. The observations related to the inappropriate enrollment of three subjects prior to completion of a washout period for a prior study, insufficient frequency of blood pressure measurements for five subjects at various visits, and failure to report adverse events of abdominal cramps, breast fullness, rectal bleeding and epistaxis for one subject and intermittent episodes of blurred vision for another subject.

Site #2 (protocol #96097A)
Susan Wehle, M.D.

Per personal communication with the Florida District Office (Mr. Ron Jackson via Ms. Brunilda Torres in e-mail of August 9, 2002), a Form FDA 483 was not issued to Dr. Wehle, nor did the investigator have any particular concerns regarding this inspection.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The requested inspections have been completed. The data submitted in support of this NDA by ——— appear acceptable. Observations at ——— site included deviations from protocol and failure to report adverse events. An EIR has not been received for ——— inspection; however, a Form 483 was not issued. No objectionable conditions were found which would preclude the use of the data submitted in support of the pending application. Should review of these EIRS have a substantial effect upon our recommendation, we will inform the Review Division.

CONCURRENCE:

Khin Maung U, M.D.
Acting Branch Chief

DISTRIBUTION:

NDA 21-355
HFD-45/Division File
HFD-46/Program Management Staff (electronic copy)
HFD-510/Project Manager/Reddy
HFD-46/Clinical Reviewer/Blay
HFD-46/CIB File #s, xxxxxx, and xxxxxx
HFD-46/Reading File

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

/s/

Sherry George
9/12/02 10:37:05 AM
TECHNICAL
Signed by Dr. El-Hage for Dr. U on 8/23/02

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: April 15, 2002

To: Michael Doroshuk Manager, Drug Regulatory Affairs	**From:** Archana Reddy, M.P.H. Project Manager
Company: Berlex Laboratories, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: 973-487-2016	**Fax number:** 301-827-4267
Phone number: 973-487-2184	**Phone number:** 301-827-4260

Subject: Fax of 3/25/02 meeting minutes

Total no. of pages including cover: 5

Comments:

Mike,

Please find attached the minutes from the teleconference that was held on 3/25/02 for Angeliq™ (NDA 21-355).

Thanks,

Archana Reddy

PM, DRUDP

Document to be mailed: ☐ YES ☑ NO

Teleconference Minutes

Date: March 25, 2002 **Time:** 1:00 – 1:15 PM **Location:** PKLN 17B-45

NDA: NDA 21-355 **Drug:** Angeliq™ (drospirenone/17-β estradiol)

Sponsor: Berlex Laboratories, Inc.

Meeting Chair: Suong Tran, Ph.D.

Type of Meeting: Chemistry (Guidance)

External Participant Lead: Michael Doroshuk

Meeting Recorder: Archana Reddy, M.P.H.

Indication: _____ moderate to severe vasomotor symptoms and vulvar and vaginal atrophy in _____ menopausal women

External Participants:
Michael Doroshuk, Manager, Drug Regulatory Affairs
Jeff Millington, Regulatory Affairs
Shawn Hoskins, Senior CMC Representative
Tom Lupo, Manager, Quality Assurance Operations
Jeff Farkas, Manager, Quality Control

FDA Participants:
Archana Reddy, M.P.H., Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580
Suong Tran, Ph.D., Chemistry Reviewer, DRUDP, HFD-580

Background:
Angeliq™ (drospirenone/17-β estradiol) is a type 4 NDA (new combination) submitted by Berlex Laboratories, Inc. on December 14, 2001, and received on December 17, 2001, for hormone replacement therapy. In the original NDA submission, it is stated that the drug product specification is implemented on the bulk product, not the packaged product. On February 1, 2002, the sponsor was informed that release testing should be performed on the final drug product (i.e., packaged and labeled product). On February 15, 2002, the sponsor submitted additional information on the procedures for final release (for distribution) of packaged drug product.

Meeting Objectives:
To inform the sponsor that the their proposal for release testing as indicated in their submission dated February 15, 2002 is not adequate.

Discussion:
FDA comments

- the Division indicated to the sponsor that release testing on the final drug product is required
- release testing (per drug product specification) performed on the bulk drug product is not acceptable
- 21 CFR 211.165 requires testing of the drug product prior to release for distribution (i.e., commercial distribution)
- the bulk drug product is not released for commercial distribution; it is released for further manufacturing- packaging and labeling. 21 CFR 210.3 defines "manufacture" of a drug product to include packaging and labeling operations
- therefore, testing performed on the bulk drug product is considered to be in-process testing
- the drug product specification should be implemented on the final drug product (packaged and labeled drug product)

Sponsor comments

- sponsor stated that it is the industry standard to conduct release testing at the bulk drug stage and not on the packaged product
- sponsor stated that the same testing procedures for the bulk product and the same packaging operations, without any testing performed on the packaged product other than visual identification, have been approved for other products (such as Betapace Tablets, NDA 19-865)

Decision reached:
The Division will inform the sponsor of the Agency's response with regard to the sponsor's proposal for release testing.

Action Items:
The PM will fax the minutes of this teleconference to the sponsor within 30 days.

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

Suong Tran, Ph.D.
Review Chemist

Post-Meeting Addendum:
A final decision has been made by FDA and is as follows. Release testing of the drug product performed on the bulk drug product is acceptable provided that:

- There are acceptable release procedures for the bulk tablets at the manufacturing site that include all required physical and chemical testing of the tablets.
- All packaging and labeling specifications for the bulk product are met.
- There are acceptable procedures for receipt and handling of incoming bulk tablets at the packaging site, as well as procedures for repackaging the bulk tablets into market containers.
- There are acceptable release procedures to ensure that all packaging and labeling specifications are met prior to release.
- Other requirements for stability and expiration dating on the bulk and market containers, and for container-closure qualification are met.

FDA review of procedures, specifications, and other requirements for stability and expiration dating delineated above is currently ongoing.

Cc:
Arch NDA
HFD-580/Division Files
HFD-580/Reddy/Tran/Rhee/Kober/Shames

Created by: Archana Reddy, March 25, 2002
Concurrence: st/March 27, 2002
Finalized: ar/April 11, 2002

Meeting Minutes

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

/s/

Archana Reddy
4/15/02 02:24:36 PM