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

FACSIMILE TRANSMITTAL SHEET

DATE: April 12, 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

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

Please provide a response to the following requests.

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

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

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 readings, but so few disappear for the E2 group? There were 10 safety reading 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 reading of hyperplasia in the women taking E2 alone, and the efficacy reading resolved only 3 of them.

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

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?

BERLEX

UPS OVERNIGHT

April 11, 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

Dear Dr. Shames:

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.

In accordance with 21 CFR 314.5(d)(5)(vi)(b), attached please find the first Safety Update Report submitted for NDA 21-355. This update is being submitted approximately 4 months after the initial NDA submission.

The reporting interval for this Safety Update is June 1, 2001 – March 15, 2002. These dates correspond to the cut-off date for inclusion of data into the NDA 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) 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

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

md040

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

FACSIMILE TRANSMITTAL SHEET

DATE: March 21, 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 information request letter for Angeliq

Total no. of pages including cover: 7

Comments:

Mike,

Please find attached a courtesy copy of the CMC information request letter for Angeliq.

Thanks,

Archana Reddy

PM, DRUDP

Document to be mailed: X YES NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-355

INFORMATION REQUEST LETTER

Berlex Laboratories, Inc.
Attention: Michael Doroshuk
Manager, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07470-4100

Dear Mr. Doroshuk:

Please refer to your December 14, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Angeliq™ (drospirenone/17-β estradiol).

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

1. Please include the drug substance specifications in the NDA.
2. Indicate whether acceptance (confirmatory) testing of drug substance batches is performed upon receipt at the drug product manufacturing site. Provide specifications and analytical methods if such testing is performed.
3. Provide appropriate references to indirect food additive regulations (21 CFR 174-186) or other safety information on the ~~~~ bags (primary packaging for tablets in bulks).
4. Include a full description of the tablet in the acceptance criteria for Appearance. Appearance for the ~~ mg drospirenone/1 mg estradiol tablet should state "Round, biconvex, ~~~~ ~~~~ pink, film-coated tablet, with the embossment ~~~~ inside a hexagon ~~~~ ~~~~ . Appearance for the ~~ mg drospirenone/1 mg estradiol tablet should state "Round, biconvex, ~~~~ ~~~~ pink, film-coated tablet, with the embossment ~~ inside a hexagon ~~~~
5. Release testing should include testing for impurities and degradation products.
6. Clarify whether confirmatory identity testing of ~~~~ bottles by ~~ is performed at the packaging facility.
7. Clarify whether confirmatory identity testing by ~~ of the ~~~~ closures by ~~ is performed at the packaging facility.

8. The specification for the [redacted]

9. State whether the testing of packaging materials will be performed at the packaging site or a certificate of analysis from the vendor will be accepted in lieu of the full testing at the packaging site.

10. The acceptance criteria for Decomposition products of drospirenone should be: [redacted]

11. The acceptance criteria for Decomposition products of estradiol should be: [redacted]

12. Based on the data on pages 52 and 109 of the Methods Validation section, [redacted]

    Propose and justify an acceptance criterion for this impurity.

13. The proposed matrixing design for the post-approval stability protocol is acceptable only for routine monitoring of the drug product stability, not for post-approval changes. Stability documentation for post-approval changes should follow FDA guidance "Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation". The stability commitment should include a post approval stability protocol with a full study design for post approval changes.

14. The proposal to [redacted] support an extension of the expiry is not acceptable. The stability commitment should 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.

15. Provide container and carton labels for the physician sample.

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

17. Revise the container and carton labels as follows:

    (The same revisions should be applied to the labeling for the [redacted] mg drospirenone/1.0 mg estradiol dosage strength. The underlined text is to be added, and the crossed-out text is to be deleted.)

2 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 7

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

Sincerely,

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products, HFD-580
DNDC II, Office of New Drug Chemistry
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/

Moo-Jhong Rhee
3/20/02 04:43:32 PM

BERLEX

UPS OVERNIGHT

March 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, 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
OTHER: Response to February 26, 2002 Request for Information: Data Management questions 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 conversation on February 26, 2002 and a followup telefax on February 27, 2002 from your representative, Archana Reddy who relayed a request from the Statistical Reviewer for a written response to the following data management questions specific to protocol 96097A, the endometrial protection study:

1. **Please provide the names and affiliations of all blinded readers used for reading of the endometrial biopsy slides.**

All biopsies (pre-study, non scheduled in-study, and end-of-study) were evaluated for safety at [redacted]. The safety reads were read there by one of the staff pathologists [redacted].

The efficacy reads that followed were done by:

2. **Please clarify what does the variable RPTDATE (specimen report date) refer to; the safety read report or another report? If another report, please describe.**

The variable RPTDATE in the data set — refers to the safety read report date by the

3. **Please provide the SAS data set and variable for the subject randomization date.**

The SAS data set is provided as a SAS transport file contained in the compact disc (CD) **(ATTACHMENT A).**

4. **Please clarify what the variables FIRSTDAY and LASDAY in the SAS data set MEDDATE represent.**

The variable FIRSTDAY and LASTDAY represent the subject's first study medication day and last study medication day, respectively. To clarify, the variable name "LASDAY" should be "LASTDAY" as in the SAS data set MEDDATE.

5. **In Section 14.3 of the protocol and protocol amendments documents for protocol 96097A (Procedures for Processing and Evaluating Endometrial Biopsies). It is mentioned that "all biopsies will be evaluated for safety by one of the pathologist assessors." Please clarify who this pathologist assessor(s) is (are) and their affiliation.**

All biopsies (pre-study, non scheduled in-study, and end-of-study) were evaluated for safety at

NDA 21-355 is a fully electronic submission; therefore, we are also submitting this request for additional information 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

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/029

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 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 statistical information

Total no. of pages including cover: 2

Comments:

Mike,

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

Thanks,

Archana Reddy

PM, DRUDP

Document to be mailed: ☐ YES ☑ NO

STATISTICAL COMMENTS FOR THE SPONSOR

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

Please provide a written response to the following statistical comments for protocol 96097A for the endometrial protection study.

1) Please provide the names and affiliations of all blinded readers used for reading of the endometrial biopsy slides.

2) Please clarify what does the variable RPTDATE (specimen report date) refer to: the safety read report or another report? If it is another report, please describe.

3) Please provide the SAS data set and variable for the subject randomization date.

4) Please clarify what the variables FIRSTDAY and LASTDAY in the SAS data set MEDDATE represent.

5) In Section 14.3 of the Protocol and protocol amendments document for protocol 96097A (Procedures for Processing and Evaluating Endometrial Biopsies), it is mentioned that "all biopsies will be evaluated for safety by one of the pathologist assessors." Please clarify who this pathologist assessor(s) is(are) and their affiliation.

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 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: Meeting minutes from the February 15, 2002 teleconference

Total no. of pages including cover: 4

Comments:

Mike,

Please find attached a copy of the meeting minutes from the February 15, 2002 teleconference for Angeliq.

Thanks,

Archana Reddy

PM, DRUDP

Document to be mailed: ☐ YES ☑ NO

Teleconference Minutes

Date: February 15, 2002 **Time:** 10:00 – 10:15 AM **Location:** PKLN 17B-45

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

Sponsor: Berlex Laboratories, Inc.

Meeting Chair: Diane Moore

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
Sharon Brown, Director, Regulatory Affairs

FDA Participants:
Archana Reddy, M.P.H., Project Manager, Division of Reproductive and Urologic Drug Products, HFD-580
Diane Moore, 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.

Meeting Objectives:
To inform the sponsor that the indication for _____

Discussion:
FDA comments

-
-
-

Sponsor comments

- [redacted]

Decision reached:

- the sponsor agreed to inform the FDA of their decision regarding their pursuit of these indications

Action Items:

1) The PM will convey the sponsor's comments to the review team for Angeliq™.
2) The PM will fax the minutes of this teleconference to the sponsor within 30 days.

Post-Meeting Addendum:

The sponsor was informed on February 19, 2002 that should they wish to pursue the indications [redacted]

following guidance:

1) "New Drug Evaluation Guidance Document Refusal to File" posted on November 26, 1999 and
2) "Guidance for Industry Formal; Formal Dispute Resolution; Appeals Above the Division Level" posted February 2000.

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.

Diane Moore
Regulatory Project Manager

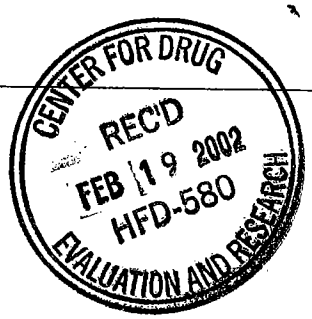
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Diane V. Moore
2/26/02 03:50:33 PM

DUPLICATE

UPS OVERNIGHT



BERLEX

February 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, 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

NDA ORIG AMENDMENT

N-15C

Dear Dr. Shames:

Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
OTHER: Response to request for information

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 made to a telephone request on February 1, 2002, wherein your representative, Archana Reddy, relayed a response from Dr. Su Tran, Chemistry Reviewer in the Division of Reproductive and Urologic Drug Products, regarding release testing of the final packaged product described in NDA 21-355. Specifically, Dr. Tran's concern was:

The fact that Berlex plans to only perform release testing on the commercial bulk tablets prior to packaging was unacceptable. Dr. Tran indicated that Berlex needs to show that release testing would be performed on the final packaged product.

For clarification, the process for the testing and release of Angeliq drug product is outlined below:

For each batch of Angeliq drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. The Schering AG facility located in Weimar, Germany, will conduct laboratory testing on the bulk drug product per

Stability Reports No. A06107 and A06113 contain data generated on bulk drug product in the shipping container ——————. The stability data indicates that after 24 months storage at 25C/60% RH and after —— storage at 40C/75% RH the bulk drug product remained stable. All reported findings were well within the specifications. Photostability Working Reports No. A03306 and A03726 indicate that drug product is stable against exposure to light and may be stored in containers unprotected from light. Therefore, there is sufficient assurance that the quality of the drug product will not be effected during packaging at ——→

The final release for distribution of packaged drug product, including Quality Assurance Inspection reports that include a visual identification, review of —— packaging records, and reconciliation is performed by the Berlex Quality Assurance Unit.

Therefore, the appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, is performed prior to release on bulk drug product. In addition, the Berlex Quality Assurance Unit ensures that the identity of the packaged drug product conforms to specifications through visual identification inspections prior to the final release for distribution.

Berlex Laboratories hopes the above information serves to clarify the procedures performed to meet the requirements for release testing. Berlex Laboratories is requesting which specific quality concerns underlie Dr. Tran's request for release testing on the final packaged product and Dr. Tran's specific interpretation of release testing in this instance.

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
Dr. Su Tran

CMD/letter/angeliq015

UPS OVERNIGHT

DUPLICATE

BERLEX

February 8, 2002

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

BS

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:
Response to Statistical Information Request

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 request on January 31, 2002 wherein your representative, Ms. Archana Reddy, asked for the following statistical information regarding Study 96097A ("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")

Specifically, the following dates were requested:

Date first patient was enrolled in Study 96097A
Date last patient completed in Study 96097A
Date database was locked for Study 96097A
Date database was unlocked for Study 96097A

Berlex is providing the above requested information in a one-page table with this correspondence. **(ATTACHMENT A)**

NDA 21-355 is a fully electronic submission, therefore, we are also 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

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

md014

UPS OVERNIGHT

BERLEX

February 1, 2002

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

Dr. Su Tran, Chemistry Reviewer
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. Tran:

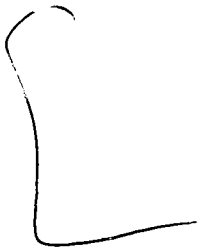
Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
OTHER: Response to January 23, 2002 Request for Information: Tablet Description and Examples of Tablets

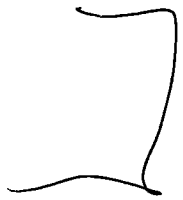
Reference is made to NDA 21-355 submitted on December 14, 2001 for ANGELIQ™ drospirenone and 17β-estradiol tablets, a hormone replacement therapy.

Reference is also made to your telephone request on January 23, 2002 for additional description of the identifying markings on the ANGELIQ™ to-be-marketed tablets described in NDA 21-355 along with examples of the tablets for your review.

1.

2.





NDA 21-355 is a fully electronic submission; therefore, we are also submitting this request for additional information 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

Screening of New NDA
Division of Biometrics II

NDA #: 21-355

Trade Name: Angeliq

Generic Name: Drospirenon/Estradiol

Indication: Hormone Replacement Therapy

No. of Controlled Studies: 1

Medical Officer: Lesley Furlong, M.D., HFD-580

Project Manager: Archana Reddy, HFD-580

Screened by: Sonia Castillo, Ph.D., HFD-715

Volume numbers in statistical section: Electronic submission

Priority Classification: 4S

Applicant: Berlex Laboratories, Inc.

Date of Submission: December 17, 2001

User Fee Goal Date: October 17, 2002

Date of 45-Day Meeting: January 30, 2002

Anticipated Review Completion Date:September 16, 2002

Comments: This application is fileable from a statistical point of view.

CHECKLIST

Item	Check (NA if not applicable)
Index sufficient to locate necessary reports, tables, etc.	X
Original protocols & subsequent amendments available in the NDA	The one amendment is not available
Designs utilized appropriate for the indications requested	X
Endpoints and methods of analysis spelled out in the protocols	X
Interim analyses planned in the protocol and appropriate adjustments in significance level made	NA
Appropriate references included for novel statistical methodology (if present)	NA
Sufficient data listings and intermediate analysis tables to permit statistical review	X
Data from primary studies on diskettes and/or CANDA submitted	X
Intent-to-treat analysis	X
Effects of dropouts on primary analyses investigated	X
Safety and efficacy for gender, racial, and geriatric subgroups investigated	NA

BRIEF SUMMARY OF CONTROLLED CLINICAL TRIALS

Study Number (Dates Conducted)	Number of Centers (Locations)	Total Sample Size	Treatment	Type of Control	Design	Duration of Treatment
A02827 (1-22-98 to 4-28-01)	53 (USA)	1142	0.5 mg drospirenone + 1 mg estradiol 1.0 mg drospirenone + 1 mg estradiol 2.0 mg drospirenone + 1 mg estradiol 3.0 mg drospirenone + 1 mg estradiol	1 mg estradiol	Double Blind, Randomized, Parallel Group	Thirteen 28-day cycles

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

/s/

Sonia Castillo
2/1/02 11:35:17 AM
BIOMETRICS
This document includes a fileability statement and supercedes the previously submitted document.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: OPDRA Request/HFD-400
Parklawn Building
Attention: Dr. Phillips, Associate Director for Medication Error Prevention/Sammie Beam, Project Manager
PKLN Room 15B23

FROM: Archana Reddy, M.P.H., Project Manager for Shelley Slaughter, M.D., Ph.D., Acting Deputy Director, HFD-580/Daniel Shames, M.D., Acting Division Director, HFD-580

DATE: 1/31/02	IND NO.	NDA NO. 21-355	TYPE OF DOCUMENT: Draft Proposed Labeling for Original NDA submission	DATE OF DOCUMENT: December 14, 2001
NAME OF DRUG: Angeliq™	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG: Estrogens	DESIRED COMPLETION DATE: July 31, 2002

NAME OF FIRM: Berlex Laboratories, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Sammie,
Please provide a tradename review for NDA 21-355 (Angeliq™). Attached is the draft labeling, including vial and container labels, for this drug product.
Thank you,
Archana
PM
DRUDP

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

See ATTACHMENT (Draft Labeling)

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/s/

Archana Reddy
1/31/02 11:41:47 AM

Memo to the file

1-31-2002
Subject: NDA 21-355 filing meeting

NDA 21-355 – Angeliq tablets (Drospirenone and 17B-Estradiol is filable from the P/T prospective.

Krishan L. Raheja
P/T reviewer

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/s/

Krishan L. Raheja
1/31/02 10:46:15 AM
PHARMACOLOGIST

Alexander W. Jordan
2/4/02 10:19:53 AM
PHARMACOLOGIST

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-355**	**Brand Name**	**Angeliq**
OCPB Division (I, II, III)	**DPE II**	**Generic Name**	**Drospirenone/17β-estradiol**
Medical Division	**DRUDP**	**Drug Class**	**Progestin/Estrogen**
OCPB Reviewer	**Venkat Jarugula**	**Indication(s)**	**Hormone Replacement**
OCPB Team Leader	**Ameeta Parekh**	**Dosage Form**	**Tablet**
		Dosing Regimen	**DRSP/1mg E2**
Date of Submission	**12/14/01**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**9/14/02**	**Sponsor**	**Berlex**
PDUFA Due Date	**10/14/02**	**Priority Classification**	**4S**
Division Due Date	**9/14/02**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	1		
Isozyme characterization:	X	7		
Blood/plasma ratio:	X			
Plasma protein binding:	X	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	6		
multiple dose:	X	3		
Patients-				
single dose:	X			
multiple dose:	X			
Dose proportionality -				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:	X			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1		
In-vivo effects of primary drug:	X	2		
In-vitro:	X			
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:	X			
renal impairment:	X	1		
hepatic impairment:	X			

PD:				
Phase 2:	X	12		
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	**X**	**1**		
Relative bioavailability -				
solution as reference:	X	1		
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	2		
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	**1**		
Dissolution:	**X**	**1**		
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		36		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	**X**	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**Bioequivalence of estradiol component from the combination to Estrace in support of efficacy in terms of relief of vasomotor symptoms** **Does progestin (DRSP) in the combination interact with estradiol?**	

Other comments or information not included above	**According to the sponsor, bioequiavelnce of E2 component from Angeliq to Estrace was shown by means of the following:** **1). A single dose BE study between sponsor's E2 component only tablet (2 mg E2) and Estrace 2 mg tablet** **2). A multiple dose BE study between Angeliq (2mg DRSP/1 mg E2) and Estrace** **3).Comparative dissolution to link sponsor's E2 component only formulation and Angeliq formulation.** **The above approach was discussed with the Agency (meeting on August 11, 1998) and has been acceptable** **The highest dose proposed in the label for DRSP is — while the multiple dose BE study was conducted with 2mg DRSP/1 mg E2 combination. Whether DRSP interacts with estradiol is an issue that needs to be addressed. Sponsor submitted a drug interaction study between DRSP and E2 which looked at the effect of various doses of DRSP (0.5, 1, 2, and 4 mg) in combination with 1 mg E2 on the pharmacokinetics of E2.** **To be marketed formulation is identical to the clinical formulation except for the color in film coating and the site of manufacture. Sponsor submitted dissolution comparison data to support these changes.** **A drug interaction study with simvastatin and a hepatic impairment study are ongoing.** **Sponsor should be requested to clarify when these studies will be submitted to the NDA.**
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

CC: NDA 21-355, HFD-850(Electronic Entry or Lee), HFD-580(Reddy), HFD-870(Parkeh, Malinowski, Hunt), CDR (B. Murphy)

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/s/

Venkateswar Jarugula
1/30/02 04:11:42 PM
BIOPHARMACEUTICS

Ameeta Parekh
1/31/02 03:14:50 PM
BIOPHARMACEUTICS
I concur

Meeting Minutes

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

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

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

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Filing Meeting

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

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

FDA Attendees:
Shelley Slaughter, M.D., Ph.D., Acting Deputy Director, Division of Reproductive and Urologic Drug Products, (DRUDP; HFD-580)
Lesley Furlong, M.D., Medical Officer, DRUDP (HFD-580)
Diane Moore, Regulatory Project Manager, 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)
Venkat Jarugula, Ph.D., Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics @ DRUDP (HFD-580)
Sonia Castillo, Ph.D., Statistical Reviewer, Division of Biometrics II (HFD-715)

Meeting Objective: To discuss the fileability of NDA 21-355. The filing date is February 15, 2002.

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-spirolactone, 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:

- NDA is fileable
- drug product contains drospirenone (relatively potent anti-mineralocorticoid)
- electrolyte abnormalities found with Yasmin® are a concern
- potential for electrolyte abnormalities is a concern
- there have been three post-marketing reports of hyperkalemia in users of Yasmin®; however, no serious reactions related to hyperkalemia have been reported.
- single pivotal endometrial safety study submitted with additional pharmacokinetic study data
- Division concurred with vasomotor (VMS) and vulvar and vaginal atrophy (VVA) indications based on bioequivalence to Estrace at an industry guidance meeting held in 1997
- [redacted]
- [redacted]
- endometrial protection data appears clean; hyperplasia differences between the safety and efficacy databases will be explored
- lipid profiles should be evaluated
- single pivotal endometrial safety study submitted with additional pharmacokinetic study data

Chemistry:

- NDA is fileable
- the commercial tablet is embossed; the applicant should clarify which batches reported in the NDA are or are not embossed; additional dissolution data may be needed to link the non-embossed clinical batches to the embossed commercial product
- it is not acceptable to perform release-testing of the drug product (in bulk) prior to packaging; the applicant should resolve this deficiency as soon as possible

Pharmacology/Toxicology:

- no issues, NDA is fileable
- no additional studies are required

Biopharmaceutics:

- NDA is fileable
- two bioequivalence studies (single and multiple dose studies) and dissolution data to support the VMS indication
- hepatic study is ongoing; simvastatin drug interaction study with DRSP alone is ongoing

- color and size change only difference between the clinical and to-be marketed formulation

- no food effect studies submitted

Statistics:
- no issues, NDA is fileable

Other Issues:
- financial disclosure is acceptable

- DSI – Selection of Study Sites for audit
  The following sites were identified by the Medical Officer for DSI audit:
  1) Edward Gillie, M.D.
     Medical Suites, Florida
     12751 New Brittany Boulevard, Suite 501
     Fort Myers, FL 33907
     (941) 936 – 5515
  2) Susan Wehle, M.D.
     ICSL Clinical Studies
     3105 W. Waters Avenue, Suite 109
     Tampa, FL 33614
     (813) 936 - 9764

Decisions made:
- NDA is fileable
- final reviews are due to the team leader by September 14, 2002
- the action package will be forwarded to the team leader two weeks before the NDA goal date and to the division director one week before the goal date

Action Items:
(1) The PM will convey the following CMC requests to the sponsor:
- The commercial product is embossed on one side of the tablet. Samples of the commercial product have been requested. The applicant will be required to clarify which batches in the NDA are or are not embossed.
- Release testing of the drug product is performed on the bulk product, prior to packaging. The applicant will be notified that release testing should be performed on the product after packaging.

(2) The PM will request the following information from the sponsor:
- The expected timing of the submission of the drug-interaction study for simvastatin to the NDA
- The following information for Protocol 96097A:
  1) Date the first patient was enrolled

2) Date the last patient finished study
3) Date the database was locked
4) Date the database was unlocked

(3) The PM will finalize the DSI audit form and forward the form to DSI.

(4) The PM will forward the tradename consult to OPDRA for review.

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

Concurrence Chair

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
HFD-42/Ibarra-Pratt/Lewin
Drafted by: ar/January 31, 2002/nda21355filingminutes.doc
Concurrence: dm/February 1, 2002, st/February 4, 2002, sc/February 4, 2002,
laf/February 4, 2002, kr/February 4, 2002, ss/February 8, 2002, vj/February 11, 2002
Finalized: ar/February 11, 2002

MEETING MINUTES

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/s/

Shelley Slaughter
2/20/02 02:28:52 PM
I concur.

MEMORANDUM

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

Date: January 24, 2002

From: Jeanine Best, M.S.N., R.N.
Senior Regulatory Associate
Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: NDA 21-355

I have reviewed the financial disclosure information submitted by Berlex Laboratories, Inc. in support of their NDA 21-355 for Angeliq™ (drospirenone/17β-estradiol) Tablets.

Six pivotal studies were conducted to assess the safety and efficacy Angeliq™ (drospirenone/17β-estradiol) Tablets, indicated for hormone replacement therapy in postmenopausal women. The study numbers and the results of the review of financial disclosure documents are summarized below:

Study Number/Title	Study Status	Financial Disclosure Review
Study 96097/ "A Multicenter, Double-Bind, 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"	Study Start: 22-JAN-1998 Study Complete: 28-APR-2000	Appropriate documentation received, no financial disclosure submitted.
Study 303063 / "Open-Label Study to Assess the Effect of 3 mg Drospirenone (DRSP) on Serum Potassium and to Evaluate the Pharmakokinetics of DRSP in female Volunteers with Impaired or Normal Renal Function After Repeated Oral Administration Over 14 Days"	Study Start: OCT-1999 Study Complete: MAR-2000	Appropriate documentation received, no financial disclosure submitted.
Study 304181/ "Open-Label, Cross-Over 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 Coadminstered with 75 mg Indomethacin in Healthy Postmenopausal Volunteers"	Study Start: MAR-2001 Study Complete: JUN-2001	Appropriate documentation received, no financial disclosure submitted.

Study303741/ "Open-Label, Randomized, Cross-Over 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"	Study Start: FEB-2000 Study Complete: MAY-2000	Appropriate documentation received, no financial disclosure submitted.
Study 97071/ "Study for the Evaluation of the Bioequivalence of 17β-Estrsdiol (1 mg), Relative to Estrace (1 mg) Tablet, a Marketed 17β-Estradiol Product"	Study Start: 10-SEP-1997 Study Complete: 03-NOV-1997	Appropriate documentation received, no financial disclosure submitted.
Study 307-11/ "Study for the Evaluation of the Bioequivalence of 17β-Estradiol from Estradiol 2 mg Tablets Relative to Estrace 2 mg Tablets, a Marketed Estradiol Product"	Study Start: MAY-1994 Study Complete: AUG-1994	Appropriate documentation received, no financial disclosure submitted.

Documents Reviewed:

- FDA Form 3454, *Certification: Financial Interests and Arrangements of Clinical Investigators*
- Financial Disclosure section of NDA, Volume 1.1 (submitted December 14, 2001)
- Clinical Study Reports submitted in NDA
- Additional Financial Disclosure Information submitted January 21, 2002 (as per information requests made via telephone on January 4 and 9, 2002)

Study 96097

There were 53 principal investigators and 233 subinvestigators (investigators) at 53 sites in this trial, enrolling 1,147 patients. Financial disclosure information was received from all principal investigators; no disclosable financial information was reported. 66 (28.3%) of the subinvestigators failed to submit financial disclosure forms (35 (15.0%) subinvestigators left the employment of their site during the study; there was no response (despite follow-up letters) from 23 (9.8%) of the subinvestigators, and 8 (3.4%) of the subinvestigators refused to sign the financial disclosure forms. The largest site in this trial enrolled 5.5% of the patients, so there was no one site enrolling a significant majority of the patients.

Study 303063

There was 1 principal investigator and 2 subinvestigators (investigators) at 1 site in this trial, enrolling 28 patients. Financial disclosure information was received from all investigators and none reported any disclosable financial information.

Study 304181

There was 1 principal investigator and 1 subinvestigator (investigators) at 1 site in this trial, enrolling 33 patients. Financial disclosure information was received from both investigators and neither reported any disclosable financial information.

Study 303741
There was 1 principal investigator and 1 subinvestigator (investigators) at 1 site in this trial, enrolling 24 patients. Financial disclosure information was received for the principal investigator and no disclosable financial information was reported. The subinvestigator did not submit financial disclosure information and has left the employment of the site (after the completion of the study). The sponsor did not collect the information while the study was underway as required per the Financial Disclosure Rule (study start date was after February 2, 1999), but, instead, collected the financial disclosure information retroactively.

Study 97071
There was 1 principal investigator and 3 subinvestigators at 1 site in this trial, enrolling 37 patients. Financial disclosure information was received for 2 of the subinvestigators and no disclosable financial information was reported. The 1 principal investigator and 1 of the subinvestigators did not submit financial disclosure information. They have both left employment of the site. This study was conducted in 1997, prior to the Financial Disclosure Rule, and the sponsor has made adequate attempts to retroactively collect the information.

Study 307-11
There was 1 principal investigator and 1 subinvestigator at 1 site in this trial, enrolling 36 patients. Financial disclosure information was received from both investigators and neither reported any disclosable financial information.

Conclusion:
Adequate documentation was submitted to comply with 21 CFR 54. While the sponsor could have used other means to obtain documentation from non-compliant investigators, the rate of return is acceptable. There was no disclosure of financial interests that could bias the outcome of the trials.

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/s/

Jeanine Best
1/24/02 01:57:56 PM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: January 24, 2002

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

Subject: Acknowledgement letter and Meeting Request Letter for Angeliq™

Total no. of pages including cover: 7

Comments:

Michael,

Please find attached a faxed copy of the response to your meeting request and a copy of the acknowledgment letter for Angeliq.

Archana

Document to be mailed: ☑ YES ☐ NO

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, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07470-4100

Dear Mr. Doroshuk:

We received your January 16, 2002 correspondence on January 17, 2002, requesting a 90-Day conference to discuss the general progress and status of the NDA application for Angeliq™ (drospirenone/17β-estradiol). We considered your request and concluded the meeting is premature. When deficiencies or issues are identified in the NDA application, you will be notified via a written correspondence or teleconferences.

If you disagree with our decision, you may discuss the matter with Archana Reddy, M.P.H., Regulatory Project Manager, at 301-827-4260. If the issue cannot be resolved at the division level, you may formally request reconsideration according to our guidance for industry titled *Formal Dispute Resolution: Appeals Above the Division Level* (February 2000). The guidance can be found at http://www.fda.gov/cder/guidance/2740fnl.htm.

Sincerely,

{See appended electronic signature page}

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

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/s/

Daniel A. Shames
1/23/02 10:48:03 AM

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, Drug Regulatory Affairs
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

Dear Mr. Doroshuk:

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

Name of Drug Product:	Angeliq™ (drospirenone/17β-estradiol)
Review Priority Classification:	Standard (S)
Date of Application:	December 14, 2001
Date of Receipt:	December 17, 2001
Our Reference Number:	NDA 21-355

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 15, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 17, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the

application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

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

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

Sincerely,

{See appended electronic signature page}

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jeanine Best
1/22/02 11:49:46 AM
Signing for Terri Rumble

BERLEX

TELEFAX
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

January 21, 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
OTHER: Response to January 4, 2002 Request for Financial Disclosure Information

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 request on January 4, 2002 wherein Ms. Jeanine Best, Senior Regulatory Associate in the Division of Reproductive and Urologic Drug Products, telephoned to request additional financial disclosure information for the pivotal safety and efficacy studies described in NDA 21-355. Ms. Best supplied us (via telefax) with a table format to use in compilation and presentation of the requested financial disclosure information.

Reference is also made to a second telephone request on January 9, 2002, wherein Ms. Jeanine Best relayed an additional request from the medical reviewer for financial disclosure information for two bioequivalency studies described in NDA 21-355.

Attached to this correspondence is the requested financial disclosure information for all studies in question **(ATTACHMENT A)**

NDA 21-355 is a fully electronic submission, therefore, we are also 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 Room
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

Telefax: Ms. Archana Reddy
Desk Copy Ms. Jeanine Best

CMD/letter/angeliq008

DUPLICATE

BERLEX

TELEFAX
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

January 16, 2002

MR
NEW CORRESP

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
OTHER: Request for 90 Day conference

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 made to a telephone conversation between the undersigned and your representative, Ms. Archana Reddy, on January 3, 2002. During this telephone conversation, the undersigned inquired about the potential for the Division to grant Berlex a 90-Day conference (pursuant to 21 CFR 314.102) we had requested in the cover letter to the NDA. Ms. Reddy informed the undersigned that a request for a meeting would have to be made formally. It was our understanding that a request for a 90-Day conference could be formally made in the cover letter to the NDA.

Pursuant to 21 CFR 314.102, Berlex is herewith formally requesting a 90-Day conference. In accordance with the regulation, Berlex hopes to be informed about the general progress and status of the application. In addition, Berlex requests to be advised of any deficiencies that may be identified. Depending on the issues, it will be decided at a later point to request a face-to-face meeting or a teleconference. I will call in the next few days to confirm receipt of this request and to start the process for this interaction.

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

Telefax: Archana Reddy

CMD/letter/angeliq007

DUPLICATE

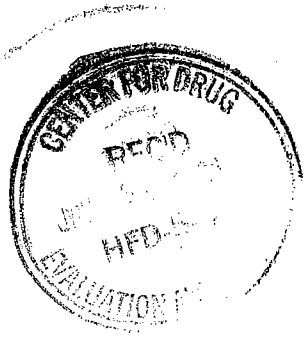
BERLEX

TELEFAX
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

January 14, 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:

BC -
NDA 0BIO AMENDMENT

Re: NDA 21-355
Drospirenone/Estradiol (DRSP/E2) Tablets
OTHER: Response to January 10, 2002 Request for Information on Facility for release testing of final packaged drug product

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 made to a telephone request on January 10, 2002, wherein Dr. Su Tran, Chemistry Reviewer in the Division of Reproductive and Urologic Drug Products, telephoned to request the following information on release testing on the final packaged product.

Will final release testing of the packaged drug product be performed at Berlex? If so please confirm and provide a street address for that facility.

Final release for distribution of packaged drug product, including review of — packaging records, QA Inspection reports that include visual ID, and reconciliation is performed at:

Berlex Laboratories, Inc.
300 Fairfield Road, Wayne, NJ 07470.

In addition, the Quality Assurance Unit at the Berlex facility is responsible for:

- Incoming statistical inspection, which includes visual identification inspections on bulk drug product shipped from the Weimar Plant to Berlex.
- Release of bulk drug product from Berlex to [redacted] for packaging.
- Quality Assurance Inspection following the current inspection procedures to monitor the packaging at [redacted]

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

Telefax: Dr. Su Tran

CMD/letter/angeliq006

BERLEX

UPS OVERNIGHT

December 14, 2001

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

Susan Allen, M.D. MPH, Director
DIVISION OF REPRODUCTIVE
AND UROLOGIC DRUG PRODUCTS, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation & Research
U. S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

Dear Dr. Allen:

Re: NDA 21-355 – ANGELIQ™ TABLETS
Drospirenone 1 mg and 17β-Estradiol 1 mg,
Drospirenone 3 mg and 17β-Estradiol 1 mg Tablets
(DRSP/E2)
ORIGINAL NEW DRUG APPLICATION

Pursuant to Section 505 (b) of the Federal Food, Drug and Cosmetic Act and to 21 CFR §314.50, Berlex Laboratories, Inc. is submitting herewith a New Drug Application for ANGELIQ TABLETS

DRSP 1 mg in combination with E2 1 mg] for oral hormone replacement therapy.

This New Drug Application is being submitted as a fully electronic submission following the guidance set forth in *Guidance for Industry Providing Regulatory Submissions in Electronic Format – NDAs*, issued by the Center for Drug Evaluation and Research in January 1999. This New Drug Application is provided on five (5) compact disks (CDs). Berlex Laboratories, Inc. certifies that the CDs have been scanned for viruses and are virus free using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54.

Drospirenone (DRSP) is a novel progestin, a derivative of 17α-spirolactone, and similar to natural progesterone, possesses progestogenic and aldosterone-antagonistic properties. In addition, it is anti-androgenic and devoid of androgenic, estrogenic, and glucocorticoid activity. The combination of these characteristics differentiates DRSP from other marketed progestins. DRSP is currently marketed as the progestin component in the oral contraceptive product YASMIN® NDA 21-098 (DRSP 3.0 mg in combination with ethinyl estradiol 0.030 mg). YASMIN® was approved by the Division on May 11, 2001.

Berlex is seeking approval of **ANGELIQ™** for the following indications:
1. Treatment of moderate to severe vasomotor symptoms associated with the menopause
2. Treatment of vulvar and vaginal atrophy

To obtain these indications, Berlex has conducted a clinical development program which included a bioequivalence study (B274) in 36 patients, and a 1-year endometrial protection study (A02827) in 1142 patients.

The estradiol bioequivalence program, designed to demonstrate equivalence between E2 and Estrace®, was discussed between representatives of Berlex and the FDA Division of Reproductive and Urologic Drug Products during a Phase 3 meeting for the oral contraceptive, DRSP/EE (YASMIN®) on February 12, 1997. Study 97071 (Report B274) was conducted as a Phase 1 study using a single-center, open-label, randomized, multiple-dose, 2-period, crossover design. The primary objective of the study was to evaluate bioequivalence of 17β-estradiol (E2) from a tablet containing 1 mg E2/2 mg DRSP relative to Estrace® 1-mg tablet, a marketed E2 product. The bioequivalence program for DRSP/E2 was deemed by the Division to be satisfactory at the pre-NDA meeting with the Division on January 24, 2001, but would be subject to review in the context of the entire NDA.

Study 96097 (Report A02827) was a double-blind, parallel-group, randomized, multicenter study to evaluate the effects of 4 doses of DRSP/E2 (1 mg E2/0.5 mg DRSP, 1 mg E2/1 mg DRSP, 1 mg E2/2 mg DRSP or 1 mg E2/3 mg DRSP) tablets given orally, once a day, compared to E2 (1 mg) alone for endometrial protection in postmenopausal women.

The following outcomes are the result of agreements reached at the pre-NDA meeting between representatives of Berlex and the FDA Division of Reproductive and Urologic Drug Products on January 24, 2001:

- Berlex has included the final clinical study report from the indomethacin-interaction study (A00824) in the assessment for potential risk for the development of hyperkalemia in Item 6. This study will also provide data on 24-hour urinary calcium excretion.
- Results from the hepatic-impairment study will be submitted within 7 months of the NDA submission.
- Data analysis sets for the primary variable and SAS transport files are provided as part of this electronic submission.

PROPOSED TRADENAME

ANGELIQ™ is proposed as the worldwide name for the combination product of DRSP and 17β-estradiol (E2), presented in this application. Market research on the proposed name is included in Item 20 of this application.

CMC DOCUMENTATION

Drug substance information for DRSP and E2 is presented in the corresponding Type II Drug Master Files. Letters authorizing the Agency to refer to these DMFs are provided in Item 4 of this

application. The final packaging

CLAIMED EXCLUSIVITY

Berlex is claiming a period of 3 years of marketing exclusivity for ANGELIQ™. A "Statement of Claimed Exclusivity" has been included in Item 14, Patent Certification.

FINANCIAL CERTIFICATION

A statement regarding financial certification and completed financial disclosure forms for covered studies, as described in Regulation 21 CFR 54, is provided in Item 19.

FOREIGN MARKETING EXPERIENCE

None of the DRSP/E2 combinations are yet approved or marketed anywhere in the world, nor are there pending applications anywhere in the world.

Pursuant to 21 CFR 314.102, Berlex wishes to request a ninety-day conference. In accordance with the regulation, Berlex hopes to be informed about the general progress and status of the application. In addition, Berlex requests to be advised of any deficiencies that may be identified. Depending on the issues, it will be decided at a later point to request a face-to-face meeting or a teleconference. I will call in the next few days to confirm receipt of this application and to start the process for this interaction.

Please call me at (973) 487-2184 or telefax me at (979) 487-2016 to answer any questions regarding this submission.

Sincerely,

BERLEX LABORATORIES

Michael Doroshuk
Manager
Drug Regulatory Affairs

cc telefax: Diane Moore (letter without attachment)

019-cmd

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Berlex Laboratories, Inc.
P.O. Box 1000
Montville, New Jersey 07045-1000

2. TELEPHONE NUMBER *(Include Area Code)*

(973) 487 - 2157

3. PRODUCT NAME

Angeliq [Drospirenone/Estradiol] Tablets

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-355

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4093

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	Manager, Regulatory Submissions and Information	November 7, 2001

FORM FDA 3397 (4/01)

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

MEETING MINUTES

Date: January 24, 2001 **Time:** 1:00 - 2:30 PM **Place:** Parklawn; Potomac Room

IND: 53,842 **Drug Name:** Drospirenone and Estradiol Tablets (DRSP/E_2)

Indications: Hormone Replacement Therapy (HRT)

Type of Meeting: Pre-NDA

External Constituent: Berlex Laboratories, Inc.

FDA Lead: Dr. Susan Allen

FDA Participants:
Florence Houn, M.D., M.P.H. – Director, ODE III (HFD-103)
Susan Allen, M.D., M.P.H. - Director, Division of Reproductive and Urologic Drug Products DRUDP (HFD-580)
Shelley Slaughter, M.D. - Medical Team Leader, (DRUDP; HFD-580)
Lesley Furlong, M.D. – Medical Team Leader, DRUDP (HFD-580)
Terri Rumble – Chief, Project Management Staff, DRUDP (HFD-580)
Diane Moore - 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)
Suong T. Tran, Ph.D. – Review Chemist, DNDC II @ DRUDP (HFD-580)
Krishan Raheja, D.V.M., Ph.D. - Pharmacologist, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Venkateswar R. Jarugula, Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
Mike Welch – Biometrics Team Leader, Division of Biometrics II (DBII; HFD-715)
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

External Participants:
Norbert Benda, Ph.D. - Biometrics, Schering AG (SAG)
Hartmut Blode, Ph.D. - Section Head Clinical Pharmacokinetics, Schering AG (SAG)
Nancy Bower – Toxicologist, Nonclinical Sciences, Berlex
Sharon Brown - Director, Drug Regulatory Affairs (DRA), Berlex
Wolfgang Eder, Ph.D.- International Project Manager, SAG/Berlex
Marie Foegh, M.D. - Medical Director, Female Health Care (FHC), Berlex
Adel Karara, Ph.D. – Associate Director, Clinical Pharmacology, Berlex
Geoffrey P. Millington – Manager, Drug Regulatory Affairs, Berlex
Harji Patel, Ph.D. – Associate Director, Statistics, Berlex
Rolf Schuermann, M.D. – Head Clinical Pharmacology, SAG
Marita Schollmeyer – Section Head, Analytical Services, SAG

Meeting Objective: To discuss the content, presentation and format of the proposed NDA and to discuss any potential issues prior to the submission of the NDA.

Background:
Pre-meeting package was submitted on December 21, 2000. The targeted date for NDA submission is May 2001.

Discussion Items:
- the sponsor noted that the drug used in the clinical trials is the same as the to-be-marketed formulation
- the method for reading and evaluating pathology slides was explained in detail by the sponsor (see attached handouts)
- the Belgium menopausal symptoms study has been completed
- Yasmin is currently being marketed in Germany and the product launch for Europe is ongoing

Decisions:
- GENERAL QUESTIONS
- **Question 1:** Berlex plans to cross reference non-clinical and clinical pharmacology DRSP information previously submitted to the Yasmin® NDA (21-098) currently under review. Does the Division agree with this approach?
- **Answer to Question 1:**
  - this is acceptable

- **Question 2:** If the Division agrees with the approach presented in Question 1, Berlex plans to submit an electronic NDA in accordance with the January 1999 Guidance for Industry: Providing Regulatory Submissions in Electronic Format—NDAs. Does the Division agree?
- **Answer to Question 1:**
  - electronic NDA submission is acceptable

- DRAFT INDEX
- **Question:** Does the Division have any comments regarding the DRAFT NDA Index?
- **Answer:**
  - the draft NDA index, as proposed, with the addition of a financial disclosure section, is acceptable
  - ODE III suggests the addition of a separate risk management section that can be included in the Clinical section of the NDA; this section could contain a summary of the pre-marketing (e.g., additional studies), and post-marketing risk management plans for this product (no FDA guidance publication is available for such a section, however, the sponsor can reference information from their Yasmin NDA)

- DRAFT LABELING
- The DRAFT package insert for our drospirenone/estradiol tablets product (proposed trade name, "Angeliq") which appears in this item was prepared using the latest available revision of the Yasmin (drospirenone/ethinyl estradiol) package insert under review by the Division as part of NDA 21-098.
- **Question 1:** Does the DRAFT labeling meet the requirements of the Division?
- **Answer:**
  - labeling is a review issue; however, the proposed format is acceptable

- **Question 2:** Is the proposed tradename, ANGELIQ™, acceptable?
- **Answer:** the tradename will be assessed by OPDRA; as this is a review issue, no decision regarding the acceptability of the tradename is available at this time

- the tradename can be submitted to OPDRA for an opinion prior to the NDA submission; however, even if it were found to be acceptable prior to NDA submission, the tradename would still need to be reviewed during the NDA review cycle and may not be acceptable at the time of the final review (90 days before the action)

- CHEMISTRY, MANUFACTURING AND CONTROLS
- **Question 1:** Does the Division agree with the proposal to provide drug substance information via Type II Drug Master Files?
- **Answer:**
  - reference to the DMF used for the Yasmin NDA is acceptable

- **Question 2:** Does the Division concur that the described stability data submission plan is adequate to support a ——— expiration date?
- **Sponsor Comment:** Berlex claims to have ——— of pilot data in the blister packages in addition to other stability data that should be sufficient to support a——— expiration date
- **Answer:**
  - the stability data generated from the blister packaging is supportive data and subject to review; the actual expiration dating will be determined during the NDA review
  - if the product is to be sold in bottles, blister stability data is not needed; however, all available data will be reviewed

- NONCLINICAL PHARMACOLOGY AND TOXICOLOGY
- **Question:** Does the Division concur that the type, duration and overall design of the nonclinical studies conducted is sufficient to assess the safety of DRSP/E2 Tablets?
- **Answer:**
  - the proposal appears to be appropriate

- HUMAN PHARMACOKINETICS AND BIOAVAILABILITY (Item 6)
- **Question 1:** Does the Division concur that studies summarized in item 6 will adequately support filing of the NDA?
- **Answer:**
  - yes
  - the sponsor should submit all the information regarding the single-dose versus multiple-dose bioequivalence studies and a justification for their inclusion in the proposed NDA
  - the studies linking DRSP/E_2 to Estrace should be submitted to the NDA

- **Question 2:** Does the Division agree that the proposed Indomethacin interaction study design achieves study objectives?
- **Answer:**
  - AUC data may not provide the clinically meaningful information needed, i.e., the risk of developing hyperkalemia
  - the endpoint proposed by the sponsor is not clinically meaningful; the study is considered a safety study; the mean potassium concentrations and the proportion of women who respond with potassium levels in the hyperkalemic range should be assessed
  - daily measurements of potassium are acceptable
  - FDA proposes the following study modifications:
    - increase the dose of Indomethacin to 150 mg daily

- a series of potassium levels should be added to the first day of the study, as planned in the hepatic impairment study
- six patients per arm is not sufficient; 25-50 patients should be enrolled in the study
- the sample size is too small for adequate and meaningful results; the FDA proposed a primary endpoint of at least one potassium level above normal limits; suggested a non-inferiority study with parallel treatment arms, a one-sided 97.5 % confidence interval (CI) around the difference in proportions of subjects with at least one potassium level above normal limits and power of at least 80%

- **Question 3:** Twenty-four hour urinary calcium excretion will be determined in the indomethacin interaction study prior to the administration of the indomethacin when subjects are at steady state of DRSP. Does the Division concur that the planned urinary calcium excretion measurement provides meaningful conclusions regarding urinary calcium excretion?
- **Answer:**
  - useful safety data will be obtained by the proposed non-steroidal anti-inflammatory drug (NSAID) study

- **Question 4:** Does the Division agree that the proposed hepatic impairment study design achieves study objectives?
- **Answer:**
  - it appears that the study design will support achievement of the study objectives
  - the Agency noted that the major metabolites of DRSP should be monitored as the drug is extensively metabolized
    - the sponsor maintained that no activity is indicated from the metabolites and that there is no laboratory method currently available to measure the metabolites (the RIA method used to measure DRSP does not detect the metabolites)
    - **the Division response**: if there is no way to measure the metabolites and the sponsor has reason to believe the metabolites are not active, these assertions should be included in the NDA submission

- **Question 5:** Does the Division agree that the planned indomethacin interaction and hepatic impairment studies can be submitted during the NDA review?
- **Answer:**
  - the Division prefers that the results from the indomethacin-interaction study be included in the initial NDA submission; however, the Division is aware that during the March 24, 2000 meeting with the sponsor, the sponsor was told that abnormal laboratory results such as hyperkalemia from a drug-drug interaction study could be submitted with the 4-month safety update in the NDA
  - the primary safety concern with DRSP is the potential risk for development of hyperkalemia; therefore, as much data as possible related to this risk should be submitted with the NDA
  - the results of the hepatic impairment study can be submitted within seven months of the submission date; any submissions after the 7-month time-point could be considered a major amendment and cause the goal date to be extended by three months

- <u>CLINICAL DATA</u>
- **Question:** Is the proposed clinical program (in conjunction with bioequivalence to Estrace) adequate to support the filing of the NDA?

- **Answer:**
  - the lowest effective dose for each indication should be demonstrated
  - the sponsor may have sufficient data to support the VMS and VVA indications, however, because DRSP is an NME,
  - [redacted]

- STATISTICS
- **Question 1:** Do the format, content and plan for data analysis for the pivotal studies meet the requirements of the Division?
- **Answer:**
  - the sponsor should add center by treatment interactions to the ANOVA models
  - in addition, the sponsor should list results by center and assess looking for differences across centers
  - the proposed analysis of variance for ranked hot flush data is nonstandard; the submission should include a conventional non-parametric analysis
  - analysis of efficacy and safety by age and ethnicity should be submitted
  - for the hyperplasia data, the sponsor should look at withdrawals to insure no non-informative censoring occurred
  - data analysis sets for the primary variable and SAS transport files should be submitted in SAS transport format to the electronic document room (EDR)

- **Question 2:** Do the methods for summarizing the overall results for the NDA (e.g., ISE, ISS) meet the requirements of the Division?
- **Answer:**
  - if the recommendations provided by the Division for each of the preceding questions are taken into account by the sponsor, the methods for summarizing results in the ISS and ISE would appear to support fileability of the application

- CASE REPORT TABULATIONS and ITEM 12: CASE REPORT FORMS
- **Question:** Are the proposals for presentation of CRF tabulations and CRFs for deaths and dropouts acceptable?
- **Answer**
- CRFs for all serious and adverse events and for all patient dropouts should be included in the NDA

• **Action Items**	**Responsible Person:**	**Due Date:**
• provide minutes to sponsor	DRUDP	one month

Signature, minutes preparer

Signature, Chair

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.

32 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 8

/s/

Diane V. Moore
2/26/01 04:29:12 PM

Susan Allen
2/26/01 04:49:29 PM