BERLEX

Facsimile
Transmittal Sheet

FROM: John Hegarty	TELEPHONE: (973) 487-2166
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: Cdr. Frank Cross Sr. Regulatory Management Officer Division of Dermatologic and Dental Drug Products	Telephone: (301) 827-2063
SUBJECT: NDA 21-470 FINACEA™ (azelaic acid) Gel, 15% Response to Proposed Phase 4 Commitments: Nonclinical Toxicology	FAX NUMBER: (301) 827-2075 DATE: December 16, 2002 TOTAL NUMBER OF PAGES (INCLUDING COVER SHEET): 4

Dear Cdr. Cross,

Please see the attached letter, which provides responses to the proposed Phase 4 Commitments – nonclinical toxicology, which we received from the Division via telefax on December 12, 2002. This submission will be sent in electronic format to the CDER Central Document Room on 1 diskette.

Sincerely,

BERLEX LABORATORIES

John Hegarty

John Hegarty
Regulatory Associate
Drug Regulatory Affairs

JJH/Fax/Finacea079

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DEC 18 2002
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BERLEX

TELEFAX AND UPS DELIVERY

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DEC 23 2002
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Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

December 16, 2002

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products – HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

Re: NDA 21-470
FINACEA™ (azelaic acid) Gel, 15%
AMENDMENT TO PENDING NDA
OTHER: RESPONSE TO FDA REQUEST FOR INFORMATION
PROPOSED PHASE 4 COMMITMENTS - NONCLINICAL

Dear Dr. Wilkin:

Reference is made to NDA 21-470, submitted on March 20, 2002 for FINACEA™ (azelaic acid) Gel, 15%. Reference is also made to the Division's facsimile transmission of December 12, 2002, which provided comments on our November 14, 2002 responses to the initial proposed nonclinical toxicology Phase 4 Commitments for NDA 21-470. Further reference is made to the Division's facsimile transmission of December 12, 2002, which provided revised proposed nonclinical toxicology Phase 4 Commitments for NDA 21-470. These proposed Phase 4 Commitments for NDA 21-470 are repeated below in **bold** text followed by our responses in unbold text.

Please review the following proposed Phase 4 Commitments for your NDA 21-470, Finacea (azelaic acid) Gel, 15%. If acceptable, please submit your commitments to the same.

Commitment Category: NON-CLINICAL TOXICOLOGY

1. **The Applicant commits to conducting a photoco-carcinogenicity study in male and female mice with the azelaic acid 15% gel.**
   - **Protocol submission: Within 4 months of the date of the Approval Letter for this NDA**
   - **Study Start: Within 6 months of the date of the approval of the protocol**
   - **Final Report Submission: Within 12 months after the study completion**

Based on the response from the Division to our submission dated November 14, 2002, Berlex Laboratories, Inc. proposes the Phase 4 commitment below as an alternative to the commitment outlined above.

Berlex Laboratories, Inc. will agree to the following Phase 4 commitment:

- Berlex Laboratories, Inc. agrees to submit the [redacted] to the Division for review by [redacted]. If the Division deems this study acceptable to determine the photoco-carcinogenic potential of the azelaic acid 15% gel, Berlex Laboratories, Inc. will have met its Phase 4 obligation concerning photoco-carcinogenicity and will conduct no additional studies.

- If the Division determines that the [redacted] study is not adequate to determine the photoco-carcinogenic potential of the azelaic acid 15% gel, Berlex Laboratories, Inc. will commit to the conduct of a photoco-carcinogenicity study in male and female mice with azelaic acid 15% gel. Timelines will be as follows:

- Protocol submission: Within [redacted]s of the date of the notification of Berlex Laboratories, Inc. by the Division to the outcome of the Division review of the [redacted]

- Study Start: Within 6 months of the date of the approval of the protocol

- Final Report Submission: Within 12 months after the study completion

2. **The Applicant commits to conducting an alternative, dermal carcinogenicity study in transgenic mice (Tg.AC assay) with the azelaic acid 15% gel.**

   - **Protocol submission: Within 5 months of the date of the Approval Letter for this NDA**

   - **Study Start: Within 6 months of the date of the approval of the protocol**

   - **Final Report Submission: Within 12 months after the study completion**

Berlex Laboratories, Inc. agrees to this Phase 4 Commitment.

Berlex Laboratories, Inc. hopes these proposals will be acceptable to the Agency.

Since NDA 21-470 was submitted in electronic format, this submission was prepared in electronic format in accordance with the *Guidance for Industry Providing Regulatory Submissions in Electronic Format - NDAs*, issued by the Center for Drug Evaluation and Research in January 1999. This submission contains 1 floppy diskette that has been scanned for viruses using Trend Office Scan, Version 3.54.

Please call the undersigned at (973) 487-2166, if you have any questions concerning this application.

Sincerely,

BERLEX LABORATORIES

John Hegarty
Regulatory Associate
Drug Regulatory Affairs

JJH078

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Berlex Laboratories, Inc.	December 16, 2002
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
(973) 487-2166	(973) 487-2016
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
340 Changebridge Road PO Box 1000 Montville, NJ 07045-1000	RECEIVED DEC 23 2002 DEC 18 2002 MEGA/CDER

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-470

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
azelaic acid (USAN)	FINACEA™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
1,7-Heptanedicarboxylic acid (IUPAC)	AzA Gel, 15%

DOSAGE FORM: gel	STRENGTHS: 15% (w/w)	ROUTE OF ADMINISTRATION: Topical

(PROPOSED) INDICATION(S) FOR USE:
Topical application in the treatment of inflammatory papules and pustules and [redacted] rosacea

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Response to FDA Request for Information

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 floppy diskette | THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☒ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND [redacted] NDA 20-428, IND [redacted]
DMF [redacted] DMF [redacted] DMF [redacted] DMF [redacted] DMF [redacted] DMF [redacted] DMF [redacted] DMF [redacted] DMF [redacted] DMF [redacted]

This application contains the following items: *(Check all that apply)*

☒	1. Index	
☐	2. Labeling *(check one)*	☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50(c))	
☐	4. Chemistry section	
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)	
☐	B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)	
☒	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)	
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)	
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))	
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)	
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)	
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)	
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)	
☐	12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)	
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))	
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A)	
☐	15. Establishment description (21 CFR Part 600, if applicable)	
☐	16. Debarment certification (FD&C Act 306(k)(1))	
☐	17. Field copy certification (21 CFR 314.50(k)(3))	
☐	18. User Fee Cover Sheet (Form FDA 3397)	
☐	19. Financial Information (21 CFR Part 54)	
☐	20. OTHER *(Specify)*	

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
John Hegarty	John Hegarty Regulatory Associate, Drug Regulatory Affairs	December 16, 2002

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
340 Changebridge Road, PO Box 1000, Montville, NJ 07045-1000	(973) 487-2166

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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

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.

OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

A N NDA 21-470 Drug: FINACEA™ (azelaic acid) Gel, 15% Applicant: Berlex Labs, Inc. Type: 3
PM: Cross Phone: 827-2020 HFD- 540
USER FEE GOAL DATE: 1//21/03 DATE CHECKLIST COMPLETED: 12/13/02

Arrange package in the following order (include a completed copy of this CHECKLIST):	Check or Comment
1. ACTION LETTER with supervisory signatures Are there any Phase 4 commitments?	AP_X__ AE____ Yes___ No____
2. Have all disciplines completed their reviews? If no, what review(s) is/are still in draft?	Yes ___ No__X__
3. LABELING (package insert and carton and container labels). (If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.)	Draft_____ Revised Draft_____ Final_____X_____
4. PATENT INFORMATION	_____X_____
5. EXCLUSIVITY CHECKLIST	_____X_____
6. PEDIATRIC PAGE (all NDAs)	_____X_____
7. DEBARMENT CERTIFICATION (Copy of applicant=s certification for all NDAs submitted on or after June 1, 1992).	_____X_____
8. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status. If no audits were requested, include a memo explaining why.	_____X_____
9. REVIEWS & MEMORANDA: DIVISION DIRECTOR'S MEMO | If more than 1 review for any	_____
GROUP LEADER'S MEMO |1 discipline, separate reviews	_____
MEDICAL REVIEW | with a sheet of colored paper.	12/16/02
SAFETY UPDATE REVIEW |Any conflicts between reviews	_____
STATISTICAL REVIEW |must have resolution documented	11/19/02
BIOPHARMACEUTICS REVIEW	10/17/02 12/9/02
PHARMACOLOGY REVIEW (Include pertinent IND reviews)	10/19/02
Statistical Review of Carcinogenicity Study(ies)	N/A
CAC Report/Minutes	N/A
CHEMISTRY REVIEW	12/19/02, 12/23/02 (e-mail)
ODS Review Memorandum	12/18/02 12/19/02 (2 e-mails
Date EER completed	12/23/02
FUR needed ___N/A_____ FUR requested __N/A__	
Have the methods been validated?	Yes (attach)__ No____XXX____
Environmental Assessment Review /FONSI	12/19/02
CMC MICROBIOLOGY REVIEW	10/18/02
CLINICAL MICROBIOLOGY REVIEW	N/A
What is the status of the monograph?	N/A
10. CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes	_____X_____
11. MINUTES OF MEETINGS Date of End-of-Phase 2 Meeting: _9/27/02None_____ Date of pre-NDA Meeting: _8/30/01_____	_____X_____
12. ADVISORY COMMITTEE MEETING MINUTES _____ or, if not available, 48-Hour Info Alert or pertinent section of transcript.	Minutes___ Info Alert_____ Transcript_____ No mtg__X__

CONSULTATION RESPONSE
Division of Medication Errors and Technical Support
Office of Drug Safety
(DMETS; HFD-420)

DATE RECEIVED: SEPT-30-2002	**DUE DATE:** DEC-13-2002	**ODS CONSULT #:** 02-0190

TO: Jonathan Wilkin, MD
Director, Division of Dermatologic and Dental Drug Products
HFD-540

THROUGH: Frank Cross
Project Manager
HFD-540

PRODUCT NAME: Finacea (Azelaic Acid Gel) 15% **NDA #:** 21-470	**SPONSOR:** Berlex Laboratories, Inc.

SAFETY EVALUATOR: Marci Ann Lee, PharmD

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

DMETS RECOMMENDATION: DMETS does not recommend use of the proprietary name, Finacea. DMETS also recommends implementation of the labeling revisions described in Section III.

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

Jerry Phillips, RPh
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; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: DEC-3-2002

NDA NUMBER: 21-470

NAME OF DRUG: Finacea (Azelaic Acid Gel) 15%

NDA SPONSOR: Berlex Laboratories, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Dermatologic and Dental Drug Products, for assessment of the proprietary name "Finacea", regarding potential name confusion with other proprietary or established drug names.

Azelaic acid is currently available in the US as a topical 20% cream (NDA 20-428). The proprietary names associated with this product include "Azelex" [ALLERGAN][i] and "Finevin" [Distributed by BERLEX for ALLERGAN][ii].

PRODUCT INFORMATION

Finacea (Azelaic Acid Gel) is used to treat inflammatory papules and pustules [redacted] of rosacea. Before application, the skin should be thoroughly washed and patted dry with a soft towel. Only very mild soaps or mild soapless cleansing lotions should be used for cleansing. A thin layer of Finacea should be applied twice daily, in the morning and evening, to the entire affected areas and gently massaged in to the skin.

The use of occlusive dressings or wrappings should be avoided, and the hands should be washed following application. During application, contact with the eyes should be avoided. In case of accidental exposure, the eyes should be rinsed with plenty of water. The duration of use of Finacea varies depending upon the severity of rosacea. In the majority of patients, improvement of the dermatosis was observable after 4 weeks.

Patients may use non-irritating cosmetics. Cosmetics should only be applied after Finacea has dried. Finacea will be available as a 15% topical gel formulation. Finacea is for dermatologic use only, not for ophthalmic or intravaginal use. Finacea will be available in 30 gram and 50 gram collapsible tubes.

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[i] http://www.allergan.com/site/products/consumers/home.asp?id=azelex&largeText=no
[ii] http://www.berlex.com/products/dermatology.htm

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of a standard published drug product reference texts[i] as well as several FDA databases[ii] for existing drug names which sound or look similar to Finacea to a degree where potential confusion between drug names could occur under the usual clinical practice settings. The Saegis[iii] Pharma-In-Use database was searched for drug names with potential for confusion. An Expert Panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Finacea. 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. DDMAC did not have any concerns with Finacea in regard to promotional claims.

2. The Expert Panel identified ten medication names that have potential for confusion with Finacea. These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.

Table 1. Potential sound-alike and look-alike names identified by DMETS Expert Panel

Product Name	Dosage form(s); Generic name	Usual adult dose*	Look-alike or Sound-alike
Finacea	Azelaic Acid Gel 15% 30 grams and 50 grams	Apply twice daily.	
Finevin	Azelaic Acid Cream 20% 30 grams	Apply twice daily.	Look-alike
FIV-ASA	Mesalamine 500 mg Suppository	500 mg PR twice daily. Usual course is 3 to 6 weeks depending on symptoms.	Look-alike and Sound-alike
Femara	Letrozole 2.5 mg Tablet	2.5 mg PO daily	Look-alike
Benicar	Olmesartan 5 mg, 20 mg, 40 mg Tablet	20 mg PO daily	Look-alike
Zinacef	Cefuroxime 750 mg, 1.5 gram, 7.5 gram Powder for injection Premixed frozen (750 mg, 1.5 g) ADD-Vantage vials 10 mL and 20 mL vials	750 mg – 1.5 grams IV/IM every 8h	Look-alike

[i] Facts and Comparisons, 2002, Facts and Comparisons, St. Louis, MO. http://www.cfactsweb.com/index.asp, 2001 Drug Topics RED BOOK

[ii] The Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-02, and online version of the FDA Orange Book.

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

Product Name	Dosage form(s), Generic name	Usual adult dose	Look-alike or Sound-alike
Finacea	Azelaic Acid Gel 15% 30 grams and 50 grams	Apply twice daily.	
Fenesin	Guaifenesin 600 mg Sustained-Release Tablet	600 mg – 1200 mg PO twice daily.	Look-alike and Sound-alike
Ferocon	Ferrous fumarate, folic acid, intrinsic factors, vitamin B12 and vitamin C as oral capsules	Dietary supplement.	Look-alike
Propecia (and Finasteride – established name similarity)	Finasteride 1 mg Tablet (Propecia) 5 mg Tablet (Proscar)	Alopecia: 1 mg PO daily BPH: 5 mg PO daily	Sound-alike
Echinacea	Various formulations.	Dietary supplement	Sound-alike
Finac**	Over-the-counter (OTC) Salicylic acid 2% Lotion 60 mL	Apply as needed for acne.	Look-alike and Sound-alike

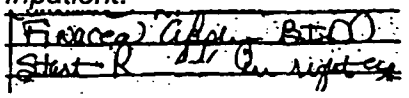
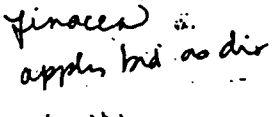
* Frequently used, not all inclusive

**Listed in Drug Facts and Comparisons. However, this product has not been available for several years.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology for Finacea studies.

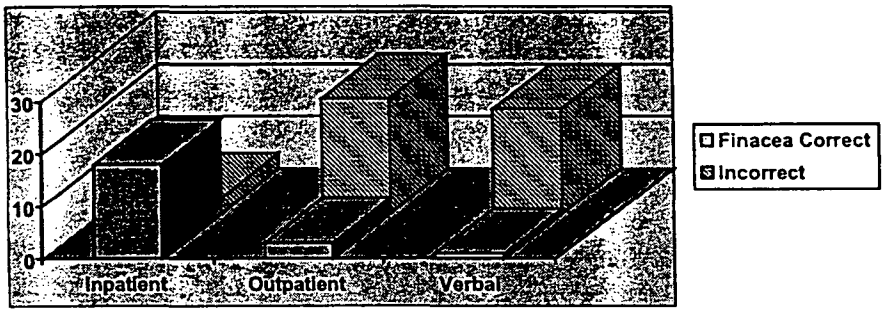
Studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Finacea with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 106 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. DMETS staff members wrote inpatient and outpatient prescriptions for Finacea, each consisting of a combination of marketed and unapproved drug products. These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one DMETS staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Finacea	
Inpatient: 	*Verbal:* "... calling in six prescriptions for ... Finacea. Apply twice a day as directed. Number one. "
 *Outpatient:*	

2. Results for Finacea studies

Results of these exercises are summarized below:

Study	No. of participants	# of responses	"Finacea" response	Other response
Written: Inpatient	32	21 (66%)	18 (86%)	3 (14%)
Written Outpatient	39	25 (64%)	3 (12%)	22 (88%)
Verbal:	35	21 (60%)	1 (5%)	20 (95%)
Total:	106	67 (63%)	22 (33%)	45 (67%)



Among the two written prescription studies, 25 of 46 (54%) participants interpreted the name incorrectly. The most common misinterpretation was *Finacen*. Other incorrect responses included *Finacin, Funacea, Linacea, Linacen, Tinacea, Tinacen, Fenacea* and *Finaceq.* None of the drug name misinterpretations were similar to an approved product.

Among the verbal prescription study participants for Finacea, 20 of 21 (95%) participants interpreted the name incorrectly. However, many of the incorrect responses were phonetically equal to Finacea. The most common misinterpretation was *Phenacia.* Other phonetically equal responses included *Phenetia, Fenacia, Fanasia, Finacia, Finatia,* and *Fonecia.* The order was also misinterpreted as *Synesha, Chinecea* and *Feracia.* None of the drug name misinterpretations were similar to an approved product.

II. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, Finacea, the primary concerns raised by the expert panel were related to one proprietary name that already exists in the US marketplace, Finevin. We conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Finacea could be confused with Finevin. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. Other misinterpretations did not overlap with any other currently approved drug names.

It is also interesting to note that the most common misinterpretation of the verbal prescription was *Phenacia.* This interpretation is phonetically equal to Finacea. This is likely due to the fact that practitioners are familiar with other medical or chemical names that begin with

"Phen-". For example, *phenytoin, phenylephrine, phentermine, Phenergan, phenobarbital,* and others. In this case, the only drug name that was considered for potential confusion with Finacea that begins with "Phen-" was Phenacetin. Since Phenacetin has not been available for several years, the risk for confusion is unlikely.

Finevin has potential for look-alike confusion with Finacea. Finevin contains the same active ingredient as Finacea. Both products are topical formulations applied twice daily. Both products are from Berlex Laboratories, Inc., which may increase the likelihood for look-alike labeling and packaging. Prescribers of Finacea and Finevin are likely to be dermatology specialists. Although Finevin is available as a 20% cream and Finacea is a 15% gel, these differences are very subtle and not likely to prevent medication errors. Since both products are available as a single strength, prescribers may omit this information on the prescription increasing the risk for confusion. While Finacea is indicated for rosacea and Finevin is indicated for acne, both are skin conditions and this is also unlikely to prevent medication errors between Finacea and Finevin. Finally, it is likely that these products will be stored near or next to one another in many pharmacies. This will increase the risk for confusion between Finacea and Finevin.

Finevin Finacea

FIV-ASA has potential for look-alike and sound-alike confusion with Finacea. Although both medications are used twice daily, Finacea has a different indication, route of administration, dosage strength and dosage formulation. All of these factors minimize the likelihood for confusion between FIV-ASA and Finacea.

Fivase Finacea Fivase Finacea

Femara has potential for look-alike confusion with Finacea. Femara is available as a 2.5 mg oral tablet used to treat advanced breast cancer. Unlike Finacea, Femara is administered by mouth once daily. Femara is typically prescribed by oncology specialists, further decreasing the likelihood for confusion. Due to the differing indication, route of administration, dosing schedule, dosage strength and prescribing specialists, the likelihood for confusion is minimized.

Femara Finacea Femara Finacea

Benicar has potential for look-alike confusion with Finacea. However, the risk for confusion is minimized because there is not overlap of indication, dosage strength, dosage formulation, dosing schedule, or route of administration.

Benicar Finacea Benicar Finacea Benicar Finacea

Zinacef has potential for look-alike confusion with Finacea. It is possible for "Zinacef 1.5 (grams)" to be interpreted as "Finacea 15 (percent)" when handwritten. However, the risk for confusion is minimized because there is not overlap of indication, dosage formulation, dosing schedule, or route of administration. In addition, these products are not likely to be stored near each other in most pharmacies.

Finacea Zinacef Finacea

III. COMMENTS TO THE SPONSOR

The Division of Medication Errors and Technical Support does not recommend the use of the proprietary name, Finacea. In reviewing the proprietary name, Finacea, the primary concern was related to the proprietary name Finevin, which already exists in the US marketplace.

Finevin has potential for look-alike confusion with Finacea. Finevin contains the same active ingredient as Finacea. Both products are topical formulations applied twice daily. Berlex Laboratories, Inc. is the sponsor for Finacea and distributor for Finevin, which may increase the likelihood for look-alike labeling and packaging. Prescribers of Finacea and Finevin are likely to be dermatology specialists. Although Finevin is available as a 20% cream and Finacea is a 15% gel, these differences are very subtle and not likely to prevent medication errors. Since both products are available as a single strength, prescribers may omit this information on the prescription increasing the risk for confusion. While Finacea is indicated for rosacea and Finevin is indicated for acne, both are skin conditions and this is also unlikely to prevent medication errors between Finacea and Finevin. Finally, it is likely that these products will be stored near or next to one another in many pharmacies. This will increase the risk for confusion between Finacea and Finevin.

Finevin Finacea

In the review of the draft container labels and carton labeling for the 3 gram (sample), 30 gram and 50 gram packaging and draft insert labeling for Finacea, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement.

A. GENERAL COMMENT

The draft labels and labeling submitted to DMETS do not include the artwork and font sizes that will be used in the final printed labels and labeling. Therefore, it is not possible to fully assess the safety of the labels and labeling based upon these drafts.

B. CONTAINER LABEL AND CARTON LABELING (3 grams, 30 grams, and 50 grams)

1. Increase the amount of space between "15%" and the expression of the quantity to prevent confusion.

2. Ensure the drug name and dosage strength is the most prominent information on the container and carton.

3. Ensure that the design for the container and carton of Finacea differs from Finevin (Azelaic Acid Cream) also from Berlex Laboratories, Inc. The Finacea product should look distinctly different from Finevin (See APPENDIX A).

4. [redacted]

5. [redacted]

IV. RECOMMENDATIONS

A. DMETS does not recommend use of the proprietary name, Finacea.

B. DMETS recommends implementation of the labeling revisions described in Section III.

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

Marci Lee, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support (DMETS)

Concur:

Denise Toyer, PharmD Date
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

1 page(s) of revised draft labeling has been redacted from this portion of the review.

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

/s/

Marci Ann Lee
12/17/02 01:13:52 PM
PHARMACIST

Denise Toyer
12/17/02 04:04:07 PM
PHARMACIST

Carol Holquist
12/17/02 04:14:19 PM
PHARMACIST

Jerry Phillips
12/18/02 09:01:07 AM
DIRECTOR

WITHHOLD 16 PAGE (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: December 12, 2002 Number of Pages (including cover sheet) – 1

TO: John Hegarty, Regulatory Associate
COMPANY: Berlex Laboratories
FAX #: 973-487-2016

MESSAGE: Comments from our Pharmacology/Toxicology Review of your NDA 21-470, FINACEA™ (azelaic acid) Gel, 15%, submission dated November 14, 2002, follow:

1. The Sponsor's request to postpone the study to determine the photoco-carcinogenic potential of the 15% azelaic acid gel until the Division has reviewed the [redacted] is acceptable. It would be preferable to submit the final study report to the NDA when it becomes available instead of submitting the [redacted] in [redacted] The Sponsor's proposal for conduct of a [redacted]

2. The Sponsor's request to change the timeframe for submission of the protocol for the dermal carcinogenicity study conducted in transgenic mice (Tg.AC assay) with the 15% azelaic acid gel to [redacted] 5 months after the approval letter for this NDA is acceptable.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: December 12, 2002 Number of Pages (including cover sheet) – 2

TO: John Hegarty, Regulatory Associate
COMPANY: Berlex Laboratories
FAX #: 973-487-2016

MESSAGE: Please review the following proposed Phase 4 Commitments for your NDA 21-470, Finacea (azelaic acid) Gel, 15%. If acceptable, please submit your commitments to the same.

Commitment Category: NON-CLINICAL TOXICOLOGY

1. The Applicant commits to conducting a photoco-carcinogenicity study in male and female mice with the azelaic acid 15% gel.

   Protocol submission: Within 4 months of the date of the Approval Letter for this NDA

   Study Start: Within 6 months of the date of the approval of the protocol

   Final Report Submission: Within 12 months after the study completion

2. The Applicant commits to conducting an alternative, dermal carcinogenicity study in transgenic mice (Tg.AC assay) with the azelaic acid 15% gel.

   Protocol submission: Within 5 months of the date of the Approval Letter for this NDA.

   Study Start: Within 6 months of the date of the approval of the protocol

   Final Report Submission: Within 12 months after the study completion

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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2002

CDR/CDER

Drug Development & Technology
Division of Berlex Laboratories, Inc.

December 10, 2002

ORIGINAL

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

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products – HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

ORIG AMENDMENT

RECEIVED
DEC 16 2002
MEGA/CDER

Re: NDA 21-470
FINACEA™ (azelaic acid) Gel, 15%
OTHER: RESPONSE TO FDA REQUEST FOR INFORMATION

Dear Dr. Wilkin:

Reference is made to NDA 21-470, submitted on March 20, 2002 for FINACEA™ (azelaic acid gel) 15%. Further reference is made to the Division's facsimile transmission December 9, 2002, which contained an information request from the Clinical Reviewer that is reiterated below in **bold** text. Our response follows in normal text.

According to the NDA submission, standardized photographs (for demonstration purposes only) were taken from consenting patients at Study Center No. 13.

Since NDA 21-470 was submitted in electronic format, this submission was prepared in electronic format in accordance with the *Guidance for Industry Providing Regulatory Submissions in Electronic Format - NDAs*, issued by the Center for Drug Evaluation and Research in January 1999. This submission contains 1 floppy diskette that has been scanned for viruses using Trend Office Scan, Version 3.54.

Cross Jr, Frank H

From: Ju, Hsien W
Sent: Tuesday, December 10, 2002 1:55 PM
To: Gripp, Carol
Cc: Cross Jr, Frank H
Subject: RE: RE: NDA 21-470 Azelaic Acid 15% Gel (Finevin-Gel)/Dr. Kean Lawlor

Dear Carol:

Thank you.

H. W. Ju, M.D.

-----Original Message-----
From: Gripp, Carol
Sent: Tuesday, December 10, 2002 1:48 PM
To: Ju, Hsien W
Subject: RE: NDA 21-470 Azelaic Acid 15% Gel (Finevin-Gel)/Dr. Kean Lawlor

Dr. Ju:

As just discussed. This inspection report was sent to Dr. Roy Blay on Friday 12/6/02 by FED-EX. It should have arrived there yesterday. The inspection of Dr. Lawlor was conducted from 11/18/02-11/20/02. There was no FDA-483 issued and we have given the report a NAI classification pending Center Review. If you need anything else, please let me know.

Carol A. Gripp
Supervisor
Seattle District Office
Phone 425-483-4905
Fax 425-483-4996

Cross Jr, Frank H

From: Ju, Hsien W
Sent: Tuesday, December 10, 2002 10:59 AM
To: Cross Jr, Frank H
Cc: Blay, Roy A; Ju, Hsien W
Subject: FW: Dr. Steven Kempers

-----Original Message-----
From: Richard-Math, Connie L
Sent: Tuesday, December 10, 2002 10:19 AM
To: Ju, Hsien W
Subject: Dr. Steven Kempers

Dr. Ju - what follows is the summary text from investigator Jennifer A. Vollom of Minneapolis district. This is not the final endorsement as the report is still awaiting endorsement in FACTS. I expect no changes, however, and will forward an initial classification of NAI from the district.

The data validation inspection of this Clinical Investigator was scheduled per an FY 2002 High Priority User Fee assignment from the Good Clinical Practice Branch I, Division of Scientific Investigations (HFD-46) dated 10/21/02.

The assignment requested coverage of the Finacea™ (axelaic acid gel 15%) clinical study sponsored by Berlex Laboratories (Protocol #304344, NDA #21-470). This EI was conducted according to CP 7348.811.

The previous FDA inspection and data audit at this clinical site (Dr. M. Irving Katz, MD, CI) was conducted on [redacted] per an assignment for coverage of the safety and efficacy study [redacted] That data audit resulted in a 3-item FDA 483 being issued for data reporting deficiencies and deviations. That EI was classified VAI-no response required.

The current EI found no objectionable observations, and no FDA 483 was issued. Minor verbal comments were made to management at the conclusion of the EI.

FOLLOW-UP: Forward EIR with exhibits to HFD-46 for final review and classification, with a recommendation of NAI.

Constance L. Richard-Math
Supervisory Investigator
USFDA/MIN-DO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: December 9, 2002 Number of Pages (including cover sheet) – 1

TO: John Hegarty, Regulatory Associate
COMPANY: Berlex Laboratories
FAX #: 973-487-2016

MESSAGE: For your NDA 21-470, Finacea (azelaic acid) Gel, 15%, we have the following information request from the Clinical Reviewer:

According to the NDA submission, standardized photographs (for demonstration purposes only) were taken of consenting patients at Study Center No. 13.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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UPS OVERNIGHT

ORIG AMENDMENT

BC

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

December 6, 2002

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products – HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

RECEIVED
DEC 12 2002
MEGA/CDER

RECEIVED
DEC 09 2002
CDR/ODER

Re: NDA 21-470
FINACEA™ (azelaic acid) Gel, 15%
MINOR AMENDMENT TO PENDING NDA – CMC
RESPONSE TO REQUEST FOR INFORMATION: CMC

Dear Dr. Wilkin:

Reference is made to NDA 21-470 for FINACEA™ (azelaic acid) Gel, 15%, which was submitted on March 20, 2002 for use as a topical application in the treatment of inflammatory papules and pustules _____ of rosacea. Specifically, we wish to refer to the chemistry, manufacturing and controls information that was submitted in the CMC and Micro folders of the electronic NDA.

Reference is also made to the October 29, 2002 teleconference during which we discussed the Division's preliminary comments on the CMC information submitted in the NDA. For the convenience of the reviewer, a copy of the Division's minutes of the October 29 teleconference is provided in Item 20 of this submission. As noted in the minutes, the Division's comments were identified as preliminary because the reviewer, Dr. Gautam-Basak was to participate in the pre-approval inspection of the drug product manufacturer, Schering SpA, in Milan, Italy, the following week. During the teleconference, Berlex initiated a discussion concerning a minor change in the manufacturing process for the drug product. At that time, the Division noted that Dr. Gautam-Basak would evaluate the change during the pre-approval inspection and would determine whether the change should be provided for as an amendment to the pending NDA or later, i.e., after the NDA action date.

Our colleagues at Schering SpA have informed us that, during the pre-approval inspection, Dr. Gautam-Basak advised that the minor manufacturing change could be submitted as an amendment to the pending NDA. This submission amends the original NDA to provide for that

ORIGINAL

change. Furthermore, this submission includes responses to the Division's preliminary comments that were communicated to Berlex on October 29, 2002. Responses are also provided for two additional comments addressed by the investigators during the inspection. All responses are in accordance with the information communicated to the investigators during the inspection.

Amendment re: Minor Modifications in the Manufacturing Process for the Drug Product

This submission amends NDA 21-470 to provide for minor modifications to the methods by which the commercial drug product will be manufactured. These modifications are described below:

- For the primary stability batches and in the proposed commercial manufacturing process submitted in the initial NDA submission,

  For the actual commercial product, the following modifications will be adopted:

  -
  -

  is common practice in manufacturing at the manufacturing facility, Schering SpA, Milan, Italy. The nature of the does not introduce any risk of . Furthermore, because during the manufacturing process, the changes in the have no impact on the drug product and do not require additional validation.

In addition to the above changes, the representative manufacturing formula has been updated administratively with respect to format and presentation of information. A more detailed description of the changes in the documentation is provided herein in the introduction to Item 4.2.5.2. A copy of the updated version of the representative Master Batch Record for the bulk product is also included in that Item. The introduction to Item 4.4 (Executed Batch Records) has been similarly updated to reflect these changes.

Responses to the Division's October 29, 2000 Preliminary Comments

Provided below are the responses to the Division's preliminary comments, which were discussed with Dr. Gautam-Basak during the pre-approval inspection in Milan, Italy on November 4-7, 2002. The Division's comments are presented in bold type; our responses are provided following each comment.

1. **It is unclear if analytical results listed on Certificate of Analyses (COAs) are for the bulk product or the packaged product (Section 4.2.6.4). For example, analytical test results for 30 g and 50 g batches (Batch Nos. CF 065-00 and CF 070-00, packaged from bulk batch 04004) are identical. Please provide a clarification.**

The Certificates of Analysis (CoAs) that were submitted in the original NDA contain several errors, as described below:

- CoA No. 0005306 provided on page 268 in Item 4.2.6.4 erroneously refers to bulk batch number 03002 rather than the packaged batch number, CF 050-00.
- The CoAs for batch numbers CF064-00, CF76-00, CF65-00 and CF077-00 submitted in Item 4.2.6.4 incorrectly identify the bulk manufacturing date as [redacted] The correct bulk manufacturing dates are [redacted] for batches CF 064-00 and CF 076-00, and [redacted] for batches CF 065-00 and CF 077-00.

Revised Certificates of Analysis for the primary stability batches are provided in this submission in Item 4.2.6.4.[1] The headings on these CoAs have been modified to add clarity (e.g., the tube size is specified, and both the bulk and packaged batch numbers are identified). In addition, the errors cited above have been corrected.

We also wish to confirm that the analytical results of batches packaged from the same bulk batch are identical. The explanation for this is that, [redacted] when the primary stability batches were tested, the Schering SpA [redacted] procedure for testing drug product batches was to [redacted] Only [redacted] testing was performed on each single packaged batch. However, the difference in microbiological results is obviously not evident from the CoAs (i.e., results are expressed, for all batches, as [redacted]

The [redacted] procedure for drug product batches testing was revised in [redacted]. Since then, all packaged batches are [redacted], therefore, each batch packaged for the US market will [redacted]

[1] Because CoAs for the primary stability batches were also provided in Item 4.4 (Executed Batch Records) of the original NDA, copies of the revised CoAs are included in Item 4.4 of this submission. In addition, because the CoAs for batches CF 050-00 and CF 052-00 were also provided in Item 4.5 (Methods Validation Package) of the original NDA, copies of the revised CoAs for those batches are included in Item 4.5 of this submission.

2. The COA refers to Test Specification [redacted] that cannot be located.

A copy of Quality Specification [redacted] which was in effect when the primary stability batches were tested, is provided in this submission (Item 4.2.6.4 - Analytical Results). Specification [redacted] was not included in the original NDA because it was no longer valid at the time of the submission. Instead, we submitted the Quality Specification that was valid at the time of the submission, [redacted] and we identified the shelf-life specifications in that document as the Regulatory Specifications for the drug product. A description of the differences between Specifications [redacted] and [redacted] is included in Item 4.2.6.4 (Analytical Results).

3. Since [redacted] in the gel is important we recommend that [redacted] should also be performed

[redacted] is tested on [redacted] batch of drug substance as part of [redacted] Drug substance [redacted] examination of the gel is, therefore, performed after drug [redacted], i.e., both as an in-process control and as part of final release test on each drug product batch.

The gel base (i.e., the gel before addition of drug substance) is a [redacted] product manufacturing. Therefore, [redacted] is considered suitable to check [redacted], as [redacted] examination would not add any additional information.

4. The SOP for [redacted] (Testing Standard [redacted] does not adequately describe the [redacted] procedure. The [redacted] should be prepared similar to the method described for the [redacted] as described under Testing Standard [redacted]

We recognize that the Regulatory Method for the drug product (Testing Standard No. [redacted], does not describe the details for [redacted] for the [redacted] test, nor does it completely describe the calculations necessary to get the final value (i.e., with the instrument used for [redacted] testing, the raw data are expressed in [redacted] while the final result is expressed in [redacted] the Testing Standard does not describe the conversion from [redacted].

While detailed information concerning [redacted] omitted from the Regulatory Method, it is described in a Schering SpA SOP, which is entitled (after

translation), [redacted]

[redacted] The [redacted] described in the SOP reflects the current practice at Schering SpA, i.e., [redacted]

The Regulatory Method will be updated to include the details of the sample preparation and the calculations, and the updated version will be submitted after NDA approval in a "changes being effected" supplement.

5. **The acceptance criteria for Appearance should be revised to delete any reference to "[redacted]". The acceptance criteria should read as "[redacted]**

Provided in Item 4.2.6.3 of this submission is an updated version of the specification for the drug product, in which the term "[redacted]" has been replaced by the term "gel." The appearance specification now reads as "[redacted]." The updated Quality Specification, [redacted], replaces the specification that was provided in the original NDA (Quality Specification [redacted]. The shelf life specifications included in [redacted] replace the Regulatory Specifications submitted in the original NDA.[2]

6. **The temperature for the pH measurement should be stated in the SOP provided (Testing Standard [redacted]. You have stated that the temperature of the [redacted] and the [redacted] should be the same, however, the temperature at which the pH measurements should be performed is not indicated in the SOP.**

The pH measurements for the drug product are performed according to USP (<791>) and European Pharmacopeia (2.2.3) general monographs. Samples are tested at [redacted] with temperature of sample and buffer solutions being the same. At Schering SpA, this

[2] Because Quality Specification No. [redacted] was also provided in Item 4.5 (Method Validation) and Item 7 (Microbiology) of the original NDA, copies of the updated specification [redacted] are included in Item 4.5 and Item 7 of this submission.

requirement is described in the general SOP for [redacted] testing which is entitled (after translation), "[redacted]" (SOP No. [redacted]).

The Regulatory Method will be updated to specify that the test should be performed at [redacted], and the updated version will be submitted after NDA approval as a "changes being effected" NDA supplement.

Responses to Additional Comments Addressed during the Pre-Approval Inspection

Provided below are responses to the additional comments discussed with the investigators during the pre-approval inspection at Schering SpA, Milan, Italy on November 4-7, 2002. The FDA comments (as paraphrased by the Schering SpA representatives present during the discussion) are presented in bold type; our responses are provided following each comment:

1. **Dr. Gautam-Basak recommended that the analytical validation report demonstrating the linearity of the HPLC method for azelaic acid and benzoic acid content in the gel (Report No. [redacted]) be submitted to the NDA as an integration of the validation package.**

   Report [redacted] - Linearity of the "Azelaic Acid and Benzoic Acid Content" in Testing Standard # [redacted], is provided in this submission in Item 4.2.6.5 (Suitability of the Methodology for the Drug Product) and in Item 4.5 (Methods Validation Package).

2. **Dr. Gautam-Basak indicated that, because the drug product is not a compendial formulation, the current label on tube and carton should be revised as follows: "[redacted] should be changed to "Finacea™ (azelaic acid) Gel, 15%." This change should be implemented within approximately six months of NDA approval.**

   Berlex commits to modifying the labeling for the tube and carton in accordance with the reviewer's comment, and we anticipate that this change will be implemented within approximately six months after approval of the NDA. We will submit the updated labeling in a "changes being effected" NDA supplement when the final printed labeling becomes available.

We trust that the information provided in this submission adequately responds to all of the Division's open chemistry, manufacturing and controls comments regarding NDA 21-470.

Because NDA 21-470 was submitted in electronic format, this submission has been prepared in electronic format in accordance with the January, 1999 *Guidance for Industry Providing Regulatory Submissions in Electronic Format - NDAs*. This submission contains 1 compact disk that has been scanned for viruses using Trend Office Scan, Version 3.54.

A Field Copy of this submission is being provided to the local FDA District Office. A Field Copy Provision Certification and a copy of the Field Copy Content Certification submitted with the Field Copy are provided in Item 17.

Please do not hesitate to contact me at (973) 487-2166 should you have any questions pertaining to this submission.

Sincerely,

BERLEX LABORATORIES

John Hegarty

John Hegarty
Regulatory Associate
Drug Regulatory Affairs

JMR/037

Teleconference Date: December 2, 2002 Time: 1330 Location: N225
Meeting ID: 9650

NDA 21-470, FINACEA (azelaic acid) Gel, 15%

Indication: Topical Treatment of Inflammatory Papules and Pustules [redacted] of Rosacea

CMC Discussion – NDA CMC Review

Applicant: Berlex Laboratories, Inc.

Meeting Chair: Mamta Gautam-Basak, Ph.D.

Meeting Recorder (Project Manager: Frank Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Mamta Gautam-Basak, Ph.D., Chemistry Reviewer, DNDCIII, HFD-830
Frank Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Applicant Attendees, titles and offices:

John Hegarty, Regulatory Associate

Agency:

Please submit a response to the issues previously discussed during the October 29, 2002, CMC Teleconference, i.e.,

"1. It is unclear if analytical results listed on Certificate of Analyses (COAs) are for the bulk product or the packaged product (Section 4.2.6.4). For example, analytical test results for 30 g and 50 g batches (Batch Nos. CF 065-00 and CF 070-00, packaged from bulk batch 04004) are identical. Please provide a clarification.

2. The COA refers to Test Specification [redacted] that cannot be located.

3. Since [redacted] drug substance in the gel is important we recommend that [redacted] should also be performed before the [redacted]

4. The SOP for determination of [redacted] (Testing Standard [redacted] does not adequately describe the sample preparation procedure. The sample should be prepared similar to the method described for the [redacted] test) as described under Testing Standard [redacted]

5. The acceptance criteria for Appearance should be revised to delete any reference to [redacted]. The acceptance criteria should read as [redacted]

6. The [redacted] s should be stated in the SOP provided (Testing Standard [redacted] You have stated that the [redacted] of the [redacted] and the [redacted] should be the same, however, the temperature at which the pH measurements should be performed is not indicated in the SOP.

Agency:

In addition, please submit a revised master batch record for the drug product.

Applicant:

The Applicant advised the Agency that it will get back to us shortly with its response.

The teleconference ended amicably.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

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

/s/

Mamta Gautam-Basak
12/9/02 04:25:59 PM

Wilson H. DeCamp
12/16/02 09:07:08 AM
concur; minutes are accurate

NOV 1 0 ...
CDR/CDER

November 14, 2002

Division of Berlex Laboratories, Inc.

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

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products – HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

HFC
ORIG AMENDMENT

RECEIVED
NOV 1 9 2002
MEGA/CDER

Re: NDA 21-470
FINACEA™ (azelaic acid gel) 15%
AMENDMENT TO PENDING NDA
OTHER: RESPONSE TO FDA REQUEST FOR INFORMATION
PROPOSED PHASE 4 COMMITMENTS - NONCLINICAL

Dear Dr. Wilkin:

Reference is made to NDA 21-470, submitted on March 20, 2002 for FINACEA™ (azelaic acid gel) 15%. Reference is also made to the Division's facsimile transmission of November 8, 2002, which provided proposed nonclinical toxicology Phase 4 Commitments for NDA 21-470.

The proposed Phase 4 Commitments for NDA 21-470 are repeated below in **bold** text followed by our responses in unbold text.

Please review the following proposed Phase 4 Commitments for your NDA 21-470, Finacea (azelaic acid) Gel, 15%. If acceptable, please submit your commitments to the same.

Commitment Category: NON-CLINICAL TOXICOLOGY

1. **The Applicant commits to conducting a photoco-carcinogenicity study in male and female mice with the azelaic acid 15% gel.**

- **Protocol submission: Within 4 months of the date of the Approval Letter for this NDA**
- **Study Start: Within 6 months of the date of the approval of the protocol**
- **Final Report Submission: Within 12 months after the study completion**

Berlex Laboratories, Inc. requests postponement of this commitment until the Division has reviewed the [redacted]

2. **The Applicant commits to conducting an alternative, dermal carcinogenicity study ... transgenic mice (Tg.AC assay) with the azelaic acid 15% gel.**

- **Protocol submission: Within ~ months of the date of the Approval Letter for this NDA**
- **Study Start: Within 6 months of the date of the approval of the protocol**
- **Final Report Submission: Within 12 months after the study completion**

Berlex Laboratories, Inc. commits to conduct an alternative, dermal carcinogenicity study in transgenic mice (Tg.AC assay) with the azelaic acid 15% gel; however, Berlex Laboratories, Inc. requests the scheduling change outlined below.

- Protocol submission: ~~[redacted]~~ 5 months after the anticipated date of the Approval Letter for this NDA ~~[redacted]~~
- Study Start: Within 6 months of the date of the approval of the protocol
- Final Report Submission: Within 12 months after the study completion

The dose range-finding study for the Tg.AC assay with the azelaic acid 15% gel will start in ~~[redacted]~~ The audited draft report will be available in ~~[redacted]~~ Berlex Laboratories, Inc. intends to submit this report to the Division with the protocol for the definitive Tg.AC study; therefore, this submission cannot be made before ~~[redacted]~~

Berlex Laboratories, Inc. hopes these proposals will be acceptable to the Agency. We welcome the opportunity to discuss them with the Division in a teleconference.

Since NDA 21-470 was submitted in electronic format, this submission was prepared in electronic format in accordance with the *Guidance for Industry Providing Regulatory Submissions in Electronic Format - NDAs*, issued by the Center for Drug Evaluation and Research in January 1999. This submission contains 1 floppy diskette that has been scanned for viruses using Trend Office Scan, Version 3.54.

Please call the undersigned at (973) 487-2166, if you have any questions concerning this application.

Sincerely,

BERLEX LABORATORIES

John Hegarty

John Hegarty
Regulatory Associate
Drug Regulatory Affairs

JJH068

CDR/CDER

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

November 12, 2002

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products – HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

RECEIVED
NOV 18 2002
MEGA/CDER
BZ
ORIG AMENDMENT

Re: NDA 21-470
FINACEA™ (azelaic acid gel) 15%
AMENDMENT TO PENDING NDA
OTHER: RESPONSE TO FDA REQUEST FOR INFORMATION

Dear Dr. Wilkin:

Reference is made to NDA 21-470, submitted on March 20, 2002 for FINACEA™ (azelaic acid gel) 15%. Reference is also made to a teleconference held on November 6, 2002 with the Division including various members of the clinical and biostatistical teams, and the undersigned. Further reference is made to the Division's facsimile transmission November 7, 2002, which provided the Division's minutes of this teleconference.

This submission provides responses in electronic format to the Division's clinical and biostatistical questions. Also various listings are provided in Item 8. The Division's questions are repeated below in **bold** text followed by our responses in unbold text.

Clinical

Please explain the apparent paradox between the data for erythema seen in the adverse event data versus erythema ratings for the secondary endpoint of erythema noted in Studies A03125 and A03126.

The term "Worsening of erythema" does not indicate an actual verbatim report of worsening by either the patient or the investigator, but is mathematically derived from the erythema score. Those patients, that increased by at least one score point in overall facial erythema severity from baseline to the last available visit were analyzed as patients that showed a worsening of erythema, in percent of the ITT population. As explained below in the response to the biostatistical question, this was not explicitly defined in the protocol or the statistical analysis

plan because it was felt to be apparent. The analysis of erythema rating change did not take into account changes in intermediate visit ratings.

In Report A03125, 7 patients (4%) showed worsening of erythema in the AzA group and 12 patients (7%) in the vehicle group in the ITT population with last observation carried forward. In Report A03126, 10 patients (6%) showed worsening of erythema in the AzA group and 18 patients (11%) in the vehicle group. Please see the Listing of patients with worsening erythema.

Adverse events (AEs) coded to the term "rash" reflect literal terms that are indicative of the symptoms of erythema (redness, erythema, blush, blotches), as well as of more general inflammation (irritation, inflammatory irritant reaction) and rash itself (rash, itchy rash, red rash). Provided herein is a listing of all patients that experienced one or more AEs coded to "rash" according to the HARTS 2.3 dictionary for both Report A03125 and A03126). Please see the Listing of patients with rash adverse events.

In Report A03125, there is no overlap between those patients that have a worsening of erythema according to the analysis described above, and those patients for whom rash was reported as an AE at any time during the study. That is no patient in Report A03125 had a worsening erythema rating as well as an AE coded to rash. In Report A03126, Patient 199 (Site 07) who was treated with vehicle had a worsening of erythema, as defined above, and AEs at week 4 (red blotches and burning after application). The patient discontinued due to the AEs. Patient 107 (Site 12), also treated with vehicle, had a worsening of erythema, and AEs reported as severe erythema on weeks 4, 8 and 12, indeed indicative of a worsening of overall facial erythema.

In all other patients, AEs reported as redness or erythema were either by way of their intensity or their pattern not suggestive to the investigator to reflect a more severe score for overall facial erythema at the last available visit. In addition, the analysis of change of erythema severity did not take into account changes in intermediate visit ratings, at which time an AE of redness or erythema might have occurred. Hence, these patients were not analyzed as worsened with regard to their erythema severity.

In conclusion, AEs coded to rash, and patients that showed worsening of erythema were different study events that appear not to reflect the same clinical situation. Thus, vehicle patients showed a higher percentage of worsening of erythema compared to AzA patients, although about the same number of patients showed an AE indicative of erythema in both treatment groups. As a speculation, at least some of the AEs coded to rash may reflect an episode of flushing/blushing that is not uncommon in rosacea patients, but that does not change the overall erythema severity rating. One patient (No. 107 (Site 12), Report A03126) for whom the AE reporting is actually indicative of a worsening of erythema, is in fact in this category in the erythema analysis.

We have some concern about apparent differences between the Applicant's methods of analysis for erythema scores that seem to be implied by the statistical analysis plan (SAP) and the protocol.

The study protocol provides a 4-point scale for the rating of overall facial erythema with no, mild, moderate and severe as score points (Section 7.5.1.4 of the protocol). These descriptive terms were assigned numbers in the case record forms, with a score of 1 for no erythema, to a score of 4 for severe erythema. The protocol provides for erythema severity assessment on the basis of this 4-point scale at baseline, and week 4, 8 and 12 (see Table 1 in the protocol: Summary table of trial activities and assessments). With regard to statistical analysis, the protocol lists "change in the rating of erythema severity" as secondary efficacy variable, without specifically mentioning the statistical analysis in detail. Section 7.7.1.5 of the protocol indicates that summary tables (descriptive statistics and/or frequency tables) will be provided for all efficacy variables (re: tables 33 and 34 in Report A03125; tables 34 and 35 in Report A03126).

With regard to analysis of erythema, the statistical analysis plan (version 4 – June 6, 2001) indicates the following:

> "The number and percent of patients with each rating will be displayed. The number and percent of patients, who improved, stayed the same, and worsened from baseline to End of Study will also be displayed. Treatment groups will be compared using a Cochran Mantel Haenszel (CMH) row means score test controlling for study center. Modified ridit scores will be used for this analysis."

For "End of study" analyses, including the analysis of erythema severity, the last available non-missing data point was used, as was specified in section 3.6 of the analysis plan, as well as the Analysis Plan Supplement 1 of Sept 7, 2001:

> "While efficacy data will be displayed with summaries of observed data at each visit, the data will also be summarized at the end of the study using a last observation carry forward (LOCF) approach. This approach will use the last available non-missing data point for each individual efficacy measure on each patient. For the Intent-to-Treat population, baseline values will be carried forward for patients with no post-baseline efficacy data."

We feel that the language set forth in the protocol is entirely consistent with the statistical analysis plan, except for its supplement with regard to the LOCF method.

The categories of the change in the rating of erythema severity, defined as a ——— efficacy variable in the protocol, was not explicitly defined in the protocol or in the statistical analysis plan. This was assumed to be apparent, but should have probably been defined in writing. For the analysis, each patient was grouped into 3 categories. Specifically, any single step or greater move up the scale from baseline to the last non-missing visit was regarded "Worsening", any single step or greater down was regarded as "Improvement", and erythema was regarded as "Unchanged" if the rating was identical.

Since NDA 21-470 was submitted in electronic format, this submission was prepared in electronic format in accordance with the *Guidance for Industry Providing Regulatory Submissions in Electronic Format - NDAs*, issued by the Center for Drug Evaluation and Research in January 1999. This submission contains 1 floppy diskette that has been scanned for viruses using Trend Office Scan, Version 3.54.

Please call the undersigned at (973) 487-2166, if you have any questions concerning this application.

Sincerely,

BERLEX LABORATORIES

John Hegarty

John Hegarty
Regulatory Associate
Drug Regulatory Affairs

JJH066

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: November 8, 2002 Number of Pages (including cover sheet) – 2

TO: John Hegarty, Regulatory Associate
COMPANY: Berlex Laboratories
FAX #: 973-487-2016

MESSAGE: Please review the following proposed Phase 4 Commitments for your NDA 21-470, Finacea (azelaic acid) Gel, 15%. If acceptable, please submit your commitments to the same.

Commitment Category: NON-CLINICAL TOXICOLOGY

1. The Applicant commits to conducting a photoco-carcinogenicity study in male and female mice with the azelaic acid 15% gel.

   Protocol submission: Within 4 months of the date of the Approval Letter for this NDA

   Study Start: Within 6 months of the date of the approval of the protocol

   Final Report Submission: Within 12 months after the study completion

2. The Applicant commits to conducting an alternative, dermal carcinogenicity study in transgenic mice (Tg.AC assay) with the azelaic acid 15% gel.

   Protocol submission: Within— nonths of the date of the Approval Letter for this NDA.

   Study Start: Within 6 months of the date of the approval of the protocol

   Final Report Submission: Within 12 months after the study completion

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

TELEFAX AND UPS

NOV 1 2 2002

CDR/CDER

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

November 8, 2002

ORIGINAL

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products – HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

ORIG AMENDMENT

RECEIVED
NOV 1 9 2002
MEGA/CDER

Re: NDA 21-470
FINACEA™ (azelaic acid gel) 15%
AMENDMENT TO PENDING NDA
OTHER: RESPONSE TO FDA REQUEST FOR INFORMATION
REPLACEMENT DISKETTE

Dear Dr. Wilkin:

Reference is made to NDA 21-470, submitted on March 20, 2002 for FINACEA™ (azelaic acid gel) 15%. Reference is also made to the Division's facsimile transmission of October 29, 2002 which provided a request from the Biopharmaceutics reviewer. Further reference is made to our November 4, 2002 submission of the requested information on 1 floppy diskette in electronic format. Additional reference is made to a telephone conversation on November 7, 2002 during which your representative Cdr. Frank Cross informed the undersigned that the Document Room indicated that the diskette for the November 4 submission was missing. This submission provides the requested information in electronic format on 1 floppy diskette for use as a replacement for the missing diskette.

The Division's October 29, 2002 facsimile provided the following request from the Biopharmaceutics reviewer:

Please submit the demographic data (age, gender, weight, baseline degree of skin involvement, etc.) for the individual patients enrolled in the Pharmacokinetic Study Report A03125. Please provide this data in both a summary (mean +/- S.D.) and a table listing the individual values for each subject.

The following tabular listings are provided in the "hupharm" subfolder of Item 6 [hpbio\hupharm]:

- Listing of Patient Demographics
- Listing of Baseline Clinical Characteristics
- Listing of Facial Lesion Count
- Listing of Investigator's Global Assessment, Erythema, & Telangiectasia
- Summary Table

Please note that Report A03125 was 1 of 2 primary efficacy studies provided in NDA 21-470. The demographic information from Report A03125 provided herein was from a subset of patients from study site 10 that agreed to participate in a pharmacokinetic analysis.

Since NDA 21-470 was submitted in electronic format, this submission was prepared in electronic format in accordance with the *Guidance for Industry Providing Regulatory Submissions in Electronic Format - NDAs*, issued by the Center for Drug Evaluation and Research in January 1999. This submission contains 1 floppy diskette that has been scanned for viruses using Trend Office Scan, Version 3.54.

Please call the undersigned at (973) 487-2166, if you have any questions concerning this application.

Sincerely,

BERLEX LABORATORIES

John Hegarty

John Hegarty
Regulatory Associate
Drug Regulatory Affairs

JJH063

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: November 7, 2002 Number of Pages (including cover sheet) – 3

TO: John Hegarty, Regulatory Associate
COMPANY: Berlex Laboratories
FAX #: 973-487-2016

MESSAGE: Please find attached to this facsimile transmission our minutes of our November 6, 2002, Clinical/Biostatistical teleconference regarding your NDA 21-470, Finacea (azelaic acid) Gel, 15%.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

Teleconference Date: November 6, 2002 Time: 1445 Location: N225
Meeting ID: 9484

NDA 21-470, FINACEA (azelaic acid) Gel, 15%

Indication: Topical Treatment of Inflammatory Papules and Pustules [redacted] of Rosacea

Clinical/Biostatistical Discussion

Applicant: Berlex Laboratories, Inc.

Meeting Chair: Markham Luke, M.D., Ph.D.

Meeting Recorder (Project Manager: Frank Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Markham Luke, M.D., Ph.D., Dermatology Clinical team Leader, DDDDP, HFD-540
Brenda Carr, M.D., Medical Officer, DDDDP, HFD-540
Brenda Vaughan, M.D., Medical Officer, DDDDP, HFD-540
Mohamed Alosh, Ph.D., Biostatistics Team Leader, DOBIV, HFD-725
Steve Thomson, Biostatistics Reviewer, DOBIV, HFD-725
Frank Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Applicant Attendees, titles and offices:

John Hegarty, Regulatory Associate

Agency:

Clinical:

Please explain the apparent paradox between the data for erythema seen in the adverse event data versus erythema ratings for the secondary endpoint of erythema noted in Studies A03125 and A03126.

Biostatistical:

We have some concern about apparent differences between the Applicant's methods of analysis for erythema scores that seem to be implied by the statistical analysis plan (SAP) and the protocol.

Applicant:

The Applicant thanked the Agency for the teleconference and will submit a response to the Agency's request in the near future.

The teleconference ended amicably.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

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

/s/

Markham Luke
11/7/02 03:49:23 PM

TELEFAX AND
UPS OVERNIGHT

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CDR/CDER

BERLEX

Drug Development & Technology
Division of Berlex Laboratories, Inc.

November 4, 2002

ORIGINAL

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

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products – HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

BB
ORIG AMENDMENT

RECEIVED
NOV 0 6 2002
MEGA/CDER

Re: NDA 21-470
FINACEA™ (azelaic acid gel) 15%
AMENDMENT TO PENDING NDA
OTHER: RESPONSE TO FDA INFORMATION REQUEST

Dear Dr. Wilkin:

Reference is made to NDA 21-470, submitted on March 20, 2002 for FINACEA™ (azelaic acid gel) 15%. Reference is also made to the Division's facsimile transmission of October 29, 2002 which provided the following request from the Biopharmaceutics reviewer:

Please submit the demographic data (age, gender, weight, baseline degree of skin involvement, etc.) for the individual patients enrolled in the Pharmacokinetic Study Report A03125. Please provide this data in both a summary (mean +/- S.D.) and a table listing the individual values for each subject.

This submission provides the requested information in electronic format. The following tabular listings are provided in the "hupharm" subfolder of Item 6 [hpbio\hupharm]:

- Listing of Patient Demographics
- Listing of Baseline Clinical Characteristics
- Listing of Facial Lesion Count

  Listing of Investigator's Global Assessment, Erythema, & Telangiectasia
- Summary Table

Please note that Report A03125 was 1 of 2 primary efficacy studies provided in NDA 21-470. The demographic information from Report A03125 provided herein was from a subset of patients from study site 10 that agreed to participate in a pharmacokinetic analysis.

Since NDA 21-470 was submitted in electronic format, this submission was prepared in electronic format in accordance with the *Guidance for Industry Providing Regulatory Submissions in Electronic Format - NDAs*, issued by the Center for Drug Evaluation and Research in January 1999. This submission contains 1 floppy diskette that has been scanned for viruses using Trend Office Scan, Version 3.54.

Please call the undersigned at (973) 487-2166, if you have any questions concerning this application.

Sincerely,

BERLEX LABORATORIES

John Hegarty

John Hegarty
Regulatory Associate
Drug Regulatory Affairs

JJH060

Cross Jr, Frank H

From: Cross Jr, Frank H
Sent: Wednesday, October 30, 2002 9:22 AM
To: Chaurasia, Chandra S
Cc: Bashaw, Edward D; Gautam Basak, Mamta; Decamp II, Wilson H
Subject: RE: NDA 21-470, FINACEA - Biopharm review - Conveyance of BPH comments from Biopharm review

Thanks, Chandra.

Frank

-----Original Message-----
From: Chaurasia, Chandra S
Sent: Tuesday, October 29, 2002 5:26 PM
To: Cross Jr, Frank H
Cc: Bashaw, Edward D; Gautam Basak, Mamta; Decamp II, Wilson H
Subject: RE: NDA 21-470, FINACEA - Biopharm review - Conveyance of BPH comments from Biopharm review

Since the current manufacturing site is Milan, Italy (and, the data from the batch manufactured in Berlin, Germany is supportive only), the comments may be provided to the Applicant as an informational Fax after the Action Letter is issued.

Thanks,

Chandra

-----Original Message-----
From: Cross Jr, Frank H
Sent: Tuesday, October 29, 2002 3:08 PM
To: Chaurasia, Chandra S
Cc: Bashaw, Edward D; Gautam Basak, Mamta; Decamp II, Wilson H
Subject: NDA 21-470, FINACEA - Biopharm review - Conveyance of BPH comments from Biopharm review

Hi Chandra,

Are the comments from your attached review to be provided to the Applicant:

1) Now or

2) As an Informational Fax after the Action Letter is issued or

3) As a Phase 4 Commitment?

Please let me know.

Currently, the drug product manufacturing site is Milan, Italy.

Thanks,

Frank

<< File: CNDATOPI.pdf >>

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: October 29, 2002 Number of Pages (including cover sheet) – 4

TO: John Hegarty, Regulatory Associate
COMPANY: Berlex Laboratories
FAX #: 973-487-2016

MESSAGE: Please find attached to this facsimile transmission our minutes of today's CMC Teleconference regarding your NDA 21-470, Finacea (azelaic acid) Gel, 15%.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone.

Teleconference Date: October 29, 2002 Time: 1315 Location: N225
Meeting ID: 9436

NDA 21-470, FINACEA (azelaic acid) Gel, 15%

Indication: Topical Treatment of Inflammatory Papules and Pustules ——— of Rosacea

CMC Discussion – NDA CMC Review

Applicant: Berlex Laboratories, Inc.

Meeting Chair: Wilson DeCamp, Ph.D.

Meeting Recorder (Project Manager: Frank Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-830
Mamta Gautam-Basak, Ph.D., Chemistry Reviewer, DNDCIII, HFD-830
Frank Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Applicant Attendees, titles and offices:

Jo-Ann Ruane, Manager, Regulatory Affairs
Jeffrey Farkas, Manager, Quality Systems

Agency:

As introductory comments, FDA noted that Dr. Gautam-Basak will be participating in the product-specific CGMP inspection next week. These comments are provided as a courtesy, since they may be the subject of discussions at the inspection. A response before the inspection is not needed.

From the CMC review of NDA 21-470, FINACEA (azelaic acid) Gel, 15%, the Agency provided the following preliminary comments:

1. It is unclear if analytical results listed on Certificate of Analyses (COAs) are for the bulk product or the packaged product (Section 4.2.6.4). For example, analytical test results for 30 g and 50 g batches (Batch Nos. CF 065-00 and CF 070-00, packaged from bulk batch 04004) are identical. Please provide a clarification.

2. The COA refers to Test Specification ——— that cannot be located.

3. Since ——— in the gel is important we recommend that ——— should also be performed ———

4. The SOP for ——— (Testing Standard ———) does not adequately describe the sample preparation procedure. The sample should be prepared similar to the method described for the ——— as described under Testing Standard ———

5. The acceptance criteria for Appearance should be revised to delete any reference to " [redacted] ". The acceptance criteria should read as " [redacted] ".

6. The temperature for the pH measurements should be stated in the SOP provided (Testing Standard [redacted] . You have stated that the temperature of the [redacted] and the [redacted] should be the same, however, the temperature at which the pH measurements should be performed is not indicated in the SOP.

Applicant:

The Applicant thanked the Agency for the teleconference. The Applicant also informed the Agency that they would be submitting a minor CMC amendment to this NDA discussing a manufacturing change.

Agency:

The Agency advised the Applicant to not submit this manufacturing change at this time. Reference to the "Changes to an Approved NDA" guidance was suggested.

The teleconference ended amicably.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

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

/s/

Mamta Gautam-Basak
10/29/02 02:52:10 PM

Wilson H. DeCamp
10/29/02 03:22:20 PM
concur

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: October 29, 2002 Number of Pages (including cover sheet) – 1

TO: John Hegarty, Regulatory Associate
COMPANY: Berlex Laboratories
FAX #: 973-487-2016

MESSAGE: For your NDA 21-470, Finacea (azelaic acid) Gel, 15%, we have the following request from the Biopharmaceutics Reviewer:

Please submit the demographic data (age, gender, weight, baseline degree of skin involvement, etc.) for the individual patients enrolled in the Pharmacokinetic Study Report No. A03125. Please provide this data in both a summary (mean +/- S.D.) and a table listing the individual values for each subject.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

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UPS OVERNIGHT

RECEIVED
OCT 17 2002
CDR/CDER

Drug Development & Technc
Division of Berlex Laboratories, Inc

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

October 16, 2002

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products – HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

ORIG AMENDMENT
BM

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OCT 21 2002
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Re: NDA 21-470
FINACEA™ (azelaic acid gel) 15%
AMENDMENT TO PENDING NDA
OTHER: RESPONSE TO FDA INFORMATION REQUEST

Dear Dr. Wilkin:

Reference is made to NDA 21-470, submitted on March 20, 2002 for FINACEA™ (azelaic acid gel) 15%. Reference is also made to the Division's clinical questions included in the Division's October 3, 2002 Information Request. Further reference is made to our responses, which were telefaxed to the Division on October 4, 2002 and submitted in electronic format on October 8, 2002.

As indicated in our responses, we anticipated that clinical study report A08681 entitled "A 15-week, randomized, double-blind multicenter study comparing the clinical efficacy and safety of Azelaic Acid 15% gel (SH H 655 BA) with Metronidazole 0.75% gel in patients with papulopustular facial rosacea" would be finalized by ——— Accordingly, this submission provides the following in electronic format:

- Index – Item1
- Report A08681 in Item 8.
- Case Report Tabulations as SAS datasets in Item 11.
- Case Report Forms for subjects that discontinued the study due to adverse events are provided in Item 12.

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