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 compact disk that has been scanned 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

JJH052

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

October 14, 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
BC

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

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.

Further reference is made to the chemistry, manufacturing and controls comments included in the Division's May 15, 2002 Information Request, and to our response to that request, which was submitted on June 6, 2002.

In our June 6, 2002 response, we reiterated our intention to submit updated stability data during the NDA review period (i.e., not less than 3 months prior to the NDA action date)[1], including — month data for the primary stability batches. We also proposed to incorporate the Division's preferred format for reporting stability data in the updated stability reports. In addition, we committed to provide in the amendment the requested data analysis of quantitative parameters, including an evaluation of data, plots and/or graphics, documentation of the statistical methods and formulas, and the results of the statistical analysis and estimated expiration dating period.

[1] Our intention to amend the application with additional stability data was described in our pre-NDA meeting package, submitted on August 2, 2001 and in the initial NDA submission (Drug Product Folder, Item 4.2.7.2 – Stability Data, page 329).

ORIGINAL

In accordance with our commitments in the June 6, 2002 response, this submission amends NDA 21-470 with the updated stability data and evaluation. Included in this submission is the following information:

- Updated stability reports for the primary stability batches (30-gram and 50-gram tubes), and supportive batches (gram tubes with 3-gram fill and gram fill).

  The updated reports contain updated stability data, presented in the requested format, along with the requested evaluation of quantitative parameters, including estimation of expiration dating period based on statistical analysis of the data. Information pertaining to the updated stability reports provided in this amendment is provided below:

Attachment No.	Updated Report No.	Fill Weight	Filling Batch No.	Storage Conditions	Storage Time (months)	Replaced Report No.[a]
1	A10106 Version: 1.0	30-gram	CF 050-00, CF 064-00, CF 065-00			A03224 Version: 4.0
2	A10100 Version: 1.0	50-gram	CF 052-00, CF 076-00, CF 077-00			A03546 Version: 3.0
3	A10103 Version: 1.0	3-gram	CF 038-01, CF 039-01, CF 040-01			A06034 Version: 1.0
			CF 038-01a			
4	A10113 Version: 1.0	gram	CF 051-00, CF 074-00, CF 075-00			A03545 Version: 2.0
			CF 073-00			

[a] The listed reports were submitted in the initial NDA (Item 4.2.7.2.) and are replaced by the corresponding updated reports provided in this submission.

- Information pertaining to the statistical methods and formulas used for the statistical analyses and extrapolation of the long-term stability data, as follows:
  - Attachment 5: Statistical Analysis of the 18-month data for the 30-gram batches
  - Attachment 6: Statistical Analysis of the 18-month data for the 50-gram batches
  - Attachment 7: Statistical Analysis of the 12-month data for the 3-gram batches
  - Attachment 8: Statistical Analysis of the 18-month data for the gram batches

We trust this submission satisfies the commitments made in our June 6, 2002 submission. Furthermore, we believe that the updated stability data and evaluations, plus the extensive supportive stability data that was submitted in the initial NDA submission, adequately support our proposed initial expiration dating period of 24 months.

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 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 immediately following this letter.

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/031

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 3, 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 Clinical Informational Requests:

1. Please clarify why patients with less than a score of 4 on the Investigator's Global Assessment at baseline were not considered protocol violations.

2. For Study A03126, 2 women became pregnant during the study. Please provide any available information on the pregnancy outcomes.

3. A protocol was submitted to your IND for this product to [redacted] your product. Please provide safety data, if available, from this [redacted] study. If this data is not available, please provide information regarding the current status of this study.

Thank you.

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

BERLEX

TELEFAX AND UPS SECOND DAY AIR

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

August 30, 2002

NDA CORRESPONDENCE
NC

Mr. Frank H. Cross
Division of Dermatologic and Dental Drug Products – HFD-540
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
Corporate 2, Room N229
9201 Corporate Blvd.
Rockville, Maryland 20850

RECEIVED
SEP 0 6 2002
MEGA/CDER

RECEIVED
SEP 0 4 2002
CDR MAILROOM

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

Dear Mr. Cross:

Reference is made to NDA 21-470, submitted on March 20, 2002 for FINACEA™ (azelaic acid gel) 15% for use as a topical application in the treatment of inflammatory papules and pustules of rosacea. Further reference is made to our telephone conversation on August 23, 2002 during which you reiterated requests from reviewers for a hardcopy of various portions of NDA 21-470, which was submitted only in electronic format.

Enclosed are the following review aids:

- NDA Item 3 – Application Summary - 1 hardcopy comprising 1 volume.
- NDA Item 8 – Clinical - 1 hardcopy comprising 30 volumes.
- 1 compact disc of the complete NDA electronic (PDF) format. The enclosed CD-ROM has been scanned for viruses using Trend Office Scan, Version 3.54 and is virus free.
- NDA Item 4 – Chemistry, Manufacturing and Controls – 1 hardcopy comprising 4 volumes.

These reviewer aids are not considered official copies, but are provided for the convenience of the reviewers. If you have any questions concerning the reviewer aids, please consult the official electronic archive copy of the submission or telephone the undersigned at (973) 487-2166.

Sincerely,

BERLEX LABORATORIES

John Hegarty

ORIGINAL

John Hegarty
Regulatory Associate
Drug Regulatory Affairs

JJH036

TELEFAX AND UPS OVERNIGHT

NDA PDUFA AMENDMENT
SU

RECEIVED
AUG 01 2002
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July 30, 2002

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

RECEIVED
AUG 0 2 2002
MEGA/CDER

RECEIVED
JUL 31 2002
CDR/CDER

Re: NDA 21-470
FINACEA™ (azelaic acid gel) 15%
OTHER: INITIAL SAFETY UPDATE REPORT

Dear Dr. Wilkin:

Reference is made to NDA 21-470, submitted on March 20, 2002 for FINACEA™ (azelaic acid gel) 15% for use as a topical application in the treatment of inflammatory papules and pustules of rosacea.

Pursuant to 21 CFR §314.50(d)(5)(vi)(b)(1), enclosed is the initial Safety Update Report submitted to NDA 21-470. The reporting period for this report is October 18, 2001 through June 30, 2002. This interval corresponds to the period of time between the cut-off date that was established for preparation of the original NDA and the date established for preparation of this update.

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 compact disc 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

ORIGINAL

John Hegarty
Regulatory Associate
Drug Regulatory Affairs

JJH031

NEW CORRESP NC

BERLEX

ELEFAX AND UPS OVERNIGHT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
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Telephone: (973) 487-2000

ıne 14, 2002

)nathan Wilkin, MD, Director
)ivision of Dermatologic and Dental Drug Products – HFD-540
)ffice of Drug Evaluation V
:enter for Drug Evaluation & Research
J.S. Food and Drug Administration
600 Fishers Lane
:ockville, Maryland 20857-1706

RECEIVED
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JUN 1 7 2002
CDR/CDER

Re: NDA 21-470
FINACEA™ (azelaic acid gel) 15%
GENERAL CORRESPONDENCE

Dear Dr. Wilkin:

Reference is made to NDA 21-470, submitted on March 20, 2002 for FINACEA™ (azelaic acid gel) 15% for use as a topical application in the treatment of inflammatory papules and pustules of rosacea.

The purpose of this submission is to provide an electronic copy of a letter of authorization (LOA) from Allergan, holder of NDA 20-428, which authorizes Berlex Laboratories to cross reference their IND for and NDA 20-428 in support of our azelaic acid-containing applications. This submission contains 1 floppy diskette that has been scanned for viruses using Trend Office Scan, Version 3.54.

With the LOA from Allergan, we believe this application is now a 505(b)(1) application and accordingly, have marked 505(b)(1) as the application type on the FDA Form 356h.

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

ORIGINAL

JJH/024

BERLEX

TELEFAX AND UPS OVERNIGHT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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Telephone: (973) 487-2000

June 6, 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

Re: NDA 21-470
FINACEA™ (azelaic acid gel) 15%
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% for use as a topical application in the treatment of inflammatory papules and pustules of rosacea. Further reference is made to the Division's Information Request dated May 15, 2002, regarding NDA 21-470, which contained CMC, Biopharmaceutics and Clinical requests. A copy of the May 15 request is provided in this submission.

Additional reference is made to a telephone conversation on May 31, 2002 between the undersigned and your representative, Mr. Frank Cross, during which Mr. Cross forwarded a question from the Chemistry Reviewer, Dr. Mamta Gautam-Basak. The question is paraphrased below in bold text followed by our response.

> **With regard to the table on pages 40 and 41 in Item 4 of the NDA entitled "Comparison of testing of according to the USP and EP" monographs, the document header lists pages 1 of 3 and 2 of 3. Is a page 3 of 3 missing?**
>
> The table is 2 pages in length; there is no missing page 3 for the table.

Provided below are Berlex' responses to the Division's May 15 information request for CMC, Biopharmaceutics and Clinical information. Each information request identified by the Division is in **bold** text followed by Berlex' response.

Chemistry, Manufacturing and Controls:

1. **Complete description of the container/closure system used to package the primary stability batches. The applicant should include packaging components, supplier and DMF reference.**

A complete description of the container-closure system used to package the primary stability batches can be found in the original NDA submission in the following locations:

Information Requested	File Name in CMC Product Folder	Subsection Heading	Page No. in File
Tube with screw cap	Product (Item 4.2)		116-117
DMF Reference	Product (Item 4.2)		116
Supplier	Product (Item 4.2)		325

For the convenience of the reviewer, copies of the above-cited pages are provided in this submission via blue hypertext links.

As noted in the original NDA submission, the primary stability batches were packaged in the same tubes that will be used for the commercial product *(product – page 325)*. tube suppliers are provided for in the NDA *(Product – page 116)*; tubes from all suppliers have been used in a primary and/or supportive stability study *(Product – page 325-27)*.

The screw caps used for the primary stability batches were manufactured from a different than will be used for the commercial product *(Product – page 117)*. However, this change has no influence on the primary stability studies, because the tubes are sealed ( ), and there is no contact between the product and the closure during long-term storage of the stability samples. Data generated after the tube seal has been broken, i.e., when the product is in contact with the closure, is provided in the original NDA submission *(Product – page 328)*.

2. **Regarding the primary stability data submitted in the NDA in support of the shelf-life expiration date:**

a. **The Applicant should submit stability data in the attached table format.**

All batch information listed in the table format provided by the Division is provided in this submission for each of the primary stability batches. Also provided in the tables are the folder/file name and page references where the listed batch information can be found in the original NDA submission; references are also provided for the stability reports in which the primary stability data submitted in the original NDA submission can be found.

Provided below is the table which lists the primary stability batches and provides the hypertext links to the tabulated information for each batch.

Primary Stability Batch Information		
Bulk batch Number	**Tube Size**	**Packaging Lot Number**
03002	30 gram	CF 050-00
	50 gram	CF 052-00
04003	30 gram	CF 064-00
	50 gram	CF 076-00
04004	30 gram	CF 065-00
	50 gram	CF 077-00

As noted in our original NDA submission *(Product - page 329)*, Berlex intends to submit additional stability data during the NDA review period (ie, not less than 3 months prior to the NDA action date), including —-month data for the primary stability batches. We propose to adopt the Division's preferred format when we amend our application with those updated data.

b. The following data analysis of quantitative parameters should be included:

i. Evaluation of data, plots, and/or graphics;

ii. Documentation of appropriate statistical methods and formulas used;

iii. Results of statistical analysis and estimated expiration dating period.

Berlex proposes to include the requested information when we amend our application with the — month stability data for the primary stability batches.

Biopharmaceutics:

Were in vitro drug release studies (such as Franz cell drug release test) done for "15% gel" for the purpose of comparison between clinical and to-be-marketed formulations and/or for the quality control of its manufacturing? If so please provide us with the location of the report in the original NDA submission.

In vitro drug release studies have not been performed with the to-be-marketed formulation (SH H 655 BA) because that formulation is the same as the formulation used in the important clinical, clinical pharmacology, and pharmacokinetic studies *(Summary – pages 24-26)*.

In all but one of the listed important clinical studies, one drug product batch has been used (batch No. 03002). This batch is a production batch and is one of the three primary stability batches for which data and batch records were provided in the NDA. Batch 03002 was manufactured and packaged in the same facility (Milan, Italy) and using the same equipment that will be used for the commercial product. Furthermore, the manufacturing process is nearly identical to the process that will be used for the commercial process (reference in original NDA: *CMC \ Batch *

44introduction [see page 3]). A copy of the cited pages is provided for the convenience of the Reviewer.

In Protocol . ——— (Report AU36), a ⟨ batch of the same drug product formulation was used (batch No. DA0171). Batch No. DA0171 was manufactured at — of production scale in the — plant (Berlin, Germany) using the same type of equipment and essentially the same manufacturing process that will be used for the commercial process.

Because the batches used in the important clinical studies are essentially the same as the product that will be marketed, and there have been no modifications that would have an influence on the release behavior of the product, we have not performed comparative *in vitro* drug release studies with this formulation. Furthermore, we have not performed *in vitro* drug release studies for the purpose of evaluating the quality control of manufacturing. However, should we wish to provide for formulation changes in the future, comparative in vitro release testing data (such as the Franz cell drug release test) will be generated and submitted in accordance with the May 1997 SUPAC guidance for non-sterile semisolid dosage forms.

Clinical

Regarding section 12, Safety Tabulations which are subsets of the COSTART/MEDRA preferred terms. Please provide a complete listing of the local AE' by preferred terms/LLT.

The requested listing of cutaneous adverse events by preferred term and body system for all studies is provided.

With this electronic submission, Berlex believes that we have addressed all outstanding FDA requests to date. 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

JJH/020

BERLEX

TELEFAX AND UPS OVERNIGHT

NDA ORIG AMENDMENT
BM

May 30, 2002

Drug Development & Technology
Division of Berlex Laboratories, Inc.

340 Changebridge Road
P.O. Box 1000
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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

RECEIVED
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MAY 3 1 2002
CDR/CDER

Re: NDA 21-470
FINACEA™ (azelaic acid gel) 15%
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% for use as a topical application in the treatment of inflammatory papules and pustules of rosacea. Further reference is made to a telephone conversation on May 17, 2002 between the undersigned and your representative, Mr. Frank Cross, during which Mr. Cross requested that an electronic copy of the statistical analysis plan be submitted to NDA 21-470.

In accordance with this request, enclosed is 1 diskette, which contains the following 3 documents:

1. Analysis Plan for Protocol 304342 / 304344
2. Analysis Plan Amendment 1
3. Analysis Plan Supplement 1

Please note that all of the above-noted documents pertain to both phase III protocols. Protocols 304342 and 304344 were identically designed studies, except that Protocol 304342 was amended to include measurements of steady-state plasma concentrations from 1 study center.

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

Sincerely,

BERLEX LABORATORIES

John Hegarty

ORIGINAL

John Hegarty
Regulatory Associate
Drug Regulatory Affairs

JJH/019

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: May 15, 2002 Number of Pages (including cover sheet) – 2
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 requests:

Chemistry, Manufacturing and Controls:

1. Complete description of the container/closure system used to package the primary stability batches. The applicant should include packaging components, supplier and DMF reference.

2. Regarding the primary stability data submitted in the NDA in support of the shelf-life expiration date:

   a. The Applicant should submit stability data in the attached table format.

   b. The following data analysis of quantitative parameters should be included:

      i. Evaluation of data, plots, and/or graphics;

      ii. Documentation of appropriate statistical methods and formulas used;

      iii. Results of statistical analysis and estimated expiration dating period.

Biopharmaceutics:

Were in vitro drug release studies (such as Franz cell drug release test) done for "15% gel" for the purpose of comparison between clinical and to-be-marketed formulations and/or for the quality control of its manufacturing? If so please provide us with the location of the report in the original NDA submission.

Clinical:

Regarding section 12, Safety Tabulations which are subsets of the COSTART/MEDRA preferred terms. Please provide a complete listing of the local AE' by preferred terms/LLT.

Thank you.

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

Stability Raw Data for Drug Product X, Batch Y

Product Name/Strength	Study Number	Purpose of Study
Batch Number	Batch Size	Date Study Started
Date Manufactured	Manufacturer/Site	Container/Size/Supplier
Date Packaged	Packager/Site	Closure Supplier
Storage Condition	Storage Orientation	Seal Supplier

Drug Substance Manufacturer/Site/Batch Number
Approved/Proposed Expiration Dating Period

Attributes	Method	Specification	Time (Months)							
	SOP #	(Low/High)	0	3	6	9	12	18	24	etc.
Appearance										
Assay										
Degradation Product A										
Degradation Product B										
Degradation Product C										
etc.										

BERLEX

TELEFAX AND UPS OVERNIGHT

SUPPL NEW CORR

Drug Development & Technolog
Division of Berlex Laboratories, Inc.

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

May 14, 2002

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MAY 15 2002
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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
MAY 16 2002
MEGA/CDER

Re: NDA 21-470
FINACEA™ (azelaic acid gel) 15%
GENERAL CORRESPONDENCE

Dear Dr. Wilkin:

Please refer to the teleconference with representatives of the Division of Dermatological and Dental Drug Products (DDDDP) and the Office of Generic Drugs (OGD), and the undersigned on May 8, 2002, and the request for Berlex to provide the rationale for submitting NDA 21-470 as a 505(b)(2) application. NDA 21-470 was submitted on March 20, 2002, for FINACEA™ (azelaic acid gel) 15% for use as a topical application in the treatment of inflammatory papules and pustules ——— of rosacea.

It has always been Berlex's intent to submit NDA 21-470 as a 505(b)(2) application. This was discussed with the Division at the Pre-IND/End of Phase 2 meeting held on September 27, 2000 and at the Pre-NDA meeting of August 30, 2001. As described in our pre-meeting packages for both meetings, Berlex's intent was to rely on nonclinical and human pharmacokinetic and biopharmaceutics studies submitted in Allergan Herbert's NDA 20-428 for Azelex® (azelaic acid (AzA) 20% cream) approved for the treatment of acne.

Based on agreements and direction provided by the Division in meetings and in teleconferences, Berlex proceeded to conduct the necessary studies for NDA 21-470. All requested studies were performed and specifically concerning biopharmaceutics, the Division confirmed this during the August 30, 2001, Pre-NDA meeting as stated in the minutes, "A review of the information presented in the meeting package suggests that the Sponsor has completed all of the information requests made during the September 2000 meeting."

Since AzA 15% gel is different from AzA 20% cream, the referenced product, in terms of indication, formulation and concentration, 2 adequate and well-controlled studies were conducted under IND 61,324 to demonstrate the safety and effectiveness of AzA 15% gel.

ORIGINAL

Berlex Laboratories believes it is appropriate to rely on the data in NDA 20-428 for the following reasons:

Azelaic acid, the active ingredient in AzA 15% gel, is naturally occurring in food, and endogenously formed from fatty acids. NDA 21-470 provides for AzA 15% gel in rosacea and has the same drug substance with the same synthesis and manufacturer as approved in NDA 20-428 for AzA 20% cream for the treatment of acne.

There is no generally accepted methodology for establishing bioequivalence for topical drugs. In addition, bioavailability based on plasma concentrations of AzA is established with both exogenous and endogenous AzA, only one of which is controllable. All data that have been generated attempting to measure AzA in blood show a large intraindividual variation over time, and interindividual variation within the expected concentration range.

Based on this background, the following establishes a bridge from AzA 20% cream in acne to AzA 15% gel in rosacea:

1. **Comparison of bioavailability of AzA from 2 different studies with AzA 20% cream in acne, and with AzA 15% gel in rosacea**

- Bioavailability and ADME parameters for AzA after topical application of AzA 20% cream in healthy volunteers and acne patients are established in NDA 20-428.

- As requested by the FDA, during the March 30, 2001 teleconference with Dr. Dennis Bashaw regarding bioavailability data required from the topical application of AzA 15% gel i rosacea patients, our phase III protocol was amended to provide these data and is includec in our NDA submission.

In acne patients, topical application of AzA 20% cream for 12 weeks did not increase plasma AzA concentrations above baseline. In healthy volunteers, topical application of AzA 20% cream had an AzA plasma concentration increase of about 2.5–fold over baseline concentratio after 8 days of treatment. In rosacea patients, no baseline data are available. Pretreatment plasma AzA concentrations in rosacea patients on drug for 8 weeks were higher than for vehicle-treated patients, and increased after topical application of AzA 15% gel. The values fo all 3 studies were within the same range, and within the range observed in healthy volunteers on a regular diet, without AzA treatment.

2. **Data from a study comparing urinary excretion after topical application of AzA 15% gel and AzA 20% cream in acne patients**

This was a comparative trial demonstrating that the urinary excretion data of AzA over 8 weeks of facial treatment were within the same range for both treatment groups and in the range of endogenous daily urinary excretion established in healthy volunteers with or without topical treatment with AzA 20% cream.

In conclusion, based on the pharmacokinetic data provided in both NDAs, the FDA can evalua NDA 21-470 based on the safety and efficacy data provided. We maintain that a 505(b)(2) application as provided for under 21 CRF §314.54(a) is applicable to NDA 21-470. If the

Division disagrees that NDA 21-470 can be filed as a 505(b)(2) application, Berlex requests a teleconference with the Division to discuss the fileability of NDA 21-470 prior to May 20, 2002.

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

JJH/letter/finacea 014.doc

Cross Jr, Frank H

From: Gautam Basak, Mamta
Sent: Thursday, April 25, 2002 10:41 AM
To: Riley, Bryan S
Cc: Cross Jr, Frank H
Subject: RE: NDA 21-470

Bryan,

Meeting is rescheduled for 8th May. I also wanted to let you know that Neal Sweeney was involved at the pre-NDA meeting for this product (IND 61,324).

- Mamta

-----Original Message-----
From: Riley, Bryan S
Sent: Thursday, April 25, 2002 10:38 AM
To: Cross Jr, Frank H
Cc: Gautam Basak, Mamta; Decamp II, Wilson H; Vidra, James D; Cooney, Peter H; Tuegel, Patricia J
Subject: RE: NDA 21-470

Frank,

After further review of the application, it appears to have the required product quality microbiology elements and is therefore filable as far as we are concerned. Please let me know the outcome of the filing meeting on Monday.

Thanks,
Bryan

-----Original Message-----
From: Cross Jr, Frank H
Sent: Wednesday, April 24, 2002 3:31 PM
To: Riley, Bryan S
Cc: Gautam Basak, Mamta; Decamp II, Wilson H; Vidra, James D; Cooney, Peter H; Tuegel, Patricia J
Subject: RE: NDA 21-470

Thanks,

Frank

-----Original Message-----
From: Riley, Bryan S
Sent: Wednesday, April 24, 2002 3:08 PM
To: Cross Jr, Frank H
Cc: Gautam Basak, Mamta; Decamp II, Wilson H; Vidra, James D; Cooney, Peter H; Tuegel, Patricia J
Subject: RE: NDA 21-470

Frank,

I've taken a quick look at the application and it looks to be filable from a micro standpoint. I'll take a closer look tomorrow and let you know if there are any problems. I probably won't come to the filing meeting unless there is something wrong with the application.

Bryan

-----Original Message-----
From: Cross Jr, Frank H
Sent: Wednesday, April 24, 2002 3:01 PM
To: Tuegel, Patricia J; Riley, Bryan S
Cc: Gautam Basak, Mamta; Decamp II, Wilson H; Vidra, James D; Cooney, Peter H
Subject: RE: NDA 21-470

NDA DRUG AMENDMENT
BN

BERLEX

UPS SECOND DAY AIR

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APR 23 2002
MEGA/CDER CONSOLER

APR 19 2002

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

April 18, 2002

Jonathan Wilkin, MD, Director
Food and Drug Administration
Center for Drug Evaluation & Research
Division of Dermatologic and Dental Drug Products – HFD-540
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

Re: NDA 21-470
FINACEA™ (azelaic acid gel) 15%
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% for use as a topical application in the treatment of inflammatory papules and pustules of rosacea. Further reference is made to a telephone conversation with Mathew Thomas, MD of the Division of Scientific Investigations and the undersigned on April 11, 2002. Dr. Thomas requested the following information for each study site in the pivotal studies for NDA 21-470:

1. Name and address of Investigator
2. Number of patients screened
3. Number of patients enrolled
4. Number of patients who completed
5. Number of patients considered evaluable
6. Number of patients who experienced an AE
7. Total number of AEs

Since NDA 21-470 was submitted in electronic format, the requested information was likewise 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. Enclosed is 1 compact disk (CD), which Berlex Laboratories, Inc. certifies has been scanned for viruses using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54 and is virus free.

The requested information is provided on the CD in tabular format for Protocols 304342 and 304344, entitled "A 12-week, randomized, double-blind, multicenter study comparing the clinical efficacy and safety of Azelaic Acid 15% gel (SH H 655 BA, Finevin™ –Gel) with its vehicle in patients with moderate, papulopustular facial rosacea". Please see Table 1 for information regarding study 304342 and see Table 2 for information regarding study 304344.

ORIGINAL

As per Dr. Thomas' request, this submission also specifies who conducted the monitoring and auditing of the clinical studies.

- Study monitoring of all clinical sites was conducted by [redacted] contract research organization (CRO). Please note that on January 15, 2002, [redacted] changed their corporate name to [redacted]
- Berlex Laboratories, the Sponsor of NDA 21-470 conducted audits of the clinical study sites as specified in the following table:

Protocol No.	Site No.	Audit Dates
304342	2	March 21-22, 2001
	10	April 17-18, 2001
304344	7	April 4, 2001
	15	March 29-30, 2001

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

Sincerely,

BERLEX LABORATORIES

John Hegarty

John Hegarty
Regulatory Associate
Drug Regulatory Affairs

Enclosures

Finacea 010.doc

BERLEX

PS OVERNIGHT

Drug Development & Technology
Division of Berlex Laboratories, Inc.

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

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larch 20, 2002

onathan Wilkin, MD, Director
)ivision of Dermatologic and Dental Drug Products – HFD-540
)ffice of Drug Evaluation V
:enter for Drug Evaluation & Research
J.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-1706

RECEIVED
MAR 2 2 2002
MEGA/CDER

Re: NDA 21-470
FINACEA™ (azelaic acid gel) 15%
ORIGINAL NEW DRUG APPLICATION

Dear Dr. Wilkin:

Pursuant to Section 505 (b)(2) of the Federal Food, Drug and Cosmetic Act and to 21 CFR §314.50, Berlex Laboratories, Inc. is submitting a New Drug Application for FINACEA™ (azelaic acid gel) 15% for use as a topical application in the treatment of inflammatory papules and pustules ——— of rosacea.

Electronic Submission

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 1 compact disk with an approximate file size of 675 MB. Berlex Laboratories, Inc. certifies that the CD has been scanned for viruses using *Trend Office Scan Corporate Edition for Windows NT*, version 3.54 and is virus free.

Berlex acknowledges the Division's request at the August 30, 2001 Pre-NDA Meeting for paper desk copies of various portions of the NDA. However, as per a telephone conversation on February 19, 2002, between the undersigned and your representative, Commander Frank Cross, Berlex was informed that the Division would not need paper desk copies until after the Division determines whether the NDA will be filed. Based on that conversation, the only documents included in this submission on paper are the required Items with original signatures (eg. FDA Form 356h, Items 13-14 and 16-18).

DA Application Fee

ne Application Fee totaling $313,320.00, which represents full payment of the FY 2002 pplication Fee associated with NDA 21-470, was transferred to the FDA account at the Mellon ank on February 8, 2002. It has been confirmed that the FDA User Fee Staff received the pplication Fee on February 12, 2002. User Fee ID No. 4262 has been assigned to this pplication.

ection 505 (b)(2) of the FD&C Act

lthough the results presented in this NDA are primarily derived from studies conducted by erlex Laboratories or it's parent company Schering AG, the sponsor believes that a number of tudies conducted by Allergan Herbert contain important information for which neither Berlex aboratories nor Schering AG has obtained a specific letter of reference or use. Accordingly, ursuant to Section 505 (b)(2) of the Food, Drug and Cosmetic Act and 21 CFR §314.54, Berlex aboratories requests that the Agency refer to NDA 20-428 for additional information.

his NDA contains all available reports of all clinical studies conducted with AzA 15% Gel by chering AG (including Berlex Laboratories) for all indications (eg. rosacea, acne vulgaris).

ince AzA 20% cream is approved in the US (NDA 20-428), this NDA does not describe all linical studies conducted with AzA 20% cream. The studies not included pertain to patient opulations with acne vulgaris or melasma. However, all studies conducted with AzA 20% ream pertaining to rosacea patients are included.

Commercial Marketing History

Currently, azelaic acid is approved and marketed in the United States under NDA 20-428 as a topical 20% cream (Azelex®/ Finevin™) for the treatment of mild to moderate inflammatory acne vulgaris. Berlex Laboratories is an approved distributor of Finevin™ (azelaic acid cream) 20% under NDA 20-428, which is held by Allergan Inc, Irvine, CA. Since 1988, azelaic acid 20% cream has been authorized for marketing in over 86 countries worldwide and marketed in 79 countries for the treatment of mild to moderate acne vulgaris, and melasma.

Azelaic acid 15% gel is approved in Australia and the Czech Republic for treatment of acne vulgaris, and in Switzerland for the treatment of mild to moderate acne vulgaris. No foreign applications have been submitted for the treatment of rosacea.

Proposed Tradename

FINACEA™ (azelaic acid gel) 15% is the proposed tradename for this product in the United States. On November 20, 2001, a request for a pre-marketing review of the proposed Tradename was submitted to IND 61,324 [Serial No. 021].

laimed Exclusivity

erlex is claiming a period of 3 years of marketing exclusivity for FINACEA™. A "Statement of laimed Exclusivity" has been included in Item 20, Other.

Inancial Information

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

ediatrics Waiver Request

erlex Laboratories has requested a waiver ("pediatrics waiver request") from the requirement o assess the safety and effectiveness of the drug product in the pediatrics population on the asis that rosacea is a disease that has a low incidence in the pediatric population. The ediatrics waiver request is located in Item 20 of this NDA.

FDA / Sponsor Interactions

Copies of Pre-IND and Pre-NDA meeting minutes as well as review comments from the Division are provided in Item 20, Other of this NDA.

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

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

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

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
Azelaic Acid Gel, 15%

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? 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).

5. USER FEE I.D. NUMBER
4262

6. LICENSE NUMBER / NDA NUMBER
NDA 21-470

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, on 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)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Geri A. Breita	Manager, Regulatory Submissions and Information	02/06/02

FORM FDA 3397 (5/98)

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: February 5, 2002 Number of Pages (including cover sheet) – 1

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

MESSAGE: Comments from our Chemistry Review of your IND 61,324, N020, Azelaic acid gel, 15%, follow:

1. Bulk drug product is collected [redacted] In-process controls should include visual examination under a microscope for any [redacted]

2. Based on the summary report it can not be concluded that the container/closure that will be used for the proposed studies is compatible with Metrogel. Stability data including protocol should be provided.

   In the absence of data an alternative approach (e.g., using Metrogel in its approved container, 45 g tube [redacted] may be used for blinding instead of repackaging of the approved product in a different container.

3. Metronidazole gel is a USP compound and repackaged product should meet the current USP specifications.

4. Available stability data for the repackaged Metrogel product that will be used in the proposed studies described in amendment of October 10, 2001 should be provided. At a minimum one month of stability data should be submitted in the IND before the initiation of the proposed phase 3 studies.

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

/s/

Frank Cross
2/5/02 04:26:31 PM
CSO
Faxed to Sponsor on 2/5/02.

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: August 31, 2001. Number of Pages (including cover sheet) – 9
TO: John J. Hegarty, Regulatory Associate, Drug Regulatory Affairs
COMPANY: Berlex Laboratories
FAX#: 973-487-2016

MESSAGE: RE: IND 61,324 - Azelaic Acid Gel, 15% - Pre NDA meeting minutes dated 8/30/01.

A copy of our meeting minutes is enclosed. The external constituents are responsible for notifying CDER of any significant differences in their understanding of the meeting outcomes (as reflected in the minutes).

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

MEMORANDUM OF MEETING

Meeting Date: August 30, 2001. Location: S-400 Meeting ID: 7373 Time: 1:00 pm

Sponsor: Berlex Laboratories, Inc.

IND: 61,324

Purpose: Pre NDA Meeting

Drug: Azelaic Acid Gel, 15%

Proposed Indication: For the treatment of papulopustular rosacea

Meeting Chair: Dr. Jonathan Wilkin, Director, Division of Dermatologic and Dental Drug Products

Meeting Recorder: Olga Cintron, R.Ph., Project Manager, Division of Dermatologic and Dental Drug Products

FDA Attendees:
Jonathan Wilkin, M.D., Director, DDDDP, HFD-540
Wilson DeCamp, Ph.D., Chemistry Team Leader, HFD-830
Neal Sweeney, Ph.D., Microbiologist, HFD-805
Barbara Hill, Ph.D., Pharmacology/Toxicology Reviewer, DDDDP, HFD-540
Abby Jacobs, Ph.D., Pharmacology/Toxicology Team Leader, DDDDP, HFD-540
Dennis Bashaw, Pharm. D., Biopharmaceutics Team Leader, HFD-880
Jang-Ik Lee, Pharm.D., Ph.D., Biopharmaceutics Reviewer, HFD-880
Brenda Vaughan, M.D., Clinical Reviewer, DDDDP, HFD-540
Hon-Sum Ko, M.D., Acting Clinical Team Leader, DDDDP, HFD-540
Mohamed Alosh, Ph.D., Biostatistics Team Leader, HFD-725
Olga Cintron R.Ph., Project Manager, DDDDP, HFD-540

Sponsor Attendees:
Susan Kummerer, M.S., Director, Drug Regulatory Affairs, Berlex Laboratories
Ruth Thieroff-Ekerdt, M.D., Director, Clinical Development Dermatology, Berlex Laboratories
Klaus Graupe, Ph.D., Senior Clinical Associate, Schering AG
Knut Richert, Dipl.-Stat., Senior Biometrician, Dermatology, Schering AG
James Wong, Ph.D., Director, Clinical Pharmacology, Berlex Laboratories
Nancy Bower, M.S., Manager, Toxicology, Berlex Laboratories
John Hegarty, M.S., Regulatory Associate, Drug Regulatory Affairs, Berlex Laboratories
Jo-Ann Ruane, B.S., Manager, Drug Regulatory Affairs, Berlex Laboratories
Jeffrey Farkas, M.S., Manager, Quality Control Laboratory, Berlex Laboratories
Hans-Joachim Zentel, Ph.D., Director, Project Management, Dermatology, Berlex Laboratories
Suleman Verjee, Ph.D., Senior Director, Biostatistics and Site Director for Clinical Operations, Berlex Laboratories

IND 61,324
Pre NDA Meeting

With reference to the Sponsor's briefing package dated August 2, 2001, the Agency provided the following comments:

CHEMISTRY:

We have a concern about Berlex' response to one of the CMC Regulatory History questions. There is no assurance that the supplier of azelaic acid obtains the active ingredient from non-BSE countries. The response is not adequate, "....is not derived from animals coming from countries known to have cattle afflicted with BSE" (pg. 44). The source should be from United States, New Zealand or Australia.

Since the manufacturing facility for the drug substance is in Germany, and the drug product manufacturing is in Milan, Italy, both of which are BSE countries, these facilities be "dedicated facilities". For clarification, a "dedicated facility" must be separated from any facility used for materials derived from cattle born, raised, or slaughtered in BSE countries or OIE-failing countries.

Responses to CMC questions in the pre-NDA Briefing Document

Sponsor's question #1: Does the Division agree that the information submitted in the Type II DMF for azelaic acid, including the regulatory specifications, is adequate for the NDA?

Agency's response:

The proposed specification for the drug substance submitted (Vol. 1, page 45) appears to be reasonable. The acceptability of the information in the DMF is a review issue. However, the referenced DMF is only for the [redacted] the original source should be identified from the holder of DMF and reference authorization obtained and provided in the NDA for the appropriate DMF.

Sponsor's question #2: Does the Division agree that [redacted] can be considered a noncompendial excipient and the testing according to the EP monograph for carbomers is acceptable?

Agency's response:

This is a review issue. [redacted] appears to be [redacted] Please provide information to substantiate this. The product specification is included in Appendix 3. The application should include a side by side comparison of the EP and NF testing.

Sponsor's question #3: Considering that the 3- and [redacted]-gram sizes are packaged in the identical tube, and considering the substantial body of stability data that will be submitted in the NDA for the [redacted]-gram tube, does the division agree that stability data from one batch of the 3-gram size will be adequate to demonstrate the stability of the product in the packaged size?

IND 61,324
Pre NDA Meeting

Agency's response:

This is a review issue, and will depend upon the quality and consistency of the results of the stability studies.

Sponsor's question #4: Does the Division agree that the described stability data will be sufficient to support the proposed expiration dating period for the 3-, 30-, and 50-gram packages?

Agency's response:

This is a review issue and can only be answered after evaluation of the data submitted.

In response to a Sponsor question, it was clarified that it would be necessary to evaluate the data for all sizes as submitted in the NDA. The 3 gm size, as a sample size, is outside the range of sizes that are bracketed (i.e., — to 50 gm). However, since this is a sample size, it is of somewhat less concern than marketed sizes. As a supplemental application, this addition would be acceptable with very limited data, provided that the container/closure used the same materials as the larger size. There would be a greater need for up-front stability data if a different container/closure (e.g., a pouch) were used.

Sponsor's question #5: Does the Division agree that the described NDA amendment is sufficient to support the —gram fill size and that this amendment can be filed during the review period (*i.e.*, not less than 3 months before the NDA action dates) without affecting the review clock?

Agency's response:

Yes, since the — gram size tube is proposed to be from the same suppliers and made of same materials as the tubes used to package primary stability batches (Vol. 1, page 59). Therefore, this size may be considered to be bracketed between the sample sizes and the larger marketed sizes, as long as the sample sizes are packaged in the same materials as the marketed sizes. However, the amendment should be filed not later than four months after the submission of the NDA.

Sponsor's question #6: Does the Division concur that, based on the summary information presented, the CMC information will be acceptable for filing?

Agency's response:

A commitment on this point cannot be given at this time. However, we see no obvious fileability issues in the briefing book.

MICROBIOLOGY (CMC):

Sponsor's question: Does the Division concur that, based on the summary information presented, the Microbiology information will be acceptable for filing?

IND 61,324
Pre NDA Meeting

Agency's response:

From the CMC Microbiology standpoint, information concerning Microbial Contamination (regulatory specification and test method, stability results), container-closure integrity test results, and Antimicrobial Effectiveness validation for the drug product are sufficient for filing.

PHARMACOLOGY/TOXICOLOGY:

Sponsor's question: Does the Division concur that the type, duration, and overall design of the nonclinical studies conducted and available pursuant to Section 505 (b) (2) of the Food, Drug, and Cosmetic Act and 21 CFR 314.54 is sufficient to support the filing of AzA gel, 15%?

Agency's response:

The studies conducted to date along with the dermal carcinogenicity and photoco-carcinogenicity studies being proposed as phase 4 commitments are adequate to support the submission of the 15% azelaic acid gel NDA from a pharmacological/toxicological perspective. The actual fileability of the NDA from a pharmacological/toxicological perspective will be determined upon the preliminary review of the information submitted with the NDA.

It is recommended that the Sponsor include information concerning the conduct of the dermal carcinogenicity study in TG.AC mice and the photoco-carcinogenicity study in mice with the NDA submission. In addition, it is recommended that the sponsor include a proposed timeline for completion of these studies as phase 4 commitments with the NDA submission.

It is important to note that the results of the dose range-finding study and the protocol for the definitive dermal carcinogenicity study in TG.AC mice should be submitted to the IND for review. After completion of the review of this dose range-finding study, then the results and the protocol for the definitive study will be presented to the Executive Carcinogenicity Assessment Committee for possible concurrence.

It is important to note that the results of the dose range-finding study and the protocol for the definitive photoco-carcinogenicity study should be submitted to the IND for review. Photoco-carcinogenicity study protocols do not undergo analysis by the Executive Carcinogenicity Assessment Committee at this time. The division will make the final determination of the adequacy of the dose-range finding study and the protocol for the definitive study. The results of this determination will be shared with the sponsor upon completion.

BIOPHARMACEUTICS:

A review of the information presented in the meeting package suggests that the Sponsor has completed all of the informational requests made during the September 2000 meeting. We note that according to the document the data from the population pharmacokinetic trial is

still incomplete. When will these results be available? The Sponsor indicated that the data are complete and are being analyzed at present.

CLINICAL:

Sponsor's question: Does the Division concur that the Clinical/Statistical program is sufficient to support NDA filing for the proposed indication, dosage and duration of treatment?

Agency's response:

- For NDA filing, the Division recommends that safety and efficacy be demonstrated with two independent, multicenter, randomized, double-blind, parallel group, vehicle controlled clinical studies. The Sponsor has identified two clinical studies (Protocols 304342 and 304344) that appear to satisfy this filing recommendation; however, indication, dosage, and duration of treatment are review issues.

- Additionally, data from the following topical safety studies conducted with the "to-be-marketed formulation" are needed for NDA filing:

  - [redacted]
  - [redacted]

[redacted]

Additional comments:

- (Item 8, Vol. 1., Section 8. Clinical, page 112) The sponsor's response to the clinical comments regarding the Phase 3 protocols is noted.

- Primary efficacy endpoints for the rosacea indication were discussed at the September 27, 2000 End-of-Phase 2 Meeting. Additional comments were provided regarding Protocol 304342. In addition to the analysis proposed by the sponsor, please provide in the NDA an analysis based on the ITT-LOCF population (as defined by the Agency) for the following primary efficacy endpoints:

  - change in inflammatory lesions from baseline at the end of study and
  - the proportion of patients in the active group vs. the vehicle group who achieved a static global assessment score of 0 (clear) and 1 (minimal) at the end of study as described in the Investigator's Global Assessment Score Table (pg. 6 026, Vol. 1.1, IND 61,324, Serial No.000, Protocol 304342) provided in the IND submission.

- (Appendix 1, Vol. 1, Study Endpoints, 2.2 Secondary Efficacy, pg. 173) The Sponsor has proposed multiple secondary efficacy endpoints. There were no agreements with the Division regarding the secondary efficacy endpoints. The relevance of these

secondary efficacy endpoints will be a review issue. Biostatistics will provide additional comments regarding the secondary efficacy endpoints.

- (Appendix 1, Vol. 1, Populations, 4.3 MITT, pg. 177)
  The Sponsor proposes a Modified Intent-to-Treat population defined as all patients who were randomized, dispensed study medication and who had a pre-treatment washout of ≥ 4 weeks from all topical and systemic rosacea treatment, corticosteroid, anti-inflammatory, and antibiotic medications. The purpose of assessment of a MITT population is unclear and is somewhat unusual for the rosacea indication. Please provide in the NDA a rationale for this assessment and date of the protocol amendment addressing the modified statistical plan.

- In addition to providing Case Report Forms (CRF) for deaths, and discontinuations due to adverse experiences, please provide CRFs for the following:

  a. serious adverse experiences
  b. all drop-outs
  c. a copy of a blank CRF

- (Appendix 16.2.6, Listing of Baseline Clinical Characteristics) Please add the investigator's global assessment score at baseline to the Listing of Baseline Clinical Characteristics.

- (Appendix 16.2.11, Listing of Facial Lesion Count) Please add the investigator's global assessment score to the Listing of Facial Lesion Count Table.

- To facilitate the review process, it is helpful to submit a paper desk copy of the clinical section. To facilitate the review process, please submit electronic copies of text and in-text tables in MS Word 97 files for the following sections:

  Package Insert
  Application Summary
  Clinical Data Section (excluding appendices)
  Clinical Study Protocols
  Clinical Study Reports
  ISS and ISE

BIOSTATISTICS:

In response to the Sponsor's question on whether the Clinical/Statistical program is sufficient to support NDA filing, the Sponsor's plan appears to be sufficient for filing from a statistical point of view. In preparing the NDA submission, please consider the following comments when presenting the statistical analysis results:

1. The Sponsor listed two primary endpoints: a) change from baseline to Week 12 in inflammatory facial papules and pustules counts and b) the investigator's global assessment of the severity of papulopustular rosacea. Following the Division's comments at the Pre-IND EP2 meeting, efficacy results for the investigator global

assessment based on the final score (categorized as success/failure) should also be submitted. For the threshold for success/failure refer to the clinical comments.

2. The Sponsor listed several — secondary efficacy variables for analysis; it should be noted that the Division did not have agreement concerning the appropriateness of these secondary endpoints at the Pre-IND/EP2 meeting. Consequently the utility of these secondary endpoints are a review issue. However, it should be noted that if the proposed secondary endpoints are deemed relevant, then an adjustment for multiplicity should be carried out. Such an adjustment would be needed since if the number of comparisons is large it is likely that one or more secondary endpoints reach statistical significance due to chance alone.

3. The Sponsor's approach for handling missing data in the ITT analysis implies that the LOCF would be applied only for patients who have post baseline measurements. As recommended in previous statistical comments, efficacy results for all randomized patients with LOCF including those who do not have post baseline measurements should be included as well.

4. The proposed statistical methodology for analysis of change from baseline for the inflammatory lesion counts is the Analysis of Covariance with study center and treatment as factors and baseline as covariate. As analysis of change takes into account baseline counts, please provide efficacy results without including the baseline as a covariate in the model. The Sponsor statistical methodology (page 123) does not make reference to the inclusion of center-by-treatment interaction term in the model, whereas the analysis plan of the protocol (page 179) indicates that such analysis will be performed in separate model. Please clarify. The ANCOVA model should test for center-by-treatment interaction.

5. A summary of efficacy results by age (compare above and below age 65 years), race and gender should be provided as well as a summary of efficacy results by center.

6. The NDA submission should include the patient's treatment allocation assignment along with details on how the randomization was carried out. The baseline / demographic data should include date and time of enrollment in the trial.

7. Please include in the NDA submission a copy of the original signed and dated protocol as well as any amendment to the protocol and/or the statistical analysis plan.

8. Please include in the NDA submission SAS data set, as export file, for all primary and secondary endpoints as well as the baseline/demographic data.

9. Electronic NDA submission should be acceptable as long as it is readable and easy to navigate. However, a hard copy of volume I which includes summary description of the studies and their efficacy results, along with original signed protocol and its amendments and the randomization schedule showing treatment assignments, should be provided.

IND 61,324
Pre NDA Meeting

Administrative comments:

Sponsor's question: It is currently planned to submit the NDA in electronic format in accordance with the January 1999 Guidance "Providing Regulatory Submissions in Electronic Format – NDAs". Berlex plans to use CoreDossier X Publishing Software version 5.02 with the FDA Compiler version 3.0. Does the Division agree with this proposal?

Agency's response:

It is acceptable to use the stated software to generate the electronic NDA as long as the NDA is easily navigable using the version of Adobe Acrobat Exchange (version 4.0) that the Agency is currently using. The Sponsor is advised that if the electronic NDA is not easily navigable or not readable using the version of Adobe Acrobat Exchange (version 4.0) that the Agency is currently using, this may become an NDA filing issue.

Additional comments:

1. It is recommended that a paper copy of Volume 1 only of the NDA be included with the electronic NDA submission for all review disciplines for tracking purposes. (Please refer to clinical and biostatistical comments for additional requests)

2. Please provide an additional paper copy of the volume that will include the microbiology information.

3. Please provide 3 paper copies of the Methods Validation package at the time of NDA submission.

4. It is noted that the Sponsor plans to request a waiver to the Pediatric Rule requirements since rosacea is a disease that does not occur in the pediatric population. The Sponsor is reminded that they should submit a rationale to support the waiver.

5. It is noted that the Sponsor plans to comply with the Financial Disclosure requirements. The Sponsor is referred to the following website address for additional information: http://www.fda.gov/cder/guidance/index.htm.

6. If the Sponsor has an Information for Patients leaflet/labeling, please submit it with the NDA.

When is the Sponsor planning to submit the NDA? The Sponsor indicated that the NDA will be submitted on December 20, 2001.

The meeting ended amicably.

Meeting Recorder:_____

Meeting Chairperson:_____

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

/s/

Jonathan Wilkin
8/30/01 04:16:07 PM

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: May 8, 2001. Number of Pages (including cover sheet) – 2
TO: Ms. Maria Garrigan, Manager, Drug Regulatory Affairs
COMPANY: Berlex Laboratories
FAX#: 973-487-2016

MESSAGE: RE: IND 61,324, Serial Number 000 Finevin Gel, 15%

Comments from clinical and biostatistics on the above mentioned submission follow:

Clinical:

1. A minimum of eight (— and a maximum of fifty (—) inflamed papules and/or pustules are permitted for study inclusion. A minimum of — lesions are recommended at entry since it may be difficult to demonstrate statistical superiority with less than — lesions.

2. As discussed during the EP-2 meeting, washout periods should reflect the pharmacology of the drug. The washout periods for topical therapy of at least two weeks are listed below. Traditionally, the following washout periods have been suggested:

   Topical —— treatment - 4 weeks
   Topical or systemic corticosteroids - 4 weeks
   Topical or systemic anti-inflammatories - 4 weeks
   Topical or systemic antibiotics - 4 weeks

3. Withdrawal for insufficient therapeutic efficacy was also discussed during the EP-2 Meeting. Even if demanded by the patient, the patients who withdraw from the study for insufficient therapeutic efficacy should be deemed a failure and followed for safety assessment.

4. The sponsor provided a static —-point scoring scale for the investigator's global assessment of rosacea. There appears to be minimal differences between some of the categories (e.g., minimal/mild, moderate/moderate to severe, etc.); therefore, a static 4 or 5 point scale is recommended to reduce variability among investigators.

5. Rating of overall improvement by the investigators and patients at the end of study may not have regulatory utility. See statistical comment #2.

6. Please consider adding an opacifying inactive to the vehicle to match the appearance of the active.

Statistical:

1. The sponsor proposes to analyze the change in inflammatory lesion count using an analysis of covariance model, with factors for treatment and center, but no interaction, and the number of lesions at baseline as the covariate. In a prior submission, the sponsor proposed using the percent change from baseline for this endpoint. First, as an aside, it may be noted that ANCOVA using change in absolute count from baseline with baseline absolute count as a covariate is identical to the ANCOVA with absolute counts, except that the coefficient for the covariate in the latter model is incremented by one unit. However, as noted in the Pre-IND/End-of-Phase 2 meeting (see FDA minutes dated 30 October 2000, paragraph 5, page 10) it is recommended that the lesion counts should be analyzed using BOTH absolute counts AND percent change from baseline. Presumably the latter would not require the use of baseline counts as an explicit covariate.

2. As discussed at the Pre-IND/End-of-Phase 2 meeting the investigator's global assessment should be computed as a static measure, assessing the current disease state, not defined relative to the patient's baseline, but defined relative to the physician's overall clinical experience. The sponsor's definition of the global assessment seems to fit these criteria. However, for the analysis the sponsor proposes a dichotomous endpoint that depends both upon the global assessment at endpoint AND the global assessment at baseline. It would seem that a much better approach to the analysis would be a simple binary split of the endpoint global assessment, defining success as say either "clear" or "mild or better." Both tabulations should be included.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
PHONE #: 301-827-2020
FAX #: 301-827-2075/2091

/s/

Olga Cintron
3/22/01 05:27:24 PM
CSO

BERLEX *Laboratories, Inc.*

FDA CONTACT REPORT

Product:	Finevin Gel (azelaic acid, 15%)	**Person Contacted:**	Teleconference (participants listed below)
IND:	61,324	**Division:**	Division of Dermatologic and Dental Drug Products (DDDDP)
Originator:	John Hegarty	**Date of Meeting:**	March 30, 2001

A telephone conference call was held with the Division to clarify the bioavailability requirements for the Finevin Gel (azelaic acid, 15%) NDA for treatment of rosacea.

Participants:

FDA Division of Dermatologic and Dental Drug Products (DDDDP)
Dennis Bashaw, Ph.D. Biopharm Reviewer
Olga Cintron, RHPM

Berlex Laboratories
Maria Garrigan, Drug Regulatory Affairs
John Hegarty, Drug Regulatory Affairs
Susan Kummerer, Drug Regulatory Affairs
Ruth Thieroff-Ekerdt, MD, Clinical Development, Dermatology
James Wong, PhD, Clinical Pharmacology

The Division telephoned at 3:30 PM and the participants introduced themselves. Berlex clarified that the IND was submitted for the indication of rosacea, [redacted], Berlex [redacted]

The Division indicated that it does not appear that an in vivo biostudy for rosacea patients is included in the IND, which Berlex confirmed. The Division indicated that they expect to see an in vivo biostudy for the indication. According to the Division, Berlex has two options:

1. Perform an in vivo biostudy in rosacea patients, or
2. Provide an argument that the body surface area of [redacted] patients would provide a higher bioavailability model, and relying on such a study, would thus satisfy the requirement for rosacea.

Berlex noted that extra-facial rosacea is rare. The Division indicated that [redacted] compared to rosacea, which is usually confined to the face. Also, the skin in [redacted] patients will be more permeable than the skin of rosacea patients.

The Division clarified their proposal in their letter of March 22, 2001 that Berlex should collect steady-state samples to delineate steady-state pharmacokinetics of azelaic acid. The Division theorized that due to the small surface area of rosacea, it is likely that not very much azelaic acid will be absorbed. Berlex mentioned that because azelaic acid is an endogenous compound, one would not expect to

detect levels above the circulating concentrations. The Division agreed and stated that Berlex needs to demonstrate that the circulating pool of azelaic acid is not being disturbed. It may be possible to obtain information regarding the circulating pool of azelaic acid from the literature.

Berlex indicated that all subjects in the ongoing Phase 3 studies have been dosed. The Division indicated that obtaining plasma samples from the ongoing Phase 3 study would be advantageous as these patients are from the same pool, whereas that would not be the case for patients in literature.

Berlex indicated that a peak concentration is not expected, but that the concentrations will probably be near the normal level. The Division suggested that Berlex obtain a trough plasma sample, as well as at 1, 2 and 4 hours to see if the circulating pool of azelaic acid is being disturbed. The Division suggested that about 22 randomized subjects, which should result in 10 to 12 subjects on active treatment, would be sufficient.

Berlex indicated that the phase 3 protocol would be amended.

In closing, the Division relayed the following message from Dr. Barbara Hill, the pharm/tox reviewer of the IND:

The recommended long-term toxicology studies are:

- dermal carcinogenicity,
- photo co-carcinogenicity.

No additional toxicology studies including reproduction tox studies are recommended.

Berlex thanked the Division and the teleconference concluded at 3:40 PM.

Rosacea:

1. The Division recommends the following primary efficacy endpoints for demonstrating efficacy in treatment of rosacea: 1) inflammatory lesion counts (papules and pustules) and 2) the investigator's global assessment. Clinical signs (erythema and telangietasia) should be incorporated into the global assessment.

2. As noted above, the Division recommends that the global evaluation be a static scoring system.

3. Primary variables should be clearly defined in the protocol.

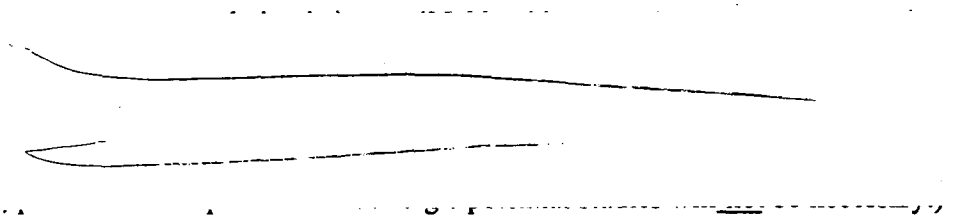
Sponsor's Question #5b, second bullet:

- The appearance of vehicle (translucent) and verum (opaque) differ. This is caused by the incorporation of the active drug substance into the vehicle. The addition of substances to change the appearance of the vehicle may cause galenical and pharmacodynamic changes. To ensure blinding during the study the following procedures are used 1) all tubes are sealed with a metal membrane, i.e. the study treatment can only be used after destruction of this membrane; 2) each tubes is packed in a separate carton; 3) the practice / clinic nurses who are not associated with patient selection and assessment will hand over the cartons to the patients; 4) the patients must return unused or partially used tubes in the cartons to the nurse prior to clinical assessment.

Agency's response: This approach is acceptable. Additionally, quantitating the amount of study drug returned should be documented as a measure of compliance.

Additional comments:

1. The Division recommends the following topical safety studies be conducted with the "**to-be-marketed formulation**" as follows:



2. (pg. 028) The term discoloration should specifically describe the adverse event (e.g., hypopigmentation, hyperpigmentation, etc.).

3. (pg. 025, Section 9.2.5.4-Anti-Inflammatory effect) Labeling claims should be supported by data, for example, any inflammatory effects.

4. Since repeated intermittent use this drug product can be expected; therefore, the Sponsor should follow ICH-E1A Guideline for Industry (The Extent of Population Exposure to Assess Clinical Safety: for Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions) on sample size for patients on the Sponsor's drug

MEMORANDUM OF MEETING

Meeting Date: September 27, 2000. **Location:** S-300 **Time:** 10:00 am

Meeting ID: 6137

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Pre IND/End of Phase 2 meeting

Drug: Finevin (azelaic acid) Gel, 15%

Indications: For the treatment of [redacted] moderate papulopustular rosacea.

Meeting Chair: Dr. Jonathan Wilkin, Director, Division of Dermatologic and Dental Drug Products

Meeting Recorder: Olga Cintron, R.Ph., Project Manager, Division of Dermatologic and Dental Drug Products

FDA Attendees:

Jonathan Wilkin, M.D., Director, DDDDP, HFD-540
Jonca Bull, M.D., Deputy Director, ODE V
Wilson DeCamp. Ph.D., Chemistry Team Leader, HFD-830
Kumar Mainigi, Ph.D., Pharmacology/Toxicology Reviewer, DDDDP, HFD-540
Abby Jacobs, Ph.D., Pharmacology/Toxicology Team Leader, HFD-540
Veneeta Tandon, Ph.D., Biopharmaceutics, HFD-880
Tapash Ghosh, Ph.D., Biopharmaceutics, HFD-880
Martin Okun, M.D., Ph.D., Clinical Team Leader, DDDDP, HFD-540
Brenda Vaughan, M.D., Clinical Reviewer, HFD-540
Steve Thomson, Biostatistician, HFD-725
Mohamed Al-Osh, Ph.D., Biostatistical Team Leader, HFD 725
Albert Sheldon, Ph.D., Clinical Microbiologist, HFD-520
Olga Cintron R.Ph., Project Manager, HFD-540

Sponsor Attendees:

Ruth Thieroff-Ekerdt, M.D., Medical Director, Dermatology, Berlex Laboratories
Klaus Graupe, Ph.D., Senior Clinical Associate, Center of Dermatology, Schering AG
James Wong, Ph.D., Associate Director, Clinical Pharmacology, Berlex Laboratories
Nancy Bower, MS, Research Toxicologist, Berlex Laboratories
Knut Richert, Senior Biometrician, Center of Dermatology, Schering AG
Susan Kumerer, MS Associate Director, Drug Regulatory Affairs, Berlex Laboratories
Maria Garrigan, BS, Regulatory Managar, Drug Regulatory Affairs, Berlex Laboratories
Hans-Joachim Zental, Ph.D., Project Manager, Berlex Laboratories

With reference to the Sponsor's briefing package dated August 21, 2000, the Agency provided the following comments:

CHEMISTRY:

The proposed product is a reduced strength (15% vs. 20%) of azelaic acid (approved under NDA 20-428 as a cream). The bulk drug supplier is the same for both applications. The formulations are substantially different.

1. The description of the product as ' [redacted] is inconsistent with any compendially recognized dosage form. Please refer to the CDER Data Standards Manual (available on the Internet) for dosage form definiotions. Additional information should be developed to establish the appropriate dosage form description. Pending submission of that information, the product may be called a gel with no assurance that this dosage form will be acceptable when an NDA is submitted.

2. On pg. 104, you indicate that the vehicle contains " [redacted] of lecithin, medium-chain triglycerides, and Polysorbate 80." Please clarify if you intend to suggest that these components form a [redacted] and whether you plan to claim any special benefits to this particular ratio of excipients.

3. The CMC section as submitted in the briefing book is sufficient for the original IND submission, except for stability data.

4. Stability data supporting the claim in 11.2.9.4 (pg. 117) should be included in the initial submission.

5. We recommend that a stability protocol be developed and submitted to the IND, if not at the initial submission, then as an early amendment. Stability studies for the developmental batches should follow this protocol.

6. The IND should include appropriate investigational labels.

7. Although azelaic acid can be obtained from plant sources, it can also be obtained from oleic acid isolated from animal fats as a starting material. Please obtain assurance from your supplier that any animal products used in the manufacture of azelaic acid are from non-BSE countries.

8. Please supply absorption spectra in the range of [redacted] for all components of your product.

9. Cross referencing between the [redacted] IND and the rosacea IND is acceptable.

PHARMACOLOGY/TOXICOLOGY:

Sponsor's question #1: Can pharmacology, ADME, and toxicology available in N20-428 for Azelex 20% cream and associated INDs from another Sponsor be used for nonclinical assessment of azelaic acid 15% gel?

Agency's response: Some information for the approved product may be used. Note that studies conducted in support of the approved product may be insufficient by today's standards. It is not clear that the marketed azelaic acid was isolated from plants. It may have been a semi-synthetic product from a nonplant source. Long-term effects of azelaic on the skin have not been described.

Sponsor's question #2: Is information sufficient for a phase 3 study?

Agency's response: It is not clear how much azelaic acid is in the diet. It has been reported that azelaic acid can form as an artifact of urine analyses in small volumes in plastic containers. It has also been reported that azelaic acid is a photochemical reaction product of biogenic fatty acids.

The 5-alpha reductase activity of azelaic acid and its impact on development of the fetus should be addressed in the submission. Inhibition of 5-alpha-reductase activity and resulting fetal genital changes would not be picked up in standard Segment 2 studies. When azelaic acid is used topically, first pass metabolism in the liver is bypassed. Systemic bioavailability data can be used to support a rationale for not being concerned about effects on the fetus.

Sponsor's question #3: Can pharmacology, ADME, and toxicology available in N20-428 for Azelex 20% cream and associated INDs from another Sponsor be used to support marketing of azeleic acid 15% gel?

Agency's response: It is not clear that the marketed azelaic acid is isolated from plants. Rather it may have been a semi-synthetic product. To support marketing, a dermal carcinogenicity, with complete systemic evaluation, and a study to address the photococarcinogenicity potential of the proposed product will be needed. There are mechanisms of enhancing UV carcinogenicity, such as changing the optical properties of the skin, that do not depend on the product absorbing light. Azelaic acid is pharmacologically active in the skin and its carcinogenicity potential in the skin has not been addressed adequately. These studies could be conducted Phase 4.

Sponsor's question #4: Can carcinogenicity studies be waived?

Agency's response: The marketed azelaic acid may have been prepared semisynthetically from a nonplant source and not isolated from plants. The gel formulation is reported to have greatly increased skin biovailability than the marketed cream. To support marketing, a dermal carcinogenicity study will be needed. Azelaic acid is pharmacologically active in the skin and its carcinogenicity potential in the skin has not been addressed adequately.

Sponsor's question #5: Can [redacted] photococarcinogenicity studies be waived?

Agency's response: [redacted] A study to address the photococarcinogenicity potential of the proposed product will be needed. There are mechanisms of enhancing UV carcinogenicity, such as changing the optical properties of the skin, that do not depend on the product absorbing light.

BIOPHARMACEUTICS:

Sponsor's question #4 (under Clinical and Clinical Pharmacology): The Sponsor seeks concurrence that the clinical pharmacology and pharmacokinetic studies performed with AzA 15% gel and the evidence gathered from clinical pharmacology and pharmacokinetic studies conducted for AzA 20% cream are sufficient to support Phase 3 clinical trials and marketing approval of Finevin™ Gel for the proposed indications of mild to moderate acne

Agency's response: Four clinical studies (AQ 86, AQ 87, AE 14, AE 15) were conducted in Europe, ——— for rosacea indications) with 15% gel formulation of azelaic acid (AzA). However none of these studies had any pharmacokinetics component. The Sponsor mentioned a study (——), where AzA 15% gel was compared with AzA 20% cream. However, that study was done on acne patients only and not much detail (e.g, number of patients, dose, frequency and surface area of administration etc) is included in the package. Table 9.2.2, that is supposed to contain the summary of the study is absent in the package. In general as cream and gel are two different dosage forms, we would like the Sponsor to conduct *in-vivo* biostudy in patients with moderate rosacea, consistent with the maximum exposure planned for their clinical trial and proposed labeling. The objective of such a trial would be to determine the extent of absorption of AzA as well as its degradation products/metabolites via skin under maximal use. The study should be a multiple dose study using the maximum amounts per site and dosing frequency contemplated with the final to-be-marketed dosage form. Due to systemic presence of azeliac acid from endogenous and dietary sources, careful attention should be given to the dietary intake by the patients.

The Sponsor has mentioned *in-vitro* skin permeation study results with the proposed product across excised hairless mouse skin. However, the sponsor is recommended to conduct an *in-vitro* skin permeation study across freshly excised human cadaver skin to generate more meaningful data on penetration of AzA and its metabolites across different layers of human skin. Design of *in-vitro* study should also address mass balance of AzA. An *in-vitro* incubation study with freshly excised human cadaver skin homogenate may be appropriate to monitor the permeation of intact AzA and its major metabolites. Information gained during such studies is also useful in post-approval changes of the drug product.

CLINICAL MICROBIOLOGY:

There are no clinical microbiology issues included in the briefing package. However, if the Sponsor would like to include susceptibility information in the product label, current in vitro data will be required. In addition, the relevance of the in vitro spectrum of the pathogens to the indications sought must be provided.

CLINICAL:

Sponsor's question #1: The Sponsor seeks the Division's concurrence that, together with the clinical data and other evidence gathered to date, one appropriately powered, vehicle-

controlled pivotal trial is sufficient to support Phase 3 clinical trials and marketing approval of Finevin™ Gel for the proposed

Agency's response:

Sponsor's question #2:

Sponsor's question #3: The Sponsor seeks concurrence that, together with the clinical data and other evidence gathered to date, two appropriately powered, vehicle-controlled, Phase 3 pivotal trials of Finevin™ Gel (AzA 15% gel) are sufficient to support Phase 3 clinical trials and marketing approval of Finevin™ Gel for the proposed indication of moderate papulopustular rosacea for the gel formulation.

Agency's response: For NDA submission, the Division recommends submission of data for two appropriately powered, vehicle-controlled, Phase 3 pivotal trials of Finevin™ Gel (AzA 15% gel) in the proposed indication of moderate papulopustular rosacea. Marketing approval of Finevin™ Gel for the proposed indication of moderate papulopustular rosacea would depend upon the adequacy of the data.

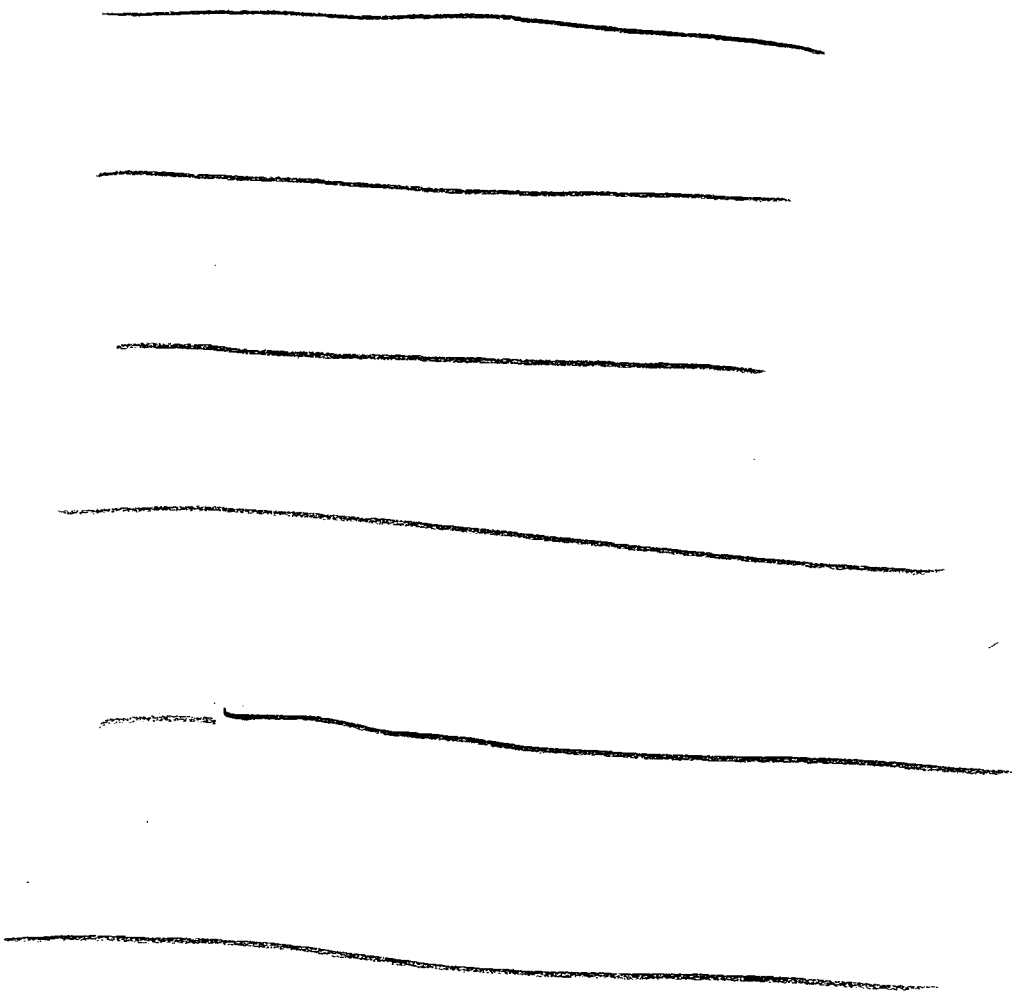
Question for the Sponsor:
Have dose ranging studies been conducted for rosacea indications?
If not, what is basis for selection of the optimal dose?

The Sponsor was referred to the ICH guidance document regarding the dose ranging studies. The Sponsor is encouraged to conduct dose ranging studies to identify the optimal dose for their formulation (i.e., concentration, frequency of application, etc.).

Sponsor's Question #5a (first bullet): The Sponsor seeks concurrence that the proposed clinical study protocols are acceptable for the Phase 3 clinical trials in — rosacea. In particular the Sponsor seeks concurrence on the following:

- That 3 primary variables (percent reduction in papules/ pustules count, percent reduction in total lesion count, and investigator's overall assessment) are required in the analysis of the — study.

Agency's response:



product in trials to demonstrate safety.

5. The protocols should be submitted under separate INDs for administrative and tracking purposes.

Protocol comments : [redacted]

1. (Pg. 577, Section 7.20 According to the submission, no subgroup analysis based on demographic or other baseline variables is planned. A rationale supporting this position is requested. Baseline severity subgroup analysis may be useful. Gender analyses are required under the CFR. The entry criterion regarding age does not have an upper age limit stated; therefore, a subgroup analysis based on age may be required. The Sponsor may refer to the Agency's Demographic Rule published in the Federal Register (1998).

2. Pg. 574, Section 7.1,Washout) Washout periods should reflect the pharmacology of the drug. The washout periods listed on page 574 are acceptable except for washout for preceding topical therapy of at least two weeks. Traditionally, the following washout periods have been suggested:

   Topical — treatment - 4 weeks
   Topical or systemic corticosteroids - 4 weeks
   Topical or systemic anti-inflammatories - 4 weeks
   Topical or systemic antibiotics - 4 weeks
   Systemic retinoids - 3 months

3. (Pg. 579, Section 7.3.3, Removal of patients from treatment or assessment, Withdrawals) Insufficient therapeutic efficacy is listed as a reason to justify a premature termination from the study. This withdrawal criterion seems somewhat unusual for an efficacy study for acne vulgaris. Prematurely eliminating failures might inflate end of study efficacy results; however, if permitted, as a reason for withdrawal, the patient should be deemed a failure and followed.

4. (Pg. 584, Antibiotics). The Sponsor should stratify for antibiotic use since use of oral tetracycline and oral erythromycin are permitted per protocol for a maximum of 10 days if needed for treatment of a concurrent disease.

5. (Pg. 581, Section 7.4.5, Selection of timing of dose for each patient, Mode of application) Under the second bullet, three examples of mild, non-medicated soaps with neutral pH are listed in the protocol. The protocol should not restrict use to a limited number of products, instead should try to simulate actual conditions of use.

Protocol comments (Rosacea indication):

1. The protocol comments above also apply.

2. Since rosacea is a disease that does not occur in the pediatric population, the Sponsor should request a waiver along with the rationale for the rosacea indication to satisfy the Pediatric Rule requirements.

The preferred design of phase 3 trials is for these trials to emulate as closely as possible intended use upon product approval as described in the intended labeling. Thus, the Sponsor should provide a scientific rationale for the exclusion of pregnant or lactating females and females planning pregnancy, as well as for performing a pregnancy test at baseline. There appears to be an asymmetry, for example, between Sponsor's mandating a negative urine pregnancy test at baseline in the phase 3 studies, yet not mandating such a test in actual clinical use.

If the Sponsor's perspective is that the use of this drug product in the above-mentioned populations constitutes a risk, and that these exclusions are necessary to minimize this risk, then this risk would be explicitly identified in labeling. If the Sponsor's perspective is that there is uncertainty about the risk, then this uncertainty could be conveyed to study participants in the informed consent form and to the general population in the product labeling. If the Sponsor's perspective is that there is no potential for risk, then there would seem to be no ethical or scientific rationale for these exclusions.

BIOSTATISTICS:

These comments apply to the draft protocols 304342 - 304344

1. In all protocols, the Sponsor defines the intent-to-treat (ITT) patient group as those subjects "who had at least one administration of the randomly assigned, double-blind, study medication and who provide at least one post-baseline data." (page 594/628) The preferred definition in the Division of Dermatological and Dental Drug Products is all subjects randomized and dispensed medication.

2. In all protocols, the Sponsor proposes that the primary population for analysis will be the per protocol group. Following ICH guidelines the recommended population group for superiority trials is the ITT population. This is usually implemented using last-observation-carried-forward (LOCF) technology as the Sponsor proposed to use with the per protocol group.

3. For the ⟵ trial the Sponsor will need to test for superiority of the Sponsor's drug product over its vehicle and non-inferiority over the reference drug product. For non-inferiority trials a non-inferiority limit, "delta", should be pre-specified in agreement with the Division. This "delta" should be used in the power/sample size calculations.

4. For the trial the Sponsor proposes to use three variables:

   - "The percent change from baseline in inflammatory papules and/or pustules count.
   - The percent change from baseline in total lesion count (sum of comedones, papules, and/or pustules, . . .).
   - Investigators global assessment of response (with five categories: excellent improvement, good improvement, moderate improvement, no improvement, deterioration)." (page 589)

   "The primary time point for analysis of these efficacy variables will be the last visit conducted for a given patient" (Page 594)

- First the variables should be defined as the overall sum of the cited variables, i.e., the "and/or"s in the definitions above should be changed to simple "and"s. Note that the definitions on page 573 are consistent with this recommendation, but those on page 569 incorporate the "and/or"s.

- Second, as indicated by the Medical Officer, absolute lesion counts or change from baseline scores, not just percent change from baseline, should be included as primary endpoints for each set of lesions. Note that all three sets of inflammatory lesions, non-inflammatory lesions (i.e., comedones), and total lesions should be analyzed. The Sponsor will "win" if they win on two of the three sets of lesion counts, plus the investigator's global assessment.

- Third, as discussed by the Medical Officer, the investigator's global assessment should be computed as a static measure, not defined relative to the patient's baseline as apparently suggested by the Sponsor, but defined relative to the physician's overall clinical experience. For the analysis, the global assessment should be reduced to a binary "success-fail" scale.

5. For the 304342/304344, rosacea, trials the Sponsor proposes to use two of the variables used in the trial above.

    - "The percent change from baseline in inflammatory papules and/or pustules count.
    - Investigators global assessment of response (with five categories: excellent improvement, good improvement, moderate improvement, no improvement, deterioration).

    As above, for inflammatory lesions, the total should be defined as the sum of the cited variables and both this total (or its change score from baseline) and the percent change from baseline should be analyzed as primary endpoints.

    Second, as before, it is recommended that the investigator's global assessment should be reduced to a binary "success-fail" scale.

6. The Sponsor proposes to analyze the continuous variables above using an "ANOVA model with the factors treatment and center, but does not include the treatment by center interaction term. The possibility of a potential interaction between treatment and center will be evaluated in a supportive analysis model including the two main effects and the center-by-treatment interaction term. An interaction will be deemed significant at the 0.15 level. Additional analysis of variance will be performed for the rank transformed data to assess the robustness of the results. Type III sums of squares will be used to adjust for unequal group sizes across centers and treatments." (pages 595 & 629).

    - The Sponsor states that a supportive ANOVA of the model including interaction will be performed, but gives no details about what procedure will be used if the interaction term if found to be statistically significant. It may be noted that for simple models like these, Type III sums of squares perform tests that, at least in this reviewer's opinion, are quite interpretable even in the presence of interaction.

- Similarly the Sponsor states that robustness will be investigated using rank transformed data, but does not give details about the actions to be taken if these tests and the original ANOVA's are discrepant. It would seem that the ANOVA of the rank-transformed data should be considered as a secondary analysis. However, it is appropriate as a primary analysis if the assumptions justifying the ANOVA are violated.

- For lesion totals the Sponsor may wish perform a similar ANCOVA with baseline score as a covariate. Note that if this is done, analysis of the total lesion counts and the corresponding change scores should give identical results for factors.

7. The Sponsor proposes to analyze the physician's global evaluation using a Cochran-Mantel-Haenszel test stratified on center. This seems quite appropriate.

8. For the 304342/304344 rosacea trials the Sponsor proposes subgroup analyses be performed only on gender, with no subgroup analysis in the [redacted] trials. Although this is a decision for the Medical Officer it does seem that subgroup analyses stratified on age, gender, and possibly race (white versus other) may be useful.

9. The power calculations performed by the Sponsor do seem to be appropriate. However, non-inferiority trials usually require more subjects than superiority trials. The Sponsor is encouraged to recalculate the estimated sample size adjusting for these requirements. However, if the Sponsor believes that this product will not necessarily achieve non-inferiority they may, with Division concurrence, propose other measures a priori that justify the use of their drug product.

10. For phase 3 trials sample size calculations should be based upon the primary endpoints agreed upon by the Division. In making such a calculation at some specified alternative, the usual minimal power of 80, is recommended, with allowance for dropouts.

ADMINISTRATIVE COMMENTS:

1. Pediatric Rule:

   The Sponsor was reminded of the following:

   The Food and Drug Administration Modernization Act [FDAMA] of 1997, Section 111, Pediatric Studies of Drugs, effective April 1, 1999, requires the following:

   Per 21CFR 314.50(d)(7), NDA applications are required to contain "A section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications, a reference to the full descriptions of such studies provided under paragraphs (d)(3) and (d)(5) of this section, and information required to be submitted under Section 314.55."

   A waiver can be requested in accordance with 21 CFR 314.55(c).

2. Financial Disclosure:

For applications submitted after February 2, 1999, per 21CFR 54.3 and 21CFR 54.4, an NDA applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests.

3. Labeling:

If the Applicant has an Information for Patients leaflet/labeling, please submit it with the NDA.

4. Comments are based upon the Pre-IND/End of Phase 2 Briefing Package, which is an unofficial briefing document submitted as information. The final protocols should be submitted for review and comments prior to initiation of the trials. Because there are several items that would require additional discussions no commitments can be made at this time.

5. The Sponsor is encouraged to request a Pre-NDA Meeting at the appropriate time.

The meeting ended cordially.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

Handout: Briefing Package, dated August 21, 2000.

cc:
HFD-105/ DeLap
HFD-105/Bull
HFD-540/ Wilkin
HFD-540/ Okun 10/18/00
HFD-540/ Vaughan 9/27/00
HFD-540/ Jacobs 9/27/00.
HFD-540/Mainigi
HFD-540/ DeCamp 9/27/00.
HFD-725/ Al-Osh
HFD-880/ Bashaw
HFD-880/Ghosh 9/27/00
HFD-604/Hare
HFD-520/Sheldon 9/29/00
HFD-540/Cintron

2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.