cc:
Archival NDA 20-748
HFD-540/Div. Files
HFD-540/O.Cintron
HFD-540/Wilkin
HFD-540/Walker
HFD-540/Huene
HFD-540/DeCamp
HFD-540/Timmer
HFD-540/Jacobs
HFD-540/Mainigi
HFD-160/Greenman
HFD-160/Cooney
HFD-880/Bashaw
HFD-880-/Lee
HFD-725/Farr
HFD-725/Srinivasan
DISTRICT OFFICE

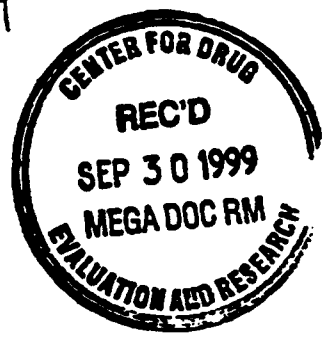
Drafted by: OC/October 5, 1999
Initialed by:
final:
filename: ADAPAL.AC

CLASS 2 RESUBMISSION ACKNOWLEDGEMENT (AC)
(DDR: Update the user fee goal date based on the class of resubmission.)

GALDERMA

Patt
10/18/99

September 29, 1999



ORIG AMENDMENT
BM

Olga Cintron
Project Manager
Division of Dermatological and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

RE: NDA 20-748
DIFFERIN® (adapalene cream) Cream, 0.1%
Documentation for the FDA Clinical Investigations Branch

Dear Olga:

Reference is made to the Amendment to NDA 20-748 dated September 7, 1999. Reference is also made to our telephone conversation on September 27, 1999 regarding information needed for submission to Dr. Jose Carreras in the Division of Scientific Investigations.

I have pulled together certain information from the Amendment which I expect will be of interest to Dr. Carreras as he has requested similar materials in the past. I of course will be happy to provide any other materials to Dr. Carreras that he may need to support the audit of the new clinical study (1.GUS.04.SRE.18035).

Information Materials for Clinical Study No. 1.GUS.04.SRE.18035

- Tabulated Summary of Clinical Study 1.GUS.04.SRE.18035 from TABLE 1b of the Amendment – *Safety and Efficacy Comparison of DIFFERIN® (adapalene cream) Cream, 0.1% and DIFFERIN® (adapalene cream) Cream Vehicle in the Treatment of Acne Vulgaris*
- Summary of Serious Medical Events for Clinical Study 1.GUS.04.SRE.18035
- Names and Addresses of Investigators for Clinical Study 1.GUS.04.SRE.18035 including numbers of patients by investigator and by treatment
- Clinical Study Protocol 1.GUS.04.SPR.18035, Protocol Amendments, and Sample Case Report Form

If I can be of further assistance in this regard please contact me.

Sincere regards,

Christine Shank

Christine Shank
Telephone (817) 263-2676 • FAX (817) 263-2738

c: Archival Copy to HFD-540 Document Control Room

ORIGINAL

GALDERMA LABORATORIES, INC.
P.O. BOX 331329 • FORT WORTH, TEXAS 76163-1329 U.S.A. • TEL. (817) 263-2600 • FAX (817) 263-2738

GALDERMA

September 7, 1999

AZ

Jonathan K. Wilkin, M.D.
Director
Food and Drug Administration
Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
9201 Corporate Blvd.
Rockville, Maryland 20850

RE: NDA 20-748
DIFFERIN® (adapalene cream) Cream, 0.1%
Major Amendment
Response to the FDA Not Approvable Letter Dated July 9, 1998

Dear Dr. Wilkin:

This amendment to NDA 20-748 for DIFFERIN® (adapalene cream) Cream, 0.1% is submitted pursuant to 21 CFR 314.60 (a) in response to the FDA Not Approvable letter dated July 9, 1998. The amendment constitutes a complete response to correct the major deficiencies. In addition, the Applicant provides a complete response to each of the technical review comments itemized in the Not Approvable letter. Thus, in accordance with the regulation, the Applicant agrees to the extension of the review period as required for the Agency to reach a decision on the application.

Administrative elements provided in Volume 1 of the amendment include:

- Certification pursuant to 21 CFR 314.60 (c) that a Field Copy of the applicable sections of the amendment has been sent to the Applicant's home FDA District Office; and,
- Certification pursuant to 21 CFR 54 of Financial Interests and Arrangements of Clinical Investigators who participated in the second pivotal vehicle-controlled safety and efficacy study submitted for demonstration of substantial evidence of efficacy.

Revised Draft Labeling
As a result of the conduct and reporting of the human pharmacokinetic and the clinical safety and efficacy studies, revised draft labeling is submitted in Volume 1 of the amendment. Review copies of Volume 1 are provided for each technical discipline.

ORIGINAL

GALDERMA LABORATORIES, INC.
P.O. BOX 331329 • FORT WORTH, TEXAS 76163-1329 U.S.A. • TEL. (817) 263-2600 • FAX (817) 263-2738

Pediatric Use – 21 CFR 314.55 (c)(3)(ii)

The Applicant requests a waiver of the requirement to assess use of the drug in additional subgroups of the pediatric population. The Applicant has conducted studies in pediatric patients from 12 up to 16 years of age. The subgroup analysis provided in this amendment for this pediatric age group demonstrated that there were no appreciable differences in the safety or efficacy responses in comparison with the adult patients (16 years and older) enrolled in the studies. Since acne vulgaris usually develops after the onset of puberty, and largely affects teenagers and young adults, the Applicant certifies that adequate and well-controlled studies to evaluate the drug in patients below the age of 12 would be highly impractical. Principally, the number of patients below the age of 12 would be a small percentage of the population with acne vulgaris and would be widely dispersed.

Contact Person

It is requested that any questions or comments regarding this amendment be directed to the person named as follows:

Ms. Christine Shank
Sr. Director, Regulatory Submissions
Galderma Laboratories, Inc.
P.O. Box 331329
Fort Worth, Texas 76163

Telephone (817) 263-2676
Fax (817) 263-2738

The Applicant extends its sincere appreciation to the agency staff and reviewers for their time spent in review and consideration of this amendment.

Sincere regards,

Christine Shank

Christine E. Shank
Director, Regulatory Submissions

2 Desk Copies of Volume 1 - Ms. Olga Cintron, FDA Project Manager

c: Mr. Stephen W. Clark
President, Galderma Laboratories, Inc.

Mr. Paul M. Clark
Director, Regulatory Affairs
Galderma Laboratories, Inc.

Dr. Christopher Hensby
Vice-president, Corporate Regulatory Affairs
Galderma S.A.

DUPLICATE

GALDERMA

NDA ORIG AMENDMENT

BC

September 18, 1998

Mr. Nicholas Falcone
Food and Drug Administration
Custom's House Room 900
2nd & Chestnut Streets
Philadelphia, PA 19106

Ms. Myriam M. Sosa
Food and Drug Administration
466 Fernandez Juncos
San Juan, PR 00902

RE: NDA 20-748
DIFFERIN® (adapalene cream) Cream, 0.1%
Methods Validation - Samples and Information Submission

Dear Sir or Madam:

In accordance with the request for test materials and information needed to perform methods validation studies on DIFFERIN® (adapalene cream) Cream, 0.1% in connection with NDA 20-748, please find enclosed:

- Comprehensive Information Package - contains information supplemental to the Samples and Method Validation Package (Volumes 1.5 - 1.7) provided to each District Laboratory.
- DIFFERIN® (adapalene cream) Cream, 0.1% Lot MEEM
- Adapalene reference standard
- Methylparaben reference standard
- Phenoxyethanol reference standard
- Propylparaben reference standard

A complete description of the test materials and their Certificates of Analysis are provided in the information package.

Tests, specifications, and analytical method changes are fully described in the information package.

The name, address, and Central File (C.F.) Number for the drug product manufacturer is provided in the information package.

GALDERMA LABORATORIES, INC.
P.O. BOX 331329 • FORT WORTH, TEXAS 76163-1329 U.S.A. • TEL. (817) 263-2600 • FAX (817) 263-2738

If there are any questions regarding this submission, please contact the applicant as follows:

Ms. Christine Shank
Galderma Laboratories, Inc.
Telephone (817) 263-2676
Fax (817) 263-2738

Field Copy Certification
Pursuant to the requirements of 21 CFR 314.60 (c) a complete copy of this amendment is provided to the FDA Dallas District Office, the applicant's home FDA District Office. The applicant certifies that the Field Copy is a true copy of the amendment submitted to the

Sincere regards,

Christine Shank
Sr. Director, Regulatory Submissions

c: Archival and CMC Review copies to Document Control Room HFD-540
Fax of cover letter to Ms. Olga Cintron, FDA Project Manager, HFD-540

GALDERMA

SD

ORIG AMENDMENT
ORIGINAL

September 2, 1998

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

RE: NDA 20-748
DIFFERIN® (adapalene cream) Cream, 0.1%
Amendment - NDA Safety Update Report

Dear Sir or Madam:

The applicant submits herewith a Safety Update Report to NDA 20-748 pursuant to 21 CFR 314.50 (d)(5)(vi)(*b*). The report is comprehensive for all dosage forms of adapalene and includes information, as currently available, from all U.S.A. and foreign studies. This Safety Update Report is submitted in response to the agency's request in the notification, dated July 9, 1998, to the applicant that the NDA for DIFFERIN® (adapalene cream) Cream, 0.1% was found to be not approvable.

If there are any questions regarding this Safety Update Report, please contact me at (817) 263-2676.

Sincere regards,

Christine Shank

Christine Shank
Senior Director, Regulatory Submissions

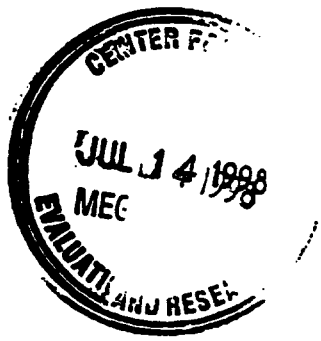
c: Ms. Olga Cintron (faxed copy of cover letter only)
Archival and Clinical Review copies

GALDERMA LABORATORIES, INC.
P.O. BOX 331329 • FORT WORTH, TEXAS 76163-1329 U.S.A. • TEL. (817) 263-2600 • FAX (817) 263-2738

GALDERMA

NC
ORIGINAL

July 13, 1998



Jonathan K. Wilkin, M.D.
Director
Division of Dermatological and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

RE: NDA 20-748
DIFFERIN® (adapalene cream) Cream, 0.1%
Notification of Intent to File and Amendment

Dear Dr. Wilkin:

Reference is made to your letter dated July 9, 1998 wherein you notified the applicant that the information presented in the New Drug Application for DIFFERIN® (adapalene cream) Cream, 0.1% was found inadequate and that the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b).

Pursuant to the provisions of 21 CFR 314.120(a)(1), the applicant hereby submits formal notification of its intent to file an amendment to the NDA to correct the deficiencies itemized in the not approvable letter.

In addition, the applicant acknowledges the request for submission of a safety update pursuant to 21 CFR 314.50(d)(5)(vi)(b). Preparation of this update has been initiated and the report will be submitted as soon as possible.

Please be advised that draft protocols for the conduct of a second pivotal Phase 3 vehicle-controlled clinical study and a multiple-dose pharmacokinetic study in acne patients were submitted to IND — for adapalene cream, 0.1% on June 2, 1998. These protocols address the critical deficiencies cited in the not approvable letter. As we stated in the Protocol Amendment cover letter, our objective is to make formal Protocol Amendment submissions to the IND by the end of July in order to start the studies as soon as possible. Thus, any significant comments or recommendations for changes in these protocols would be of immediate interest to us.

GALDERMA LABORATORIES, INC.
P.O. BOX 331329 • FORT WORTH, TEXAS 76163-1329 U.S.A. • TEL. (817) 263-2600 • FAX (817) 263-2738

I would personally like to express my thanks to you and Ms. Olga Cintron for your courteous call to me last Thursday. You have both been considerate of our interest in this application and your earlier advisory notification of the clinical and biopharmaceutic concerns was helpful and much appreciated.

Sincere regards,

Christine Shank

Christine Shank
Sr. Director, Regulatory Submissions
Telephone (817) 263-2676

c: FAX of letter to Ms. Olga Cintron

JUL 9 1998

NDA 20-748

Galderma Laboratories, Inc.
Attention: Ms. Christine Shank, Director, Regulatory Submissions
P.O. Box 331329
Fort Worth, Texas 76163-1329

Dear Ms. Shank:

Please refer to your new drug application dated July 16, 1997, received July 17, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Differin (adapalene cream) Cream, 0.1%.

We acknowledge receipt of your submissions dated August 20, September 19 (two), October 20, November 4 and 5, December 3, 17 and 18, 1997; February 2 and 5, 1998.

The User Fee goal date for this application is July 17, 1998.

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

Clinical/Statistical:

Clinical Study CR 90087 failed to demonstrate non-inferiority to its comparator, Retin-A Cream, 0.05%. Please conduct an additional vehicle-controlled clinical trial to support safety and efficacy for the indication sought, using the to-be-marketed formulation.

Biopharmaceutics:

The pharmacokinetic study assessing the systemic exposure to adapalene after topical application of the cream dosage form is not adequate. Please conduct a multiple-dose study in patients with large surface area of diseased skin using the to-be-marketed formulation to determine the maximal systemic exposure. Please contact the Agency for guidance.

Microbiology:

The Amendment of February 2, 1998, failed to adequately address requests for information in support of microbial quality of the subject drug. Please include the following additional information in the resubmission:

Microbial Limits Test:

1. References cited in Document #74.4110.00 for USP and the FDA Bacteriological Analytical Manual are not current and should be updated as provided for in Procedure #74.1001.01.

2. Establish an action limit for molds and yeasts and provide for this specification under Acceptance Criteria.

3. Provide a revised specification for Microbial Limits (Finished Product Tests and Specifications, page 0006). The specification "..... " should be replaced with those organisms required to be absent from the formulation. This change should also be made in Procedure under Acceptance Criteria.

Chemistry:

We note that the safety and efficacy studies for Differin (adapalene cream) Cream, 0.1%, were conducted utilizing formulations different from the proposed to-be-marketed formulation (CDP). Specifically, Clinical Study 90087 utilized formulation C2. Formulation C2 contained a overage of adapalene and Clinical Study 9111-CD271C-EV utilized formulation C1 which contained a overage of adapalene and no The overage was eventually dropped as described in page 2 0075. Future clinical studies for Differin Cream should be conducted with the to-be-marketed formulation (CDP).

Although not the basis for the non-approval of this application, the following requests for information should be addressed in the resubmission:

Chemistry:

1. Please develop and report impurity specifications of both the analytical testing program and the stability program for the drug substance.

2. Please provide a range for the individual excipients as part of the drug product components/composition. Cyclomethicone is available as NF grade; the rationale for using non-NF grade should be explained.

3. Compositional information on the clinical batch formulations (p. 2 0349) indicates that the overage was dropped from the commercial formulation, yet it is still listed in the manufacturing batch record. Please submit an updated unexecuted/executed batch record to reflect the deletion of the overage of adapalene.

4. Please provide all analytical methods and specifications. Not all analytical methods are present. (Procedure No. [redacted] is not present). Moreover, the numbering system is unclear. For example, the method for particle size on p. 3 0400 is listed as Procedure No. [redacted] Is this the same test as is listed on p. 3 0477 as [redacted] Are DPT Laboratories' acceptance SOPs (not specification) different from their finished product SOPs? The distinction is not clear and the numbering system is inconsistent. Please correct/revise the numbering system.

5. Please provide the following revised information regarding In-Process Controls and Tests: The application states that process inspection and testing functions are conducted in accordance with written SOPs. In-process tests such as packaging yield calculations are included in the manufacturing batch record. However, the application should unambiguously list, and include, the SOPs for the in-process test (*c.f.*, the vague in-process test at step #4 (p. 3 0180): [redacted] In addition, the frequency and time of the in-process tests should be included. You did not specify under what conditions the [redacted] will occur; that is, the adapalene [redacted] must be specified. In addition, a [redacted] should be specified at which [redacted]

6. Please provide a test for content uniformity, with sampling from the top, middle, and bottom of the product tube.

7. Please include relative humidity in all future stability submissions. In addition, a test should be developed to measure content uniformity at all stability time points.

Under 21 CFR 314.50 (d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

1. Retabulate all safety data including results of trials that were still ongoing at the time of the NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs now will facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

If you have any questions, please contact Olga Cintron, Project Manager, at (301) 827-2020.

Sincerely yours,

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:

Original NDA 20-748
HFD-540/Div. files
HFD-002/ORM
HFD-105/Office Director
HFD-101/L.Carter
HFD-830/ONDC Division Director
DISTRICT OFFICE
HFD-95/DDM-DIAB
HFD-540/O.Cintron
HFD-540/Div Dir/Wilkin
HFD-540/CLINICAL/Huene 5/11/98.
HFD-540/CHEM/Timmer 5/27/98.
HFD-540/PHARM/Mainigi 5/27/98.
HFD-725/BIOSTAT/Farr 5/27/98.
HFD-880/BIOPHARM/Lee 5/28/98.
HFD-160/MICRO/Greenman

Concurrence:

HFD-540/CLINICAL TL/Walker 6/17/98.
HFD-830/CHEM TL/DeCamp 6/3/98.
HFD-540/PHARM TL/Jacobs 5/27/98.
HFD-160/MICRO TL/Cooney
HFD-880/BIOPHARM TL/Bashaw 5/27/98.
HFD-725/BIOSTAT TL/Srinivasan
HFD-540/SUPV PROJ MGR/Kozma-Fornaro 5/26/98.

Drafted by: /May 6, 1998/
W.P. files: c:/20748.na

NOT APPROVABLE (NA)

24 pages redacted from this section of the approval package consisted of draft labeling

GALDERMA

OLIC [illegible]

ORIGINAL

February 5, 1998

Dr. Jose A. Carreras
Division of Scientific Investigations (HFD-344)
Office of Compliance
Food and Drug Administration
Metro Park North 1
7520 Standish Place
Rockville, Maryland 20855

RE: NDA 20-748
Adapalene Cream, 0.1%

Dear Dr. Carreras

Pursuant to your request in a telephone call February 3, 1998, please find enclosed information to assist with the audit and evaluation of study sites for Clinical Study 9111-CD271C-EV.

Pursuant to your selection of study sites for [redacted]. I am providing an Audit Package for each investigator containing the following information:

- Protocol and protocol amendments for Clinical Study 9111-CD271C-EV
- Adverse event tabulations for all patients enrolled in the study
- Tabulations of all patients discontinued or dropped out of the study for any reason
- Data listings of primary efficacy parameters for each investigator
- Case report forms for five patients randomly selected for each investigator

Additionally, I am providing you a replacement copy of the November 4, 1997 information package. This package contains investigator information and study protocols for the two pivotal studies identified in the NDA for Adapalene Cream, 0.1%.

If I can be of further assistance in this regard, please contact me.

Sincere regards,

Christine Shank

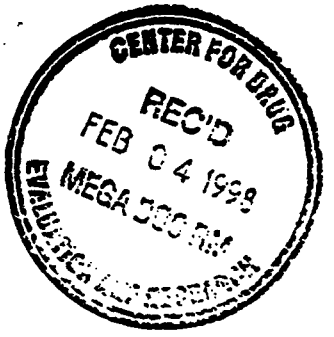
Christine Shank

c: Ms. Olga Cintron (HFD-540) - Cover Letter Only
Document Control Room (HFD-540) Archival Copy

GALDERMA LABORATORIES, INC.
P.O. BOX 331329 • FORT WORTH, TEXAS 76163-1329 U.S.A. • TEL. (817) 263-2600 • FAX (817) 263-2738

GALDERMA

February 2. 1998



Division of Dermatological and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

RE: NDA 20-748/Amendment
DIFFERIN® (adapalene cream) Cream. 0.1%
Response to Microbiology Review Comments and Requests for Information

Dear Sir or Madam:

Reference is made to a facsimile transmission dated January 16, 1998 received from Ms. Olga Cintron. This communication provided several comments and requests for information pursuant to the microbiology review of this pending application.

Please find enclosed the applicant's complete response to this request. With respect to the DPT Laboratories document numbering system, if there is still some confusion after reading the explanation please give me a call and I believe I can better clarify verbally. I appreciate the reviewer's confusion in this regard as I experienced the same when this system was first put into effect. Also. I will be happy to assist with any other concerns.

Field Copy Certification - Pursuant to the requirements of 21 CFR 314.60 (c). the applicant hereby certifies that a complete copy of this amendment has been forwarded to the FDA Dallas District Office. the applicant's home FDA District Office.

Sincere regards.

Christine Shank

Christine Shank

c: Ms. Olga Cintron (faxed copy of cover letter only)
Document Control Room (archival copy and microbiology review copy)

GALDERMA LABORATORIES, INC.
P.O. BOX 331329 • FORT WORTH, TEXAS 76163-1329 U.S.A. • TEL. (817) 263-2600 • FAX (817) 263-2738

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatologic and Dental Drug Products

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

FACSIMILE TRANSMISSION

DATE: January 16, 1998. Number of Pages (including cover sheet) 2
TO: Ms. Christine Shank
COMPANY: Galderma
FAX NUMBER: 817-263-2738
MESSAGE:

NDA 20-748 Differin Cream

Please find microbiologist's request for information.

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
TELEPHONE: 301- 827-2020 FAX NUMBER: 301-827-2075

Original NDA 20-748
HFD-540/Div Files
HFD-160/Greenman

1. Provide the following information for the Microbial Limits Test:

a. A specification for yeasts and molds should be cited. The referenced Microbial Limits Assay(page 3 0494) provides for the [redacted] but no specification for [redacted] is cited in this procedure or in the Finished Product Specifications(page 3 0467). It is noted that the incubation temperature used for [redacted] (page 3 0497) rather than the recommended [redacted] and that the procedure does not provide for the specific isolation of [redacted] Please comment.

b. The Microbial Limits Assay to be used for [redacted] should be identified and validated. The Microbial Limits Assay identified under Product Release Specifications(Page3 0467) is procedure No. [redacted], whereas the one submitted and referenced is No. [redacted]. Validation data in support of the assay procedure should be submitted prior to approval of the application.

2. Provide the following information in support of the efficacy of the preservative system:

a. Procedures for [redacted] should be described. The procedure(No. [redacted] used for validation of the efficacy of the [redacted] system in product stored for [redacted] and the procedure(No. [redacted] used for product formulated with the minimum [redacted] level [redacted] should be described. It should be indicated whether these procedures provide for use of [redacted] and whether these were used for the reported studies.

b. The [redacted] test to be used for evaluation of lots on stability should be confirmed. The assay number specified under Finished Product Tests(No. [redacted], page 3 0467) is not the same as that indicated for validation of the efficacy of minimum [redacted] levels(No. [redacted]. The test to be used for monitoring lots on stability and the test used to validate the minimum [redacted] level should be validated.

MESSAGE CONFIRMATION

01/16/98 14:52

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatologic and Dental Drug Products

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

FACSIMILE TRANSMISSION

DATE: January 16, 1998. Number of Pages (including cover sheet) 2
TO: Ms. Christine Shank
COMPANY: Galderma
FAX NUMBER: 817-263-2738
MESSAGE:

NDA 20-748 Differin Cream

Please find microbiologist's request for information.

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
TELEPHONE: 301-827-2020 FAX NUMBER: 301-827-2075

GALDERMA

BS

ORIGINAL

December 18, 1997

Ms. Olga Cintron
Project Manager
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

RE: NDA 20-748
DIFFERIN™ (adapalene cream) Cream, 0.1%
Response to Biostatistics Reviewer Request

Dear Olga:

Pursuant to our conversation yesterday involving Dr. Shahla Farr and Dr. Michael Tuley, please find enclosed the missing diskette for Study C-9111 containing the SAS code used to generate the report.

Additionally, Dr. Tuley has prepared a descriptive list of the variables for the three datasets: EVAL, CLINEVAL, and BLIND. Also attached is the format catalog for Investigators and the SAS code used to create a format catalog. Most of the SAS programs include this file at the beginning of the program. The names of the programs correspond exactly to the names that were included in the List of Tables (copy attached for reference). Running each program will exactly duplicate the report.

We hope this is helpful to Dr. Farr in her review. If she has any questions she may contact Dr. Michael Tuley directly at (817) 263-2670 on Monday of next week. Due to the holidays, the Galderma office will be closed from December 25 through January 4. Business will resume on January 5.

Sincere regards,

Christine Shank

Christine Shank
Director, Regulatory Submissions

c: Archive and Review copies of paper documents to NDA 20-748 file

GALDERMA LABORATORIES, INC.
P.O. BOX 331329 • FORT WORTH, TEXAS 76163-1329 U.S.A. • TEL. (817) 263-2600 • FAX (817) 263-2667

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DUPLICATE

54

December 17, 1997

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

RE: NDA 20-748/Amendment
DIFFERIN™ (adapalene cream) Cream, 0.1%
4-Month Safety Update Report

Dear Sir or Madam:

The applicant submits herewith the 4-Month Safety Update Report to NDA 20-748 pursuant to 21 CFR 314.50 (d)(5)(vi)(*b*). The report is comprehensive for all dosage forms of adapalene and includes information from all U.S.A. and foreign studies.

If there are any questions, please contact me at (817) 263-2676.

Sincere regards,

Christine Shank

Christine Shank
Director, Regulatory Submissions

c: Ms. Olga Cintron (faxed copy of cover letter only)
Archival and Clinical Review copies

Mr. Kurt Grimm, Vice-president, Regulatory Affairs
Galderma Laboratories, Inc.

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BB

ORIG AMENDMENT

ORIGINAL

December 3, 1997

Ms. Olga Cintron
Project Manager
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

RE: NDA 20-748
DIFFERIN™ (adapalene cream) Cream, 0.1%
Biopharmaceutic Amendment - Pharmacokinetic Data and Sponsor Evaluation

Dear Olga:

Since our discussion with Dr. Bashaw and Dr. Sue-Chih Lee on September 29, 1997 regarding the Pharmacokinetic Data submitted in support of the NDA for DIFFERIN™ Cream, we have reevaluated the data that have been generated with adapalene formulations (cream, gel, and solution). At this time we would like the opportunity to revisit the issues raised by the Biopharmaceutic review and offer our evaluation for further consideration.

According to my recollection and notes from the September 29 conference call, the key concerns expressed by Dr. Bashaw and Dr. Sue-Chih Lee were as follows:

- The Biopharmaceutics review of the pharmacokinetic data from Clinical Study CR 90087 (conducted with the cream formulation in patients with acne vulgaris) concluded that the data is inadequate because sampling was limited to only one time-point.
- The radiolabeled study with the gel formulation (Study Report 1.CG.03.SRE.4529) was also considered inadequate because the study was not conducted in patients with acne vulgaris. [As I recall, Dr. Bashaw commented that had the study been conducted in diseased patients it may have been used to extrapolate for the cream dosage form.]
- In conclusion, it was stated that data from a study in patients with maximal disease to surface area, employing multiple dosing for 2 weeks duration, and with the proposed commercial cream formulation would be required to capture the systemic absorption profile.

With regards to the first two issues, we do not disagree with the conclusions drawn by the Biopharmaceutics review. We however believe that data from at least one other study is relevant

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and deserves review and consideration.

A clinical pharmacokinetic study (**CR 90103**) with the aqueous gel formulation was conducted to assess the pharmacokinetic profile of adapalene under conditions resembling as closely as possible the maximum exposure likely to be encountered in the treatment of acne. This study was submitted in the original application for DIFFERIN Gel, 0.1% (NDA 20-380, Volume 1.47, Pages 6 0219 - 6 0436). The key design and evaluation elements of this study are outlined as follows:

- The study was conducted in six Caucasian patients (three males and three females) with acne lesions on the face and/or chest and/or shoulders. [The criteria for enrollment specified patients with acne Grades 1 to 5 according to the Cunliffe classification system.]
- An average of two (2) grams of adapalene gel 0.1% was applied once daily for 14 days to the face, shoulders, and chest (corresponding to an area of approximately 1000 cm^2) of each patient. [Application of the test material was made to the entire area, not just to sites within the area where acne lesions appeared. Also the amount of test material applied was estimated to be approximately twice the amount expected to be used under routine conditions of use.]
- Blood samples for analysis were taken prior to the first application, at 12-hour intervals on days 2, 3, 4, 5, 14, and 15, and once daily on days 1, 8, 11, 17, 21, and 28. Urine samples were collected prior to the first application and at 24-hour intervals following the first blood sample on day-1 up to day-15. Fecal samples were collected prior to the first application and at 24-hour intervals following the first blood sample on day-1 up to day-28.
- Additionally, a series of stratum corneum samples *via* tape strippings were made at one (day-15), seven (day-21), and fourteen days (day-28) following the last application of test article using different sites of the application zone on each occasion. Control strippings from an untreated part of the back were also made on day-28.

Summary of results from **Study CR 90103**:

- Generally levels of the parent drug, adapalene, were below the detection limit (——— in the plasma from 24 hours after the first application up to 14 days (day-28) following the last application. Only two subjects were found to have plasma levels of adapalene above the detection limit. A value of (——— on day-3 and trace levels ———) on day-14 were found in one subject and trace levels on day-2 in another subject.
- Analysis of the urine samples revealed a level of the parent drug generally below the limit of detection (———). In three subjects, levels of adapalene were found
- above the detection limit. Values of ——— were found in the day-11/12 samples of subjects 2 and 5, respectively and trace levels (——— were found in the day-2/3 sample from subject 5 and the day-8/9 sample from subject 6. These results are in agreement with those obtained in animal studies and confirm

the elimination of unchanged adapalene *via* the biliary route.

- Adapalene was first detected in fecal samples about 48 hours after the first application and was present in all but four of the subsequent fecal samples collected during the treatment period. The fecal levels of adapalene declined after stopping treatment with the last detectable levels (—— of dry feces) being recorded within six days of stopping treatment in all subjects. The quantities of adapalene measured were variable between individuals with the cumulative quantities of adapalene collected during and after treatment ranging from ——— (mean 6.77 ± 6.18 µg). The fecal elimination rate of adapalene reached a maximum of about — per day in two subjects with the highest cumulative elimination. These results show that under conditions resembling maximum exposure to adapalene gel in the treatment of acne, absorption is confirmed by the low quantities of parent drug in the feces. However this is not in general associated with detectable levels of circulating adapalene
- Adapalene was found only in the tape strippings performed 24 hours after the last application with no quantifiable amounts in the tape strippings from days 7 and 14 after the last application. The quantities of parent drug present in the stratum corneum varied from one subject to another and seemed to be correlated with the amount applied to the zone where stripping samples were taken.

We believe the data from this study satisfactorily addresses the Biopharmaceutic concerns and is of adequate design for assessment and evaluation of pharmacokinetics in diseased (acne) subjects. This study with the gel formulation (DIFFERIN Gel, 0.1%) is also considered to represent the "worst case" condition for exposure to the drug since it has been demonstrated in an *in vitro* diffusion cell study that adapalene is less bioavailable from the cream or solution dosage forms than from the gel formulation. [Reference is made to the comparative ***In Vitro*** **Study No. DCa/JF/92-020 (PK 91005)** summarized in NDA 20-748 in ITEM 6., Volume 1.13, pages 6 0012 - 6 0014.]

In conclusion we are providing a copy of the pharmacokinetic **Study Report CR 90103** from NDA 20-380 for review. It is of course hoped that the reviewer will concur with our assessment that this study serves as adequate evaluation of the pharmacokinetics of topically applied adapalene in acne patients and that the *in vitro* diffusion cell study adequately serves to bridge the different formulations.

We appreciate this opportunity to offer additional information and data in support of this application and will wait to hear further in this regard. Please contact me if there are any questions.

Sincere regards,

Christine Shank

Christine Shank

c. Ms. Olga Cintron (cover letter only), NDA 20-748 Archive and Biopharmaceutic Review copies

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ORIGINAL

EC

November 5, 1997

Dr. Bill Timmer
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

RE: NDA 20-748
DIFFERIN™ (adapalene cream) Cream, 0.1%
Chemistry Amendment - Revised Analytical Method

Dear Dr. Timmer

I spoke with Ms. Olga Cintron recently about a revised analytical method that I thought should be reported to the NDA. She checked with Dr. DeCamp (you were unavailable at the time) and advised that I could submit the revised method in an amendment to the application at this time.

Please find enclosed a copy of the revised analytical method entitled:

73.4600.02 - Adapalene Assay and Identification by ——→ in Topical Creams

The revisions to the method provide for quantitation of degradants in the drug product. Please note the changes in the method as follows:

Section 2:
Section 9:

The reason for this revision originated from review of the New Drug Submission (NDS) for DIFFERIN Cream by the Canadian Health Protection Branch (HPB). Since DPT Laboratories

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manufactures the drug product for the Canadian market (where it is now approved) and will also manufacture the product for the US market, naturally it is preferable to have one standard operating procedure. I thought it might be helpful if I also shared with you the HPB comments and the responses made by our Canadian affiliate relative to this matter.

The HPB comments were as follows:

> With respect to finished product specifications: The release and shelf life specifications should include limits on individual unidentified, identified and total degradation products. Limits proposed should be supported by results observed from the stability studies at the proposed expiration date.
>
> With respect to the stability: The levels of individual unidentified, identified and total degradation products placed in the stability trials should be submitted. Copies of test mentod(s) and validation report(s) should also be provided.

Subsequently in a telephone conversation, the HPB review unit manager further commented that he recognized the molecule was quite stable in the formulation but nevertheless it was a bureaucratic requirement to include degradation specifications. Therefore in response to the comments, the analytical method referenced herein was modified to include the provisions for quantitation of degradation products and the following theoretical limits were proposed:

> NMT — individual unknown degradation products
> NMT — total degradation products.

Furthermore the chromatograms of the ——— assays of adapalene of all sublots included in the stability program were examined and compared with the initial chromatograms, including those of the placebo lot. No peaks appeared in the ——— chromatograms that were not present in the initial chromatograms. The stability data for all lots of DIFFERIN Cream demonstrate that adapalene is extremely stable and that detection of degradation products even after ——— will be highly unlikely. The analytical method remains as originally validated and is stability indicating.

I am not proposing to adopt the theoretical limits for degradation products that were required by HPB unless you recommend otherwise. I think it is satisfactory to accept that the stability lots will be monitored in this regard. Relatively speaking, the limits cited above are probably not very meaningful when considered in light of the stability of the product.

Sincere regards,

Christine Shank

Christine Shank
Director, Regulatory Submissions

c: Ms. Olga Cintron
(cover letter only)

Field Copy Certification - Pursuant to the requirements of 21 CFR 314.60 (c), the applicant hereby certifies that a complete copy of this amendment has been forwarded to the FDA Dallas District Office, the applicant's home FDA district office.

Christine Shank
Director, Regulatory Submissions

Nov. 5, 1997
Date

BZ

ORIG AMENDMENT

ORIGINAL

GALDERMA

November 4, 1997

Division of Dermatological and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

RE: NDA 20-748
DIFFERIN™ (adapalene cream) Cream, 0.1%
Clinical and Statistical Data Amendment

Dear Dr. Srinivasan and Dr. Farr:

Thank you for contacting us with your concerns. We hope you will find the following helps resolve the confusion.

The following pages contain the tables that you requested. The table at the top of each page contains the least square means from the GLM model. The model contained treatment, investigator, treatment-investigator interaction, and baseline counts. The counts were transformed using a square root transformation before analyzing. The NDA report page numbers of the analyses are found in the last column of the table.

The table at the bottom of each page contains the clinical meaningful lesion counts. These means have been transformed back into the original units by squaring each mean and subtracting 0.5. The last two columns of the bottom table contain the p-values from the lesion count analyses and the p-values from the percent change analyses. The p-values for both analyses are very similar and lead to the same conclusion.

Conclusion: CD271 (adapalene) cream was significantly more effective than its vehicle at reducing non-inflammatory lesions and total lesion counts from week 2 on.

If you have any further questions or if we can assist in any way, please contact us.

Sincere regards,

Michael R. Tuley, Ph.D.
Senior Biostatistician

Christine Shank
Director, Regulatory Submissions

c: Ms. Olga Cintron
Desk Copy

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ORIGINAL

ORIG. AMENDMENT

October 20, 1997

Dr. Bill Timmer
Division of Dermatological and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

RE: NDA 20-748
DIFFERIN™ (adapalene cream) Cream, 0.1%
Chemistry Amendment - Drug Substance [21 CFR 314.50 (d)(1)(i)]

Dear Dr. Timmer:

Reference is made to your telephone call on October 16, 1997 concerning the information in the application on the bulk drug substance, adapalene.

Subsequent to our conversation I checked with our Pharmaceutics Technical personnel and can confirm that to the best of our knowledge, the process, controls, and the synthesis used in production of the bulk drug substance have not undergone any significant changes since the review of the NDAs for DIFFERIN Gel and Solution, 0.1% (NDA 20- 380 and NDA 20-338 respectively).

Thank you very much for contacting us regarding this information. I look forward to working with you as you progress in the review of this application.

Best regards,

Christine Shank

Christine Shank

Field Copy Certification - Pursuant to the requirements of 21 CFR 314.60 (c), the applicant hereby certifies that a complete copy of this amendment has been forwarded to the FDA Dallas District Office, the applicant's home FDA district office.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatologic and Dental Drug Products

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

FACSIMILE TRANSMISSION

DATE: October 20, 1997. Number of Pages (including cover sheet) #2
TO: Ms.Christine Shank
COMPANY: Galderma
FAX NUMBER: 817-263-2667

MESSAGE: NDA 20-748 Differin Cream

Please find medical officer's request.

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
TELEPHONE: 301- 827-2020 FAX NUMBER: 301-827-2075

Original NDA 20-748

HFD-540/Div Files

HFD-540/Huene

NDA 20-748 Differin Cream

reviewing medical officer has found apparent inaccuracies in the analysis of the results of Study 9111-CD271C-EV. Specifically, the p values do not seem to be correct in the analysis of the mean total non-inflammatory lesion counts. (Page 868 of Vol 1.18.) We are requesting that you verify all the p values for the primary efficacy variables in this study.

GALDERMA

BC
ORIG AMENDMENT
ORIGINAL

September 19, 1997

Dr. Bill Timmer
Division of Dermatological and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

RE: NDA 20-748
DIFFERIN™ (adapalene cream) Cream, 0.1%
Chemistry Amendment - Revised Environmental Assessment

Dear Dr. Timmer:

Thank you for telephoning me regarding the new requirements for preparation of environmental assessments. Enclosed is a revised EA for DIFFERIN Cream claiming categorical exclusion pursuant to the new regulations published in the *Federal Register* July 29, 1997.

I have provided an Archival copy and a Chemistry review copy of this amendment.

Sincere regards,

Christine Shank

Christine Shank

Copy: Ms. Olga Cintron

GALDERMA LABORATORIES, INC.
P.O. BOX 331329 • FORT WORTH, TEXAS 76163-1329 U.S.A. • TEL. (817) 263-2600 • FAX (817) 263-2667

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BP
ORIG Application

ORIGINAL

September 19, 1997

Division of Dermatological and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

RE: NDA 20-748
DIFFERIN™ (adapalene cream) Cream, 0.1%
Clinical and Statistical Amendment

Dear Sir or Madam:

Pursuant to a fax received September 18, 1997 from Ms. Olga Cintron, FDA Project Manager, this amendment responds to a request for resubmission of pages from the clinical study report 9111-CD271C-EV.

Please find enclosed pages 8 1423 - 8 1436 from Volume 1.19. These pages have been recopied to correct the problem of the poor copies provided in the original submission. Please accept my sincere apology for this oversight on my part.

I have provided an Archival copy and both Clinical and Statistical review copies of this amendment.

Sincere regards,

Christine Shank

Christine Shank

Copy Ms. Olga Cintron
(cover letter only)

GALDERMA LABORATORIES, INC.
P.O. BOX 331329 • FORT WORTH, TEXAS 76163-1329 U.S.A. • TEL. (817) 263-2600 • FAX (817) 263-2667

MESSAGE CONFIRMATION

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatologic and Dental Drug Products

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

FACSIMILE TRANSMISSION

DATE: September 18, 1997. Number of Pages (including cover sheet) 2
TO: Ms. Christine Shank
COMPANY: Galderma Laboratories
FAX NUMBER: 817-263-2667
MESSAGE:

NDA 20-748 Differin Cream, 0.1%

Please find medical officer's request for information.

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
TELEPHONE: 301- 827-2020 FAX NUMBER: 301-827-2075

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatologic and Dental Drug Products

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

FACSIMILE TRANSMISSION

DATE: September 18, 1997. Number of Pages (including cover sheet) 2
TO: Ms. Christine Shank
COMPANY: Galderma Laboratories
FAX NUMBER: 817-263-2667
MESSAGE:

NDA 20-748 Differin Cream, 0.1%

Please find medical officer's request for information.

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
TELEPHONE: 301- 827-2020 FAX NUMBER: 301-827-2075

Original NDA 20-748
HFD-540/Huene
HFD-540/Cintron

NDA 20-748
Differin Cream, 0.1%

REQUEST FOR INFORMATION

In the tabulations of the intent-to-treat analyses for the lesion counts and the global assessment in Study 9111-CD271C-EV, the p values run off the bottom of the page and cannot be read. Please submit these for our review. The tabulations referred to are contained in Vol. 1.19.

MESSAGE CONFIRMATION

09/18/97 10:32

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DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Division of Dermatologic and Dental Drug Products

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

FACSIMILE TRANSMISSION

DATE: September 18, 1997. Number of Pages (including cover sheet) 2
TO: Ms. Christine Shank
COMPANY: Galderma Laboratories
FAX NUMBER: 817-263-2667
MESSAGE:

NDA 20-748 Differin Cream, 0.1%

Please find medical officer's request for information.

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
TELEPHONE: 301- 827-2020 FAX NUMBER: 301-827-2075

GALDERMA

ORIGINAL

August 20, 1997

Division of Dermatological and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Blvd., HFD-540
Rockville, Maryland 20850

RE: NDA 20-748 - Amendment
DIFFERIN™ (adapalene cream) Cream, 0.1%
Statistical SAS Datasets

Dear Sir or Madam:

Please find herewith an amendment to pending NDA 20-748 for DIFFERIN™ (adapalene cream) Cream, 0.1%. The amendment provides diskettes containing the electronic data for the two Phase III clinical studies (9111-CD271C-EV and CR90087) in SAS format. The diskettes and a hard copy of instructions and table of contents are provided in the Statistical Review Copy. The Archival Copy contains only the hard copy information.

Should the Statistical Reviewer have any questions regarding the electronic datasets, please contact our biostatistician, Dr. Michael Tuley, at (817) 263-2670 or (800) 528-8225.

Sincere regards,

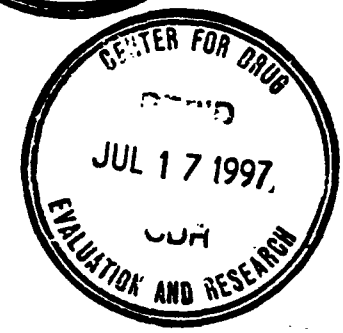
Christine Shank

Christine Shank
Director, Regulatory Submissions
(817) 263-2676

c: Ms. Olga Cintron (HFD-540)
(cover letter only)

GALDERMA LABORATORIES, INC.
P.O. BOX 331329 • FORT WORTH, TEXAS 76163-1329 U.S.A. • TEL. (817) 263-2600 • FAX (817) 263-2667

GALDERMA



July 16, 1997

Food and Drug Administration
Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation and Research
ATTENTION: Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20852

RE: NDA 20-748 (User Fee I.D. #3275)
DIFFERIN™ (adapalene cream) Cream, 0.1%
Original New Drug Application Submission

Dear Sir or Madam:

The applicant, Galderma Laboratories, Inc., is pleased to submit herewith a New Drug Application for DIFFERIN™ (adapalene cream) Cream, 0.1%. This application is submitted pursuant to Section 505 (b) (1) of the Federal Food, Drug, and Cosmetic Act and in accordance with the applicable procedures and requirements established in Part 314 of Title 21 of the *Code of Federal Regulations*.

The proposed new drug product is a topical cream dosage form of adapalene (*USAN*) indicated for the treatment of acne vulgaris. The drug product has been the subject of clinical investigations in the United States under IND — The approved commercial product will be made available to patients only by prescription from a licensed physician.

Drug Development Overview

DIFFERIN Cream, 0.1% is the third dosage form of adapalene to be sponsored by Galderma Laboratories, Inc. New Drug Applications for DIFFERIN (adapalene solution) Solution, 0.1% (NDA 20-338) and DIFFERIN (adapalene gel) Gel, 0.1% (NDA 20-380) were approved on May 31, 1996. All three dosage forms are indicated for once daily (at nighttime) application in the topical treatment of acne vulgaris.

The first U.S. clinical trials with formulated adapalene were initiated in 1988 with the solution dosage form under IND — In 1989, IND 33,540 was submitted for the gel dosage form followed by submission of IND — in 1991 for the cream dosage form. The clinical development program for all three dosage forms followed the guidance and recommendations of

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the Division of Anti-Infective Drug Products, the reviewing division of the FDA at the time. Thus, the medical officers involved in the review of this New Drug Application for DIFFERIN Cream should recognize the similarity between applications for the different dosage forms. The applicant believes the safety and efficacy data with the cream formulation corroborates the studies with the approved solution and gel dosage forms and further supports the clinical use of adapalene in the treatment of acne vulgaris as proposed in the labeling for the drug product.

The nonclinical development program has been an ongoing process that is reflected in the comprehensive integrated summary of studies with adapalene and all three dosage forms and other investigational strengths of the drug. A summary of new information from studies with the cream and gel formulations since submission and review of NDA 20-380 for DIFFERIN Gel (the most recent application incorporating all studies at the time of submission) is provided at the beginning of the discussion followed by the integrated summary. We hope this treatment of the data and information is helpful to the reviewers.

Development of a cream formulation as a third dosage form follows a typical progression of marketing initiatives in recognition of the needs and preferences of acne patients with different skin types. The DIFFERIN Cream formulation incorporates emollient and moisturizing characteristics in a traditional oil-in-water dosage form that will appeal to acne patients with dry skin. The formulation may also help provide relief from the initial drying and burning effects generally experienced with topical retinoids. The DIFFERIN Cream formulation thus offers an alternative therapeutic dosage form to the prescribing dermatologist or physician for patients who experience mild irritation with solution or gel formulations but could benefit from treatment with a topical retinoid. The components of the cream formulation were selected on the basis of proven use in pharmaceutic dosage forms and cosmetic type moisturizers available commercially.

FDA Meetings and Correspondence

There have been no specific meetings or special correspondence regarding the drug development program for the adapalene cream dosage form. Instead the cream formulation has followed the same development program as for the gel and solution. Early communications regarding adapalene that influenced the development of this application are briefly described as follows:

- September 19, 1989 - Meeting with FDA representatives. A satisfactory agreement was reached by the participants on the list of required pharmacology and toxicology studies. With respect to photocarcinogenicity, the agency advised in a letter dated April 27, 1990 to the sponsor, the wording that would be acceptable in labeling the product.
- November 7, 1990 - Discussions were held with the agency regarding the clinical development program which was based on both U.S. and European studies for the gel and solution dosage forms.
- October 19, 1992 - The format for computer generated patient line listings was discussed with the agency for the gel and solution submissions.

Contact Person
It is requested that any questions or comments regarding this application be directed to the person named as follows:

Ms. Christine Shank
Director, Regulatory Submissions
Galderma Laboratories, Inc.
P.O. Box 331329
Fort Worth, Texas 76163

Telephone (817) 263-2676
Fax (817) 263-2738

Reviewers Guide to the Application and Content and Format of the Application
In the administrative part of the application following the Form FDA 356h in Volume 1.1, reviewers are directed to the Reviewers Guide to the Application. This brief presentation describes the organizational and structural features of the application in order to orient the reviewer and assist in location of data and information. It is hoped that this will facilitate understanding of the features of the application and ease location of information; however, if we can be of assistance, please contact us directly.

The Application Index in Volume 1.1 contains a brief two-page introductory FORMAT AND CONTENT OF THE APPLICATION index that provides a quick reference to the Archive Volumes of the application and the pages of the ITEM 1. Application Index by section.

Electronic Versions of the Application
Except for SAS data sets that will be provided in electronic format for statistical evaluation of the Phase III clinical studies, this application is not available in a CANDA format. The applicant can, however, provide the **narrative text** only in electronic format to any reviewer upon request. Please direct a request to the contact person identified above and specify the format desired. All narrative text within the application was created in MICROSOFT WORD 7.0 but may be converted to other software for use by reviewers.

Field Copy Certification
A signed certification of submission of a Field Copy of the Summary Section and the Chemistry, Manufacturing, and Controls Section of the application is provided in Volume 1.2. See application index for location.

The applicant extends its sincere appreciation to the agency staff and reviewers for their time spent in review and consideration of this application. We welcome any requests for assistance and any questions regarding this application.

Sincere regards,

Christine Shank

Christine E. Shank
Director, Regulatory Submissions

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/s/

Lee Simon
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