

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**20-748**

**CORRESPONDENCE**

MAY 26 2000 10:33AM GALDERMA REG AFFAIRS  
TO: FDA DIV DERM DENTAL

NO. 0387 P. 17/18  
**GALDERMA**  
USA

AX  
Date: May 26, 2000

Number of page(s) including cover page: 13

From: Bobbi Woodward

Subject: **DIFFERIN CREAM (NDA 20,748) LABELING**

Please transmit to all individuals at your location.

To: Olga Cintron

c.: File, Chrono

Dear Olga:

We have received the final revised labeling (revision May 25, 2000) for the Differin® Cream (NDA 20,748). Galderma Laboratories is in agreement with this labeling and hereby acknowledges so.

A copy of the final labeling as well as the final product labels is attached.

Thank you for all of your help in coordinating this effort.

Regards,



Bobbi Woodward  
Manager, Regulatory Affairs

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GALDERMA LABORATORIES, L.P.

3000 Alta Mesa Boulevard, Suite 300, Fort Worth, Texas 76133, U.S.A. - Tel: (817) 263-2675 - Fax: (817) 263-2738

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

MAY. 25. 2000 2:59PM

8172632738  
GALDERMA REG AFFAIRS

NO. 6378 P. 1/9  
**GALDERMA**  
USA

**FAX**

Date : May 25, 2000

Number of page(s) 9  
including cover page :

From : Paul Clark

Subject : *NDA 20-748*

Please transmit to  
all individuals at your location.

To : Olga Cintron

c.: Christine Shank; File, Chrono

We have attached our latest version of the Differin Cream labeling. Changes agreed upon during today's teleconference are included. Changes from FDA's labeling dated May 8 are marked.

Regards,



Paul Clark  
Vice President Regulatory Affairs

---

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GALDERMA LABORATORIES, L.P.

3000 Alta Mesa Boulevard, Suite 300, Fort Worth, Texas 76133, U.S.A. - Tel : (817) 263-2675 - Fax : (817) 263-2738

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



■ May 24, 2000

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  
9201 Corporate Blvd., HFD-540  
Rockville, Maryland 20850

RE: NDA 20-748  
DIFFERIN® (adapalene) Cream, 0.1%  
Revised Draft Labeling Amendment

Dear Dr. Wilkin:

This is to document the outcome of our teleconference of May 24, 2000, regarding the labeling for Differin ® (adapalene) Cream 0.1%.

1. Description: We acknowledge that the phrase \_\_\_\_\_ does not convey specific information regarding the stability of the drug substance. We agree to remove this statement, but reserve the ability to include descriptive language to better communicate the stability of adapalene.
2. Clinical Studies: We agree to change the description of the clinical studies to:  
~~In one study patients were provided with a soapless cleanser and were encouraged to refrain from using moisturizers.~~ \_\_\_\_\_
3. Precautions - Information for Patients:
  - a. We agree to include the statement \_\_\_\_\_
  - b. We agree to remove the statement \_\_\_\_\_
  - c. Carcinogenesis, Mutagenesis, Impairment of Fertility: We agree to include information regarding the average recommended human topical dose and the maximum recommended topical human dose. These values will be \_\_\_\_\_ respectively. Information contained in subsequent sections will be changed to present both values.

*Cosmetics  
8 0978*

MAY 25 2000 10:46AM

8172632738  
GALDERMA REG AFFAIRS

NO. 6365 P. 2/3

May 25, 2000  
Jonathan Wilkin, M.D.  
Page 2 of 2

During the discussion the agency acknowledged the need to review the labeling of the other products in this class for the inclusion of information concerning the average and maximum daily doses.

In preparation for our discussion today, we have prepared a tabulation of the incidence of local cutaneous irritation using the scale more, mild, moderate, severe. The supporting references for these values are included.

We appreciate the agency's efforts to resolve these issues.

Kind Regards,



Paul Clark  
Vice President of Regulatory Affairs

C: FAX - Ms. Olga Cintron  
Christine Shank

Attachment: Data tabulation for local tolerance parameters

The data tabulations for local tolerance parameters from the two vehicle-controlled clinical study reports are identified as follows. The report tabulations and other reference materials were provided in the April 24, 2000 Amendment under Attachment E.

Local Tolerance Data Tabulation References		
Study Report No.	Report Tables	Submission Location
I.GUS.04.SRE.18035	10.1, 10.2, 10.3, 10.4, 10.5	September 7, 1999 Amendment Volume 6 of 10, pages 8 0761 - 8 0765
9111-CD271C-EV	7.1, 8.1, 9.1, 10.1, 11.1	Original Application Volume 1.18, pages 8 0881, 8 0884, 8 0887, 8 0890, 8 0894

For tabulation of the worst (maximum) scores, the percentages were calculated based on the following number of patients treated with DIFFERIN Cream:

Study Report No.	Number of Patients	Report Reference
I.GUS.04.SRE.18035	115	September 7, 1999 Amendment Volume 6 of 10, page 8 0579
9111-CD271C-EV	170	See Report Tables 7.1, 8.1, 9.1, 10.1, 11.1
<b>Total No. of Patients</b>	<b>285</b>	

The combined cutaneous irritation data for DIFFERIN Cream from the two vehicle-controlled studies is provided in the following table:

Incidence of Local Cutaneous Irritation with DIFFERIN Cream from Controlled Clinical Studies (N = 285)				
	None	Mild	Moderate	Severe
Erythema	52% (148)	38% (108)	10% (28)	< 1% (1)
Scaling	58% (166)	35% (100)	7.6% (18)	< 1% (1)
Dryness	48% (136)	42% (121)	10.4% (26)	< 1% (2)
Pruritus (persistent)	71% (201)	21% (61)	8.8% (12)	< 1% (1)
Burning/Stinging (persistent)	71% (202)	24% (69)	5.8% (12)	< 1% (2)

Erythema } as in the table  
 scaling }  
 Dryness }  
 Pruritus }  
 Burning/stinging }

48% (136)	42% (121)	10.4% (26)	< 1% (2)
71% (201)	21% (61)	8.8% (12)	< 1% (1)
71% (202)	24% (69)	5.8% (12)	< 1% (2)

$$\begin{array}{r} 115 \\ 170 \\ \hline 285 \end{array} =$$

$$\begin{array}{r} 75 \\ 73 \\ \hline 148 \end{array}$$

Erythema

18035

9111

Total % # of pts

148 52.9 115 + 170 = 285

None	73	75	108	37.9 ✓
mild	35	73	28	9.8 ✓
Moderate	7	21	1	0.35 ✓
Severe	0	1		

Scaly

None	71	95	166	58.2
mild	38	62	100	35.08
Moderate	6	12	18	6.3
Severe	0	1	1	

Dryness

100.35

None	50	86	136	47.7
Mild	48	73	121	42.46
Mod.	16	10	26	9.12
Severe	1	1	2	0.7
None	83	128	211	74.08
mild	22	39	61	21.4
Moderate	9	3	12	4.21
Severe	1	0	1	

Pruritus

None	87	115	202	70.87
Mild	22	47	69	24.21
Moderate	5	7	12	4.21
Severe	1	1	2	

Burning

100.7

**GALDERMA**

USA

AX

Date: May 24, 2000

Number of page(s)  
including cover page: 14

From: Paul Clark

Subject: ***DIFFERIN (ADAPALENE) CREAM, 0.1%  
REVISED DRAFT LABELING AMENDMENT***

Please transmit to  
all individuals at your location.

To: Olga Cintron

c.: File, Chrono

The following is a letter to Dr. Jonathan Wilkin regarding the revised draft labeling amendment for Differin® (adapalene) Cream, 0.1% and the applicant revisions to FDA labeling from a fax dated May 19, 2000. If you have any questions please contact me at 817-269-2675. Thank you.

The information accompanying this facsimile transmission is intended for the use of the recipient named above only. The information may contain confidential information which may be legally privileged, confidential and exempt from disclosure under applicable law. If the reader of this message is not the intended recipient or the employee or agent responsible for delivering the message to the recipient, you are hereby notified that any dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by telephone and return the original message to us at the address below via the U.S. Postal Service. Thank you.

GALDERMA LABORATORIES, L.P.

3000 Alta Mesa Boulevard, Suite 300, Fort Worth, Texas 76133, U.S.A. - Tel: (817) 263-2675 - Fax: (817) 263-2738



## 2. CLINICAL STUDIES

a) Please explain the reason for the agency's statement in the first paragraph ~~that~~ <sup>reference</sup> In one study patients were provided with a soapless cleanser and were encouraged to use it. In our submission dated April 24, 2000 (page 19) we clearly provided evidence from both studies demonstrating the concomitant use of moisturizers by patients. While in one study patients were permitted use of moisturizers only after talking with their investigator and in the other study use of these products was unlimited, efficacy was clearly demonstrated in both studies. Also, efficacy was substantiated regardless whether or not a soapless cleanser was used. We firmly believe that the statements (as follows) added in the *Information for Patients* subsection of the PRECAUTIONS section are adequate and appropriate and provide reasonable and sufficient advice with respect to cleansing and moisturizing during treatment with DIFFERIN Cream.

- Cleanse area with a mild or soapless cleanser before applying this medication.
- Moisturizers may be used if necessary; however, products containing alpha hydroxy or glycolic acids should be avoided.

Inclusion of this kind of information in the PRECAUTIONS section is consistent with information on the use of sunscreens and protective clothing, concomitant use of astringents, preparations containing alcohol, etc.

b) Please clarify what is meant by \_\_\_\_\_

\_\_\_\_\_ If the statement is intended to mean that no other topical medications (or drug products) (e.g., acne, corticosteroid, or rosacea products) were used, then we can accept the statement with the following minor change in wording:

c) As stated in our April 24, 2000 submission (page 18), we compared the agency's data tabulations with the tabulations from the clinical study reports. There are minor differences between the two tabulations that we cannot explain since we do not have the agency's calculations or analyses. Please provide the source and method of analysis performed to arrive at these values.

## 3. PRECAUTIONS *Information for Patients*

- Instruction number 5 was modified pursuant to the first paragraph in item 2 above.
- Instruction number 6 - \_\_\_\_\_ - was reinserted. This statement would, in our estimation, appear to be sound advice for patients being treated for acne vulgaris. We would very much appreciate having your reason for deleting this statement from the latest version of the agency's draft labeling.

4. **PRECAUTIONS** *Carcinogenesis, Mutagenesis, Impairment of Fertility and Pregnancy*

Please provide an explanation as to the origin of the \_\_\_\_\_ maximum recommended topical human dose. In our response of April 28, 2000, we included rationale supporting an average daily application to the face and the daily maximum potential exposure at the recommended clinical dose to be 750 mg (0.75 grams) and 2.5 grams respectively. This proposal was based on our conversation during the April 10, 2000 telecon. However, it appears our evaluation was not reciprocally considered pursuant to the spirit of the discussion. In our opinion, the \_\_\_\_\_ dosage suggested by the agency is not consistent with generally recognized values.

In our review of approved labeling for other related retinoid drug products, there appears to be a common basis for the comparisons of animal exposure to human exposure. Examples are provided as follows:

- *AVITA Cream and Gel* – For purposes of comparisons of the animal exposure to human exposure, the “recommended human topical clinical dose” is defined as 1.0 g of 0.025% AVITA Cream or Gel applied daily to a 50 kg person. Also, the labeling uses the expression “average recommended human topical clinical dose.”
- *RENOVA Cream, 0.05%* - For purposes of comparisons of the animal exposure to human exposure, the “recommended human topical clinical dose” is defined as 500 mg of 0.05% RENOVA applied daily to a 50 kg person.
- *RETIN-A Liquid, Cream, and Gel* – “assuming a 50 kg adult applies 250 mg of 0.1% cream topically”
- *RETIN-A MICRO* – For purposes of comparisons of animal exposure to human exposure, the “recommended human clinical dose” is defined as 1.0 g of 0.1% RETIN-A MICRO applied to a 50 kg person.

Please accept that we are still trying to reach a reasonable understanding and work out an equitable resolution of the issues. The following summarizes this effort:

- We have acknowledged the division’s recent “policy” as communicated to us in the April 10, 2000 telecon regarding conversion of mg/kg doses to mg/m<sup>2</sup> doses and have attempted to comply accordingly, although we question the reasoning behind such “policy.” An alternative approach to risk assessment, originally proposed by the health authorities in Germany, and subsequently adopted by a number of other national authorities, for topical products containing adapalene, was to compare the relative animal to human circulating levels in preference to the applied dose. This is in line with current international trends and may be a preferable choice than the proposition to quote the doses as mg/m<sup>2</sup>/day. We would very much appreciate hearing your views in this regard.
- We know of no basis for the assumption that \_\_\_\_\_ per day of DIFFERIN Cream may be used for the treatment of mild to moderate cases of acne vulgaris. Our April 28, 2000 submission discussed this issue in detail. Actually, we conclude that the *average recommended human topical clinical dose* would be between \_\_\_\_\_ grams/day. This estimation is based on average use estimates from the three controlled clinical trials submitted in the application. We have applied the generous

estimate of \_\_\_\_\_ as the basis for the calculations in the labeling submitted with this amendment. We believe this estimation is an equitable basis for the conversions and is consistent with estimates in the approved labeling for other related retinoids.

- We have again employed the Bodyweight Surface Area Conversion Table (from Freireich, E.J., *et al.* Quantitative comparison of toxicity of anti-cancer agents in mouse, rat, dog, monkey and men. *Cancer Chemother. Rep.* 50: 219, 1996) referenced in our April 28, 2000 submission. This conversion table was found acceptable to the agency with respect to a previous submission. Also, we have received no information, as we originally requested, to recommend another source or authority for basing such conversions.

5. **ADVERSE REACTIONS** – This section of the labeling was extensively discussed in our submission dated April 24, 2000. We do not understand the reason for the expansive tabulations of local cutaneous irritation potential as proposed by the agency. We also do not understand why the vehicle controlled studies and positive controlled study data are \_\_\_\_\_ Nor do we understand why the \_\_\_\_\_ was tabulated (or its relevance to the labeling of adverse reactions to the drug product) and not the reference product data. Also, we find the information in the agency's draft inconsistent with the data tabulations from the study reports. Reference is made to the information we provided in the April 24<sup>th</sup> submission (pages 20-23 and referenced attachments).

We would be most appreciative to have any available agency guidelines and/or official policy statements that dictate or elaborate the content and format for this section of the labeling. We, however, in lieu of such guidance, believe that our version conforms with the scope, intent, and direction of 21 CFR 201.57 (g) of the regulations. In accordance with the direction given in the regulation, the adverse reactions we have listed in the labeling are the **undesirable effects, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or that may be unpredictable in occurrence.** In our description of the local cutaneous irritation, defined as erythema, scaling, dryness, pruritus, and burning, the irritation potential has been categorized by severity (mild, moderate, and severe) and by frequency (percent incidence by severity category). The frequency information for both local cutaneous irritation and reports of other adverse events is from controlled clinical studies, as recommended by the regulation. The adverse reactions are listed in decreasing order of frequency with approximate estimates of incidence in keeping with the direction provided in the regulation. Further, it is noted that the information we have provided with respect to the incidence of local cutaneous irritation potential is extensive in comparison with the adverse reaction information approved in labeling for other related products such as RETIN-A and RETIN-A MICRO. The information in our estimation is also reasonably consistent with the labeling approved for TAZORAC Gel, 0.1%.

We believe that this section of the labeling as revised for this submission clearly provides adequate and factual information with respect to the kind of treatment-related experiences a clinician may observe in patients using DIFFERIN Cream. The data and information

May 24, 2000  
Jonathan Wilkin, M.D.  
Page 5 of 5

are clearly representative of the experiences from controlled clinical studies and are also reflective of the experiences the applicant has received from post-marketing reports with the use of DIFFERIN Gel and Solution.

In conclusion we appreciate your consideration of this information, our questions, our concerns, and our revisions to the draft labeling for DIFFERIN Cream, 0.1%.

Sincere regards,



Christine Shank  
Sr. Director, Regulatory Submissions

c: Fax – Ms. Olga Cintron

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



AMENDMENT

BL

May 8, 2000

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  
9201 Corporate Blvd., HFD-540  
Rockville, Maryland 20850



RE: NDA 20-748  
DIFFERIN® (adapalene) Cream, 0.1%  
**Revised Draft Labeling Amendment**

Dear Dr. Wilkin:

Please find enclosed revised draft package insert labeling for DIFFERIN® (adapalene) Cream, 0.1%. The revisions include the following:

- **Pharmacokinetics** – The following information was deleted from this section of the labeling in response to the Biopharm comments we received on April 28, 2000.

- 
- **Drug Interactions** – The second paragraph in this section regarding cumulative irritation studies with concomitant medications has been deleted from this latest version of the package insert. Deletion of this information from the package insert was discussed in the telecon on April 10, and I agreed at that time to remove the information. I apologize for the oversight in previous labeling revisions.
  - An edited version of the labeling incorporates all revisions from the amendments dated April 24 and 28, 2000 and includes the above. A clean copy of the revised package insert labeling dated May 5, 2000 is also provided.

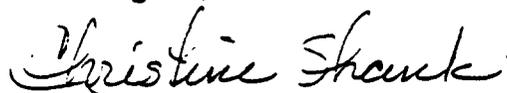
ORIGINAL



May 8, 2000  
Dr. Jonathan K. Wilkin  
Page 2 of 2

We hope this information is satisfactory and we look forward to a final decision on this application.

Sincere regards,

A handwritten signature in cursive script that reads "Christine Shank".

Christine Shank  
Sr. Director, Regulatory Submissions

c: Archival Copy  
Chemistry Review Copy  
Desk Copy - Ms. Olga Cintron

**FAX**

Date : May 1, 2000  
 From : Christine Shank  
 Dept. : Regulatory Affairs USA  
 Subject : **NDA 20-748**  
**DIFFERIN Cream, 0.1%**  
**Biopharmaceutic Comment - Labeling**  
 To : Ms. Olga Cintron  
 FDA Project Manager

Number of page(s)  
 including cover page : 1

Please transmit to  
 all individuals at your location.

c.: Paul Clark  
 File, Chrono

Dear Olga,

I am in receipt of your facsimile transmission dated April 28, 2000 providing the Biopharm response to question # 4 of my submission dated March 9, 2000.

I very much appreciate the information as it clearly communicates the reviewer's conclusions and concerns regarding the pharmacokinetic data obtained from the clinical study (CR 90087). We accept this response and agree to the deletion of the related information from the package insert labeling.

Please advise if there is something you wish me to do at this time, otherwise, I will await the results of the labeling review meeting you plan to have on May 8<sup>th</sup>.

Best regards,

*Christine Shank*  
 Christine Shank

*See: Please come by 5/1*

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GALDERMA LABORATORIES, L.P.

3000 Alta Mesa Boulevard, Suite 300, Fort Worth, Texas 76133, U.S.A. • Tel : (817) 263-2676 • Fax : (817) 263-2738



April 28, 2000

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  
9201 Corporate Blvd., HFD-540  
Rockville, Maryland 20850



AMENDMENT

RE: NDA 20-748  
DIFFERIN® (adapalene) Cream, 0.1%  
Revised Draft Labeling Amendment – Pharmacology/Toxicology Data Issues

BC

Dear Dr. Wilkin:

Pursuant to discussion with the agency on April 10, 2000, the applicant has revised the physician package insert labeling for DIFFERIN® (adapalene) Cream, 0.1%. The enclosed draft labeling has been revised based on the issues discussed relative to the preclinical data and information presented in the PRECAUTIONS *Carcinogenesis, Mutagenesis, Impairment of Fertility* and *Pregnancy* subsections.

The draft labeling provided in this amendment addresses only the issues concerning the preclinical data and information discussed on April 10, 2000. Documentation and calculations supporting the applicant's conclusions are provided. We believe that the revisions represent significant compromise as well as offer reasonable reevaluations and conclusions that hopefully will bring the labeling issues to a closure.

All significant other labeling issues discussed on April 10, 2000 were addressed in our amendment dated April 24, 2000.

We appreciate this opportunity to work closely with you and the personnel in your organization.

Sincere regards,

Christine Shank  
Sr. Director, Regulatory Submissions

c: Archival Copy, Chemistry and Pharm/Tox Review Copies, Desk Copy for Ms. Olga Cintron

DUPLICATE



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: April 28, 2000. Number of Pages (including cover sheet) - 2  
TO: Ms. Christine Shank, Director, Regulatory Submissions  
COMPANY: Galderma, L.P.  
FAX #: 817-263-2738

MESSAGE: Re: NDA 20-748 Differin Cream

Please find Biopharm's response to question # 4 included in submission dated March 9, 2000 (questions for clarification and resolution).

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

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CC: NDA 20-748  
DIV FILES (HFD-540)

The multicenter safety and efficacy study was conducted using a different formulation than the market image in that the former contains \_\_\_\_\_ Whether this formulation difference will impact on the study outcome is not clear. In addition, only one blood sample per subject was collected in the study and there appears no records of dose, dosing area and sampling time for each individual making it impossible to interpret the data. Because of these reasons, the information was not included in the FDA proposed label.

April 24, 2000

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  
9201 Corporate Blvd., HFD-540  
Rockville, Maryland 20850

RE: NDA 20-748  
DIFFERIN® (adapalene) Cream, 0.1%  
Revised Draft Labeling Amendment – Clinical Data Issues

Dear Dr. Wilkin:

Pursuant to discussion with the agency on April 10, 2000, the applicant has revised the physician package insert labeling for DIFFERIN® (adapalene) Cream, 0.1%. The enclosed draft labeling incorporates the mutually acceptable elements that were discussed. Additionally, the applicant has reevaluated other issues that were debated and has corrected, repositioned, or proposed wording better suited for presentation of certain information.

The draft labeling provided in this amendment addresses only the issues concerning clinical data and information discussed on April 10, 2000 and not the pharmacology/toxicology issues. The pharmacology/toxicology issues are pending revision by the applicant and possibly further discussion between the agency and the applicant's technical representatives. A separate amendment addressing the preclinical data issues will be submitted to the NDA this week.

I wish to thank all the agency representatives who participated in the April 10, 2000 telecon. I expect you will find that the revisions to the draft labeling are respectful of the discussions and that the documentation helps to clarify the applicant's position.

Sincere regards,



Christine Shank  
Sr. Director, Regulatory Submissions

c: Archival Copy, Chemistry and Clinical Review Copies, Desk Copy for Ms. Olga Cintron

*In a communication faxed to the Agency on 5/1/00, the sponsor indicated that they now accept our proposed PK label. Therefore no action is needed on this submission.*

*BC*



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

*10. Cintron*

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: April 11, 2000. Number of Pages (including cover sheet) - 6  
TO: Ms. Christine Shank, Sr. Director, Regulatory Submissions  
COMPANY: Galderma, L.P.  
FAX #: 817-263-2738

MESSAGE: Re: NDA 20-748 Differin Cream

Please find the tables reflecting how the Adverse Reactions section tables of the labeling were tabulated.

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

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*10-2-2000  
HFD-540/100 FILES  
Christine Shank*

Local tolerance assessments Study 18035 Sponsor data		
Severity	Differin cream	Vehicle
Erythema		
None	73 (64%)	83 (72%)
Mild	35 (30%)	28 (24%)
Moderate	7 (6%)	5 (4%)
Severe	-	-
Scaling		
None	71 (62%)	96 (83%)
Mild	38 (33%)	17 (15%)
Moderate	6 (5%)	3 (3%)
Severe	-	-
Dryness		
None	50 (44%)	75 (65%)
Mild	48 (42%)	36 (31%)
Moderate	16 (14%)	5 (4%)
Severe	1 (0.9%)	-
Pruritus		
None	83 (72%)	98 (85%)
Mild	22 (19%)	16 (14%)
Moderate	9 (8%)	2 (2%)
Severe	1 (0.9%)	-
Stinging/burning		
None	87 (76%)	106 (91%)
Mild	22 (19%)	10 (9%)
Moderate	5 (4%)	-
Severe	1 (0.9%)	-

2

Local tolerance - Study 9111 Sponsor's data					
	None	Mild	Moderate	Severe	Total
Erythema					
Differin	75 (44%)	73 (43%)	21 (12%)	1 (0.6%)	170
Vehicle	98 (57%)	68 (40%)	6 (4%)	0	172
Scaling					
Differin	95 (56%)	62 (37%)	12 (7%)	1 (0.6%)	170
Vehicle	144 (84%)	26 (15%)	2 (1%)	0	172
Dryness					
Differin	86 (51%)	73 (43%)	10 (6%)	1 (0.6%)	170
Vehicle	138 (80%)	30 (17%)	4 (2%)	0	172
Burning					
Differin	115 (68%)	47 (28%)	7 (4%)	1 (0.6)	170
Vehicle	156 (91%)	14 (8%)	2 (1%)	0	172

Local tolerance - Study 90087 Sponsor's data					
	None	Mild	Moderate	Severe	Total
Erythema					
Differin	30 (23%)	72 (55%)	25 (19%)	4 (3%)	131
Retin-A	19 (14%)	74 (55%)	34 (25%)	7 (5%)	134
Scaling					
Differin	45 (34%)	62 (47%)	18 (14%)	6 (5%)	131
Retin-A	24 (18%)	65 (49%)	39 (29%)	6 (5%)	134

Local tolerance - Study 90087 Sponsor's data					
	None	Mild	Moderate	Severe	Total
Dryness					
Differin	28 (21%)	78 (56%)	20 (15%)	5 (4%)	131
Retin-A	8 (6%)	77 (58%)	41 (31%)	8 (6%)	134
Burning					
Differin	111 (85%)	16 (12%)	3 (2%)	1 (0.8)	131
Retin-A	104 (78%)	19 (14%)	9 (7%)	2 (2%)	134

At least mild reactions - Differin cream Pooled results - Studies 9111 and 18035 - by No. Of patients Compiled by clinical reviewer			
	Study 9111 n=170	Study 18035 n=119	Total n=289
Erythema	95	42	137/289 = 47%
Scaling	75	44	119/289 = 41%
Dryness	84	65	149/289 = 52%
Pruritus	-	32	32/119 = 27%
Burning	55	28	83/289 = 29%

At least mild reactions - Vehicle Pooled results - Studies 9111 and 18035 - by No. Of patients Compiled by clinical reviewer			
	Study 9111 n=172	Study 18035 n=118	Total n=290
Erythema	74	33	107/290 = 37%
Scaling	28	20	48/290 = 17%
Dryness	34	41	75/290 = 26%
Pruritus	-	18	18/118 = 15%
Burning	16	10	26/290 = 9%

4

At least moderate reactions - Differin cream Pooled results - Studies 9111 and 18035 - by No. Of patients Compiled by clinical reviewer			
	Study 9111 n=170	Study 18035 n=119	Total n=289
Erythema	22	7	29/289 = 10%
Scaling	13	6	19/289 = 7%
Dryness	11	17	28/289 = 10%
Pruritus	-	10	10/119 = 8%
Burning	8	6	14/289 = 5%

At least moderate reactions - Vehicle Pooled results - Studies 9111 and 18035 - by No. Of patients Compiled by clinical reviewer			
	Study 9111 n=172	Study 18035 n=118	Total n=290
Erythema	6	5	11/290 = 4%
Scaling	2	3	5/290 = 2%
Dryness	4	5	9/290 = 3%
Pruritus	-	2	2/118 = 2%
Burning	2	0	2/290 = <1%

Severe reactions - Differin cream Pooled results - Studies 9111 and 18035 - by No. Of patients Compiled by clinical reviewer			
	Study 9111 n=170	Study 18035 n=119	Total n=289
Erythema	1	0	1/289 = < 1%
Scaling	1	0	1/289 = < 1%
Dryness	1	1	2/289 = < 1%
Pruritus	-	1	1/119 = < 1%
Burning	1	1	2/289 = < 1%

Study 90087 n=131 Compiled by clinical reviewer	
At least mild reactions	
Erythema	101/131 = 77%
Scaling	86/131 = 66%
Dryness	103/131 = 79%
Burning	20/131 = 15%
At least moderate reactions	
Erythema	29/131 = 22%
Scaling	24/131 = 18%
Dryness	25/131 = 19%
Burning	4/131 = 3%
Severe reactions	
Erythema	4/131 = 3%
Scaling	6/131 = 5%
Dryness	5/131 = 4%
Burning	1/131 = < 1%



Division of Dermatologic and  
Dental Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane, HFD-540  
Rockville, MD 20857

FACSIMILE TRANSMISSION RECORD

DATE: January 25, 2000 Pages (including cover) 2  
TO: Dr. Christine Shank, Sr. Director, Reg. Sub.  
COMPANY: Gilman  
ADDRESS: \_\_\_\_\_  
FAX PHONE#: 817-263-2738 Our Fax # (301) 827-2075  
Voice # (301) 827-2020

MESSAGE:

Please find Brigham request for  
information.

NOTE: We are providing the attached information via telephone facsimile 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: Ally Carter  
TITLE: Project Manager  
TELEPHONE: 301-827-2020

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

cc: NDA 20-748  
HFD-880/lee

NDA 20-748

Regarding the bioanalytical method:

a. Please clarify what \_\_\_\_\_ is and explain the purpose of \_\_\_\_\_

b. It was stated that the samples were stable for \_\_\_\_\_ under  $-20^{\circ}\text{C}$ . The results were not provided. In addition, it is unclear whether the \_\_\_\_\_ period covers the actual sample storage time in this study. Further, are there data showing that samples are stable at room temperature during processing for assay and storage?



March 31, 2000

Jonathan K. Wilkin, M.D.  
 Director  
 Division of Dermatologic 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



**NDA ORIG AMENDMENT**  
 SU / A2

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

Dear Dr. Wilkin:

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 also submitted in response to the agency's request in the notification, dated March 8, 2000, to the applicant that the NDA for DIFFERIN® (adapalene) Cream, 0.1% was found to be **approvable**. This submission, coupled with the March 9, 2000 Amendment, constitutes the applicant's complete response to the approvable letter dated March 8, 2000.

The clinical safety information provided in this report is an update of the safety information generated from foreign and domestic studies with the drug substance and topical formulations of adapalene since submission of the Major Amendment dated September 7, 1999. The September 7, 1999 Amendment included comprehensive integrated summaries of human efficacy and safety data for DIFFERIN Cream and other dosage forms of adapalene since submission of the original application. Principally, this update relates to human experience with the marketed drug product DIFFERIN® (adapalene gel) Gel, 0.1%.

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

Sincere regards,

*Christine Shank*

Christine Shank  
 Sr. Director, Regulatory Submissions

\* M.O. Barrett  
 dated May 15, 2000

Copies: Archival Copy and Clinical Review Copy (3 volumes each)  
 Pharmacology Review Copy (volume 1 only)  
 Extra Review Copy (volume 1 only)



NDA ORIG AMENDMENT

March 9, 2000

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  
9201 Corporate Blvd., HFD-540  
Rockville, Maryland 20850



BL

RE: NDA 20-748  
DIFFERIN® (adapalene) Cream, 0.1%  
**Applicant Response to FDA Approvable Letter Dated March 8, 2000 and  
Information Amending the Application**

Dear Dr. Wilkin:

Reference is made to your letter dated March 8, 2000 providing notification to the applicant that the new drug application for DIFFERIN® (adapalene) Cream, 0.1%, as amended, was found to be approvable pending acceptance by the applicant of the draft labeling. Reference is also made to a telecon with you and Ms. Olga Cintron on March 7, 2000.

Pursuant to the provisions of 21 CFR 314.110(a)(1), the applicant submits herewith an amendment to the pending application. This amendment in effect permits extension of the review period not to exceed 45 days from the date of receipt by the agency. However, as agreed in our March 7<sup>th</sup> telecon, further review, responses, and discussions with respect to the labeling for this drug should not require more than 60 days in order to effect final approval.

To facilitate this process, please find enclosed the applicant's questions and comments regarding the draft package insert labeling provided by the agency with the approvable letter. The applicant has also provided a revised draft of the labeling (March 8, 2000 version) incorporating, to the extent possible, agency recommendations. We of course await your response to our itemized questions before we can reach a final resolution on the package insert.

With respect to the primary tube and secondary carton labeling for the drug product, we submit herewith our acceptance of the recommended revisions. This labeling is, therefore, being prepared for production printing as revised. Also, we have adopted the graphic changes submitted by example in our March 3, 2000 amendment for preparation of final component artwork. We anticipate that with respect to the component labeling, no further revisions will be indicated.

ORIGINAL

Jonathan K. Wilkin, M.D.  
March 9, 2000  
Page 2 of 2

We appreciate your consideration of this amendment information and look forward to hearing from you soon. I personally thank you and Ms. Cintron for telephoning me the other evening. With your assistance in providing the clarification we need to understand the labeling issues, and with further discussion to resolve any differences, I believe we can quickly bring this application to final approval.

Please also be advised that I am in the process of preparing the requested safety update. I however would like your consideration and agreement to separate this requirement from the labeling issues and application approval process. I commit to submit the safety update as soon as possible, hopefully within the next 60 days. In the event any significant new information relating to the safety or effectiveness of this drug becomes available, I will notify you accordingly. I recently prepared and submitted composite (covering all dosage forms of adapalene) annual reports for the adapalene gel and solution investigational new drug applications and did not note new or different information with respect to what has been previously known about the drug. Thus, I do not anticipate any unexpected issues in preparation of the safety update for this application.

Sincere regards,



Christine Shank  
Sr. Director, Regulatory Submissions

c: Archival Copy  
Technical Review Copies (5)  
Desk Copy with Diskette of Revised Package Insert Labeling to Ms. Olga Cintron



March 3, 2000

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



RE: NDA 20-748  
DIFFERIN® (adapalene cream) Cream, 0.1%  
Example Tube and Carton Labeling Amendment

Dear Sir or Madam:

This amendment provides revised examples of the graphic (mock-up) representations of the primary tube and secondary carton labeling proposed for the commercial drug product. We have revised the graphics for both DIFFERIN Gel and DIFFERIN Cream pursuant to a telecon on February 28, 2000 with Ms. Olga Cintron, Dr. Wilson DeCamp, and Dr. Bill Timmer. As discussed, the revisions to the graphic representations for the two products are intended to promote product recognition and distinction between the two commercial dosage forms. The following components for DIFFERIN® (adapalene cream) Cream, 0.1% and DIFFERIN® (adapalene gel) Gel, 0.1% are provided in mock-up format for review and comparison.

- 15 gram primary container (tube) label
- 45 gram carton

Please be advised that these examples are not absolutely true to color. The "distinguishing colors" in final production printing will be \_\_\_\_\_ for DIFFERIN Cream and \_\_\_\_\_ for DIFFERIN Gel. We believe the revised "look" of the packaging will fulfill the intent to prevent product dispensing errors.

We appreciate your consideration of this additional information.

Sincere regards,

Christine Shank  
Sr. Director, Regulatory Submissions

c: Archival, Chemistry Review, and Desk Copies

DUPLICATE



January 28, 2000

BS

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



RE: NDA 20-748 Amendment  
 DIFFERIN® (adapalene cream) Cream, 0.1%  
 Biopharmaceutic Section – Response to FDA Request for Information

Dear Sir or Madam:

Reference is made to a facsimile transmission dated January 25, 2000 requesting additional information in regards to the bioanalytical method submitted to the NDA on January 21, 2000.

The following information is provided in response to this request:

**Biopharmaceutic Comments:**

Regarding the bioanalytical method:

1. Please clarify what \_\_\_\_\_ is and explain the purpose of \_\_\_\_\_
2. It was stated that the samples were stable for \_\_\_\_\_ under -20°C. The results were not provided. In addition, it is unclear whether the \_\_\_\_\_ period covers the actual sample storage time in this study. Further, are there data showing that samples are stable at room temperature during processing for assay and storage?

**Applicant Response:**

1. \_\_\_\_\_ is known to contain important quantities of \_\_\_\_\_

Adapalene is an organic acid and, as such, can undergo glucuronation. To maximize the quantities of adapalene quantified in plasma samples and have a better estimation of the systemic exposure to the drug, it was decided to proceed to a \_\_\_\_\_ before analysis of the plasma samples issued from all the clinical studies performed with this drug.

ORIGINAL



2. The stability of adapalene in plasma samples stored at  $-20^{\circ}\text{C}$  has been studied, and the mean results obtained are given in the report of the study 1.CG.03.VAL.4025, page 6 of 21.

To provide more information, the individual results obtained during the stability study are provided in the following tables (concentrations are expressed as ng/2 mL). The data are from analyses of samples stored for \_\_\_\_\_ at  $-20^{\circ}\text{C}$ .

Theoretical concentration	Measured concentration	% of error
---------------------------	------------------------	------------

Mean measured concentration: 1.03 ng/2 mL  
Coefficient of variation: —  
% of error: —

Theoretical concentration	Measured concentration	% of error
---------------------------	------------------------	------------

Mean measured concentration: 2.04 ng/2 mL  
Coefficient of variation: —  
% of error: —

Theoretical concentration	Measured concentration	% of error
---------------------------	------------------------	------------

Mean measured concentration: 5.07 ng/2 mL  
Coefficient of variation: —  
% of error: —

- Regarding the study dates, the human pharmacokinetic study was performed between December 8, 1998 and December 13, 1998.
- Plasma samples were received at Galderma R & D on December 17, 1998 for the first set of samples (first aliquots) and then on January 8, 1999 (second aliquots).
- The analysis was performed between January 20, 1999 and February 05, 1999.
- Consequently, there was a time period of less than 2 months between the blood drawing and the analysis of the plasma samples.

At the validation study time (March 08, 1994 to May 06, 1994), no formal protocol was necessary to study the stability of the samples at room temperature for assay and storage. It was however assumed that, in view of the results obtained during the validation step, these parameters were taken into account. The precision of the assay was better than \_\_\_\_\_ at the \_\_\_\_\_ concentrations studied, \_\_\_\_\_, and the accuracy better than \_\_\_\_\_, at the same concentrations. The reproducibility of the method was good. The coefficient of variation was better than \_\_\_\_\_ and the percentage of error less than \_\_\_\_\_ at the same \_\_\_\_\_ concentrations.

If there are any questions, please contact me.

Sincere regards,



Christine Shank  
Sr. Director, Regulatory Submissions

Copies:       1 Archival  
                  1 Biopharm Review



January 27, 2000

NEW CORRESP

AC BC

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



RE: NDA 20-748  
DIFFERIN® (adapalene cream) Cream, 0.1%  
Mock-up Tube and Carton Labeling and CMC Information Amendment

Dear Sir or Madam:

This amendment provides graphic (mock-up) representations of the primary tube and secondary carton labeling proposed for the commercial drug product. We would very much appreciate the agency's review of these labeling components and would like to have feedback as soon as possible. The following components for DIFFERIN® (adapalene cream) Cream, 0.1% are provided in mock-up format for review:

- 2 gram physician sample (tube) label
- 15 gram primary container (tube) label
- 15 gram carton
- 45 gram primary container (tube) label
- 45 gram carton

In consideration of this labeling, please be advised that the applicant has undergone a recent name change that is reflected in the mock-up labeling. A copy of the Certificate of Limited Partnership from the Secretary of State establishing Galderma Laboratories, L.P. as an official name change for the applicant is provided for reference. With the exception of the applicant name change, the text to be printed on the tubes and cartons is identical in content to the draft labeling submitted in the Major Amendment to the NDA dated September 7, 1999 (Archival Volume 1 of 10, Pages 2 0005 - 2 0009).

We would also like to enlist your assistance with a matter of concern involving the graphics that have been imposed for this product line by Galderma Corporate Headquarters. It has been brought to our attention by our affiliate in Canada, where both the cream and gel dosage forms are being marketed, that there have been complaints from physicians and pharmacists with respect to the similarity of the graphics for the two dosage forms. There have in fact been a number of incidences involving dispensing errors due to the "look alike" packaging for these two

DUPLICATE

dosage forms. We, Galderma Laboratories, L.P., do not wish to perpetuate this problem in the U.S. market; thus, we would like to have your opinion in the matter. For comparison I am providing mock-ups of the tube and carton labeling for the marketed gel dosage form. In a busy pharmacy dispensing environment (and possibly a physician office where samples are dispensed), packaging distinctions are critical in aiding product recognition. It is our sincere concern that the minor differences in the packages for the cream and gel are insufficient to permit easy or rapid product recognition especially as the two dosage forms will most likely be stocked together. While dispensing the gel in lieu of the cream or vice versa is probably not a significant health risk or threat, it could cause a number of problems, not the least of which would be patient confusion and complaints. Thus, we would like another opinion or perspective in the matter to aid in our internal discussions, yours of course would bear substantive consideration.

In closing there are two additional administrative items of relevance to the pending application.

We have received notification from the manufacturer of the drug substance, adapalene, of a name change. The manufacturer formerly operating under the name \_\_\_\_\_ is now identified as:

\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_ The manufacturer submitted on December 21, 1999 a revised \_\_\_\_\_ for ADAPALENE to the Food and Drug Administration DMF Staff. \_\_\_\_\_ has granted authorization to the FDA to refer to the updated version of their DMF on behalf of Galderma Laboratories. A copy of the reference authorization letter is provided.

The applicant has also received notification of a name change for the manufacturer (fabricator) of the \_\_\_\_\_ employed as primary packaging for the finished dosage form of adapalene cream. The manufacturer formerly known as \_\_\_\_\_ is now identified as:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_ has officially notified the FDA of the name change affecting the \_\_\_\_\_ Copies of the reference letters dated December 7, 1999 authorizing the agency to refer to the DMF on behalf of applications and submissions sponsored by Galderma Laboratories are provided.

January 27, 2000  
Page 3 of 3

We appreciate your consideration of this additional information. If you should have any questions or if I can be of assistance in any regard, please contact me.

Sincere regards,



Christine Shank  
Sr. Director, Regulatory Submissions  
Telephone (817) 263-2676  
FAX (817) 263-2738

Copies:       1 Archival  
               1 CMC Review  
               1 Extra Review  
               FAX of Cover Letter to Ms. Olga Cintron, Project Manager

# MESSAGE CONFIRMATION

01/25/00

11:59

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DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S. CODE
01/25 11:58	00'39"	8172632738	002/002	OK		0000



**Division of Dermatologic and  
Dental Drug Products**  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane, HFD-540  
Rockville, MD 20857

## FACSIMILE TRANSMISSION RECORD

DATE: January 25, 2000 Pages (including cover) 2  
TO: Ms. Christine Shank, Sr. Director Reg. Div.  
COMPANY: Gibson  
ADDRESS: \_\_\_\_\_  
FAX PHONE#: 817-263-2738 Our Fax # (301) 827-2075  
Voice # (301) 827-2020

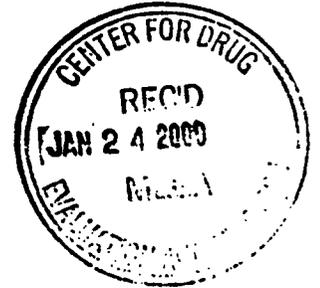
MESSAGE:  
Please find Program request for  
information.



January 21, 2000

BB

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



RE: NDA 20-748 Amendment  
DIFFERIN® (adapalene cream) Cream, 0.1%  
Biopharmaceutic Section – Response to FDA Request for Information

Dear Sir or Madam:

Reference is made to a facsimile transmission dated January 14, 2000 from Ms. Olga Cintron, FDA Project Manager, requesting the assay method and method validation for the human pharmacokinetic study conducted according to Protocol No. 1.GUS.04.SPR.18036. The results of this study were submitted in the Major Amendment to the NDA on September 7, 1999.

According to the study report submitted in the Major Amendment (Archival Volume 3 of 10, Page 6 0313 – Item 6. Human Pharmacokinetics and Bioavailability Section), the bioanalytical method and validation documentation are contained in Report No. 1.CG.03.VAL.4025.

Please find with this submission Bioanalytical Method Validation Report No. 1.CG.03.VAL.4025. This report contains the following:

- Validation documentation for the bioanalytical method \_\_\_\_\_ used in the human pharmacokinetic study.
- Bioanalytical Method No. \_\_\_\_\_ found on pages 10–16 of the validation report.
- Typical Chromatograms – found on pages 17–20 of the validation report.

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

Sincere regards,

Christine Shank  
Sr. Director, Regulatory Submissions

c: Ms Olga Cintron (fax copy)

ORIGINAL



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: January 14, 2000. Number of Pages (including cover sheet) - 1

TO: Ms. Christine Shank, Sr. Director, Regulatory Submissions  
COMPANY: Galderma Labs.  
FAX #: 817-263-2738

MESSAGE: NDA 20-748 Differin Cream

**Information request from Biopharm follows:**

**Please provide the assay method and method validation for PK study #  
1.GUS.04.SPR.18036.**

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

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*CC: NDA 20-748  
HFD-540 BIV FILES  
HFD-330/Lee*

HFD-540'01117071

NDA 20-748

OCT 7 1999

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

Dear Ms. Shank:

We acknowledge receipt on September 8, 1999 of your September 7, 1999 resubmission to your new drug application (NDA) for Differin (adapalene cream) Cream, 0.1%.

This resubmission contains additional clinical statistical, human pharmacokinetics, microbiology, chemistry, manufacturing, and controls information, and revised draft labeling for the drug product submitted in response to our July 9, 1998 action letter.

We consider this a complete class 2 response to our action letter. Please be advised that the user fee goal date is March 8, 2000.

This acknowledgement letter supersedes the letter issued on September 28, 1999.

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

Sincerely,

*MJ*  
Mary Jean Kozma-Fornaro  
Supervisor, Project Management Staff  
Division of Dermatologic and Dental Drug Products  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research