CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-748

ADMINISTRATIVE DOCUMENTS

PATENT AND EXCLUSIVITY INFORMATION (ITEM 13)

1. **Active Ingredient:** Adapalene (USAN)

2. **Strength:** 0.1% (1 mg/g)

3. **Trade Name:** DIFFERIN™

4. **Dosage Form and Route of Administration:** Cream, Topical application to the skin

5. **Applicant Firm Name:** Galderma Laboratories, Inc.

The applicant, Galderma Laboratories, Inc., is a corporate entity doing business in the U.S. at 3000 Alta Mesa Blvd., Suite 300, Fort Worth, TX 76133

6.

Applicable Patent	Expiration Date	Patent Holder
4,717,720	April 10, 2006*	Centre International de Recherches Dermatologiques (C.I.R.D.) Valbonne, FRANCE

U.S. Agent for the Patent Holder
Norman Stepno, Esq.
Burns, Doane, Swecker & Mathis, L.L.P.
699 Prince St.
Alexandria, VA 22314

* Pursuant to the provisions of the Drug Price Competition and Patent Term Restoration Act of 1984 patent term extension has been applied for subsequent to approval on May 31, 1996 of NDAs 20-338 and 20-380 for DIFFERIN™ Solution and Gel, 0.1%.

7. **Brief description of each patent which claims the drug:**

The following is a method of use patent for the drug, adapalene.

Patent No.

4,717,720 claims the compound adapalene, 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid, and its use in effective amounts in pharmaceutical compositions suitable for enteral, topical, parenteral or ocular administration.

8. **Claimed Exclusivity:**

The applicant claims three (3) years marketing exclusivity upon approval of the drug product which is the subject of this application based on the following criteria.

1) The applicant, Galderma Laboratories, Inc., is the holder and sponsor of the pioneer product applications NDA 20-338 and NDA 20-380 for DIFFERIN™ (adapalene solution) Solution, 0.1% and DIFFERIN™ (adapalene gel) Gel, 0.1%, respectively, submitted under 505 (b) (1) of the FD&C Act and approved on May 31, 1996. The approvals of these New Drug Applications were the first for the new chemical entity, adapalene. This application for DIFFERIN™ (adapalene cream) Cream, 0.1% is, thus, the third topical dosage form of adapalene sponsored by Galderma Laboratories, Inc. DIFFERIN™ (adapalene gel) Gel, 0.1% has been in commercial distribution in the U.S. since August 1996. Five years marketing exclusivity was granted for the solution and gel dosage forms upon approval of NDAs 20-338 and 20-380.

2) New clinical investigations have been conducted by the applicant with the cream dosage form of the drug in support of this New Drug Application. Five Phase I Clinical Pharmacology studies and two Phase III controlled Safety and Efficacy studies were conducted with adapalene cream, 0.1%. The applicant certifies that these studies have not previously formed the basis of approval of any other application with the drug. Please refer to **Tables 1a and 1b** (appended) for a description of the studies and location of the study reports in this application.

3) This New Drug Application is submitted pursuant to Section 505 (b) (1) of the Federal Food, Drug, and Cosmetic Act. The applicant is unaware of any published studies or other publicly available reports with a cream dosage form of adapalene which could support an approval of a New Drug Application.

4) Galderma Laboratories, Inc. is named in the Form FDA 1571 as the sponsor of IND ——— which covers the drug product, adapalene cream, 0.1%. Galderma

Laboratories, Inc. and the Galderma Research and Development Center (C.I.R.D. Galderma) in Valbonne, France, conducted or sponsored the clinical studies reported in this application. Galderma Laboratories, Inc. and C.I.R.D. Galderma are subsidiaries organized under Galderma S.A., Levallois Perret, France.

Christine E. Shank

Christine E. Shank
Director, Regulatory Submissions
Galderma Laboratories, Inc.
Authorized Company Representative

July 14, 1997
Date

Appendices: **Table 1a** - Clinical Pharmacology Studies - Adapalene Cream

Table 1b - Clinical Safety and Efficacy Studies - Adapalene Cream

EXCLUSIVITY SUMMARY FOR NDA # 20-748 SUPPL #__N/A_____

Trade Name: Differin Cream, 0.1%

Generic Name: adapalene

Applicant Name: Galderma Labs. HFD # 540

Approval Date If Known:_____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES/_X__/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X__/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /_X__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?
__3 years__

e) Has pediatric exclusivity been granted for this Active Moiety? No.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO - please indicate as such)

YES /___/ NO /_X__/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active

moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-338 Differin Solution, 0.1%

NDA# 20-380 Differin Gel, 0.1%

NDA# _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/ N/A

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS.

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations?
(The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # SRE 18035
Investigation #2, Study # 9111-CD271C-EV

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # SRE-18035

Investigation #2, Study # 9111-CD271C-EV

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided

substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # ___ YES /_X__/ NO /___/ Explain: _____

Investigation #2

IND # ___ YES /_X__/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

Signature:Date:Title: LSI 2/24/00 (Project Manager)

Signature of Office/Division Director

Signature:Da LSI 3/7/00

cc: Original NDA 20-748; HFD-540 Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 20-748 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

54 Trade and generic names/dosage form: Differin (adapalene) Cream, 0.1% Action: AP AE NA

Applicant Galderma Therapeutic Class 35

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate __ inadequate __

Proposed indication in this application Topical treatment of acne vulgaris

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ✓ Yes (Continue with questions) __ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__ Neonates (Birth-1month) __ Infants (1month-2yrs) __ Children (2-12yrs) ✓ Adolecents(12-16yrs)

__ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

__ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

__ c. The applicant has committed to doing such studies as will be required.

__ (1) Studies are ongoing,
__ (2) Protocols were submitted and approved.
__ (3) Protocols were submitted and are under review.
__ (4) If no protocol has been submitted, attach memo describing status of discussions.

__ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__ 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? __ Yes ✓ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Medical Officer's memo (e.g., medical review, medical officer, team leader)

LSI _____ 5/11/00
Signature of Preparer and Title Date

LSI 5/26/00

Please refer to attached memo. →

cc: Orig NDA/BLA # 20-748
HFD 540 /Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

..JA/BLA # 20-748 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 540 Trade and generic names/dosage form: Differin (adapalene cream) Cream, 0.1% Action: AP (AE) NA

Applicant Galderma Therapeutic Class 35

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate __ inadequate __

Proposed indication in this application treatment of acne vulgaris

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ✓ Yes (Continue with questions) __ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__ Neonates (Birth-1month) __ Infants (1month-2yrs) __ Children (2-12yrs) ✓ Adolecents(12-16yrs)

__ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

__ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

__ c. The applicant has committed to doing such studies as will be required.

__ (1) Studies are ongoing.
__ (2) Protocols were submitted and approved.
__ (3) Protocols were submitted and are under review.
__ (4) If no protocol has been submitted, attach memo describing status of discussions.

__ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__ 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? __ Yes ✓ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from medical officer (e.g., medical review, medical officer, team leader)

See attached memo

3/9/00

Signature of Preparer and Title

Date

LST 3/7/00

cc: Orig NDA/BLA # 20-748
HFD-540/Div File
NDA/BLA Action Package
HFD-006/KRoberts

(revised 10/29/97)

NDA 20-748
Differin cream 0.1%

MAR 7 2000

Memorandum to the Pediatric Page

The sponsor has requested a waiver of the requirement for studies on pediatric patients under the age of 12, on the basis that adequate and well controlled studies to evaluate patients below the age of 12 would be highly impractical. Such patients would be a small percentage of the population with acne and would be widely dispersed.

This reviewer agrees, and feels that pediatric studies below the age of 12 are not needed, as the product has little potential for use in this age group.

Phyllis A. Huene, M.D.

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

(NDA)/BLA # 20-748 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade and generic names/dosage form: Differin (adapalene cream) Cream, 0.1% Action: AP AE (NA)

Applicant Galderma Therapeutic Class 3S

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Proposed indication in this application topical treatment of acne vulgaris

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ___No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

___Neonates (Birth-1month) ___Infants (1month-2yrs) ___Children (2-12yrs) ___Adolecents(12-16yrs)

___1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___c. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing.
___ (2) Protocols were submitted and approved.
___ (3) Protocols were submitted and are under review.
___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

✓ 5. If none of the above apply, attach an explanation, as necessary. See memo →

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___Yes ✓No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from [illegible] M.D. (e.g., medical review, medical officer, team leader)

Olga Tinton - Project Manager — May 7-98

Signature of Preparer and Title — Date

69

cc: Orig NDA/BLA # 20-748
HFD-540 /Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

The information on the use in pediatric patients 12 years and older is currently inadequate. Only one clinical study has been performed in this age group; another study is needed to establish the safety and effectiveness.

MEMORANDUM OF TELEPHONE CONVERSATION

JUL 2 1998

Date: April 6, 1998.

Sponsor Participants: Christine Shank, Director, Regulatory Submissions, Galderma
Paul Clark, Managing Director, Regulatory Affairs, Galderma

FDA Participants: Jonathan Wilkin, M.D., Division Director, HFD-540
Susan Walker, M.D., Clinical Team Leader, HFD-540
Phyllis Huene, M.D., Clinical Reviewer, HFD-540
R. Srinivasan, Ph.D., Statistical Team Leader, HFD-725
Shahla Farr, M.S., Biostatistician, HFD-725
Sue Chih Lee, Ph.D., Biopharmaceutics, HFD-880
Dennis Bashaw, Pharm. D., Biopharmaceutics Team Leader, HFD-880
Olga Cintron, R.Ph., Project Manager, HFD-540

Subject: NDA 20-748
Differin (adapalene cream)Cream, 0.1%

The purpose of this telephone conversation was to inform the sponsor the results of the clinical, statistical, and biopharmaceutics review of this NDA, and the approvability of this application based on current division policy.

The following points were conveyed to the sponsor:

Clinical:

- The Agency indicated that in the vehicle-controlled clinical study submitted in the NDA, the Differin Cream demonstrated superiority over its vehicle. However, for the active-controlled study, the Sponsor selected Retin-A 0.05% as the control. This is in contrast to the other NDA's where Retin-A 0.025% was utilized in the active-controlled studies. Review of the active-controlled study revealed that Differin Cream did not show equivalency to Retin-A 0.05%.

  Based on current division policy, one successful vehicle-controlled study is not sufficient to support approval. It is recommended that the Sponsor conduct an additional vehicle-controlled clinical study.

- The Sponsor indicated that the active-controlled study was submitted as supportive safety information, not to demonstrate efficacy.

- The Agency responded that normally the data is analyzed for efficacy followed by a safety analysis.

Biopharmaceutics:

- The Agency informed the Sponsor that the PK study submitted in the NDA was not acceptable. As already informed to the Sponsor in our teleconference conducted on September 29, 1997, the Sponsor should conduct a PK study to determine the systemic absorption. The pharmacokinetic study should be a multiple-dose study conducted in patients with large surface areas of diseased skin. The study needs to be conducted using the to-be-marketed formulation. The Sponsor's response to address PK deficiencies was not acceptable since the PK studies submitted were conducted with the gel formulation.

- The Sponsor requested the rationale as to why the studies conducted with the gel formulation were not acceptable. The Sponsor believes that the data generated from the gel study satisfactorily addresses the PK concerns because they were conducted in patients with diseased skin using maximal amount of test material (gel). Additionally, in vitro tests have shown that the cream is less bioavailable than the gel. This in vitro study serves as a mechanism to bridge the cream and gel formulations.

- The use of in vitro data collected via ——— has not been accepted by the Agency as a surrogate for in vivo pharmacokinetic trials. This is due to the ——— of the ——— and other factors which make the ——— significantly different from the in vivo system. At the present time the Agency has not developed a level of comfort for the use of in vitro testing as a mechanism to bridge between different formulations to assess dermal penetration.

- The Sponsor asked if the clinical study and PK study could be combined in one study. The Agency indicated that it is acceptable provided that the studies meet both clinical and pharmacokinetic criteria.

The conversation ended cordially.

inal NDA 20-748
)-540/DIV FILE
)-540/Wilkin
)-540/Cintron
)-540/Walker
D-540/Huene 4/8/98.
D-540/Lee 4/8/98
D-540/Bashaw 4/7/98
D-725/Srinivasan
D-725/Farr

Actions:

- The sponsor will inform management of the Agency's findings and recommendation for another PK study.

The sponsor will contact the Agency to inform when the protocol will be submitted for review.

The conversation ended amicably.

cc:

Original NDA 20-748
HFD-540/ Div File
HFD-540/Wilkin
HFD-540/Walker
HFD-540/Huene
HFD-540/Cintron
HFD-880/Bashaw
HFD-880/Lee
HFD-540/Mainigi
HFD-540/Jacobs

WITHHOLD 3 PAGE (S)

CDER Establishment Evaluation Report for August 19, 1997.

Application: NDA 20748/000
Stamp: 17-JUL-1997 Regulatory Due: 17-JUL-1998
Applicant: GALDERMA
331329
FORT WORTH, TX 76133

Priority: S Org Code: 540
Action Goal: District Goal: 17-MAR-1998
Brand Name: DIFFERIN (ADAPALENE) TOPICAL C
Established Name:
Generic Name: ADAPALENE
Dosage Form: CRM (CREAM)
Strength: 0.1%

FDA Contacts:			
	O. CINTRON	(HFD-540)	301-827-2023 , Project Manager
	W. TIMMER	(HFD-540)	301-827-2048 , Review Chemist
	W. DECAMP II	(HFD-540)	301-827-2041 , Team Leader

Overall Recommendation:

ACCEPTABLE on 12-AUG-1997 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 1628114
DPT LABORATORIES INC
307 EAST JOSEPHINE
SAN ANTONIO, TX 78215

DMF No:

AADA No:

Profile: OIN OAI Status: NONE
Last Milestone: OC RECOMMENDAT 04-AUG-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities:
FINISHED DOSAGE MANUFACTURER

Establishment:

DMF No:

AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDAT 12-AUG-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities:

WITHHOLD 2 PAGE (S)

CDER OC FOREIGN INSPECTION TRACKING SYSTEM
DATA ENTRY/CONTROL FORM

TYPE	NUM	SUPPL	RECOM
N	20-338		A
N	20-380		A

C 'OL: 322-96-03-10 CFN : 9611996 NEW CFN FIRM TYPE : M TYPE EI : 3

FIRM: [redacted]

STREET: [redacted]

CITY: [redacted] ST-PROV: COUNTRY:

FIRST DATE EI: 11/9/95 LAST DATE EI: 11/14/95 DATE ENDORSED: 12/18/95 DATE OF RECOMM: 3/5/96

INITIAL CLASS: AE DATE REC'D: 3/8/96 ACTION TYPE: EIR USER FEE DATE:

PRIORITY: DATE DUE: DATE ASSIGNED: 3/25/96 CSO: MSK

COMPLETED: 4/1/96 FINAL CLASS: AE COMP. ACTION: CON RESC DATE: 7/97

COMMENTS :

No UF date. Review of EIR referred as acceptable. Firm's response did not include method validation for critical intermediate & raw material. Recovery from surface to swab not done as part of cleaning validation. Approval recommended, but firm sent letter requesting additional information on analytical methods validation.

PROFILE	STATUS
CSN	A

TYPE PROBLEM
10
17
18

+FD-322 review of 11/95 inspection report

DD-96-01-04

DATE ASSGND: 11/95 PRIORITY: 1 DATE INSPD: 11/9-14/95 GRP:
CENTRAL FILE NO.: 9611996 JD/TA: N/A CNTY: N/A PHONE:
EMPL NO: 211
STREET:
STATE: DISTRICT:

ENDORSEMENT

The inspection of this Bulk Pharmaceutical Chemical manufacturer was conducted in response to several concerns expressed by HFD-322 following inspections of 1/23-25/94 and 9/29-10/94 that covered the product Adapalene . Adapalene is the active ingredient for two pending NDAs (20-380 and 20-338) filed by Galderma, Fort Worth, TX. The inspection of 9/29-30/94 was classified VAI.

The current inspection determined that manufactured Adapalene batches in 1989/90. An additional batches were manufactured in 1994/95 using essentially the same equipment and procedures as the batches. At this time intends to manufacture commercial size batches of approximately . in the plant.

HFD-322's memo of May 19, 1994 expressed concern over discrepancies found during stability testing. Impurity was initially reported at levels up to and subsequent levels were in the range of . The current inspection found that the discrepancies were a result of stability testing conducted at versus stability testing conducted at the customer, Galderma, Fort Worth, TX. Differences in the columns used at and Galderma resulted in the variation in the reported levels of impurity

Three observations were listed on the current FD Form 483. raw materials used in the manufacture of Adapalene. The analytical methods for these raw materials had not been validated. A third observation dealt with documentation of an out of specification investigation. The original analyst failed to document his verification of original testing. Retesting confirmed the original OOS result and the retesting and rework were properly

COMPLIANCE ACHIEVEMENT DATA

PAC	PROBLEM TYPE	CORR ACTION	EST COST ACTION	DATE ACTION VERIFIED	CORR UNIT	REPT DIST	REASON FOR CORRECTION
56R806	1	9	7	11/14/95	FJ	FJ	2

EMP HOME DIST 0 EMP NUM 211

SIGNATURE DATE: 12/18/95

Salvatore J. Comado, SDWT Member

Distribution: HFC-134; HFA-224; HFD-320 w/exhibits; HFD-320 FOI; HFC-134 Haggard; SEA-DO-DIB; STL-BR-DIB; Ralph Erickson, investigator, STL-BR; Janet Burke, chemist, SEA-DO PHI-DO HFR-MA1 (D'Eramo)

DATE ASSGND: 11/95 PRIORITY: 1 DATE INSPD: 11/9-14/95 GRP:
CENTRAL FILE NO.. JD/TA: N/A CNTY: N/A PHONE:
EMPL NO:
NAME: STREET:
STATE: ZIP: DISTRICT:

performed and documented.

responded to the FD Form 483 in a letter dated November 14, 1995 agreeing to validate the analytical methods prior to next use and revise the procedure for documentation of the verification of the analysis by the original analyst.

FOLLOW-UP: Recommend that the firm be considered acceptable for profile class CCS and EIR is classified VAI.

COMPLIANCE ACHIEVEMENT DATA

PAC	PROBLEM TYPE	CORR ACTION	EST COST ACTION	DATE ACTION VERIFIED	CORR UNIT	REPT DIST	REASON FOR CORRECTION
56R806	1	9	7	11/14/95	FJ	FJ	2

EMP HOME DIST Ø EMP NUM 211

SIGNATURE DATE: 12/18/95

Salvatore J. Comado, SDWT Member
DISTRIBUTION:

DATE ASSGND: 11/95 PRIORITY: 2 DATE INSPD: 11/9-14/95 GRP:
CENTRAL FILE NO.: JD/TA: N/A CNTY: N/A PHONE:

NAME: STREET:
CITY: STATE: ZIP: DISTRICT:

RELATED FIRMS: ST-ASSGN: ITS:

REGISTRTN:

REG TYP	MO/YR	MO/YR	MO/YR	REG TYP	MO/YR	MO/YR	MO/YR	REG TYP	MO/YR	MO/YR	MO/YR
F	/	/	/	D	/	/	/	V	/	/	/
M	/	/	/	R	/	/	/	B	/	/	/

ESTAB-TYPES/ 1: M 2: 3:
IN-CODES ON OEI: 60

TOTAL ESTAB SIZE	I.S. BUSINESS RECEIVED	I.S. BUSINESS SOLD	DISTRICT USE #1	#2	#3	RECALL NO.	REFUSAL CODE	PROFIL	PASS FAIL
	(YES) NO	100%					0	Y	

ESTAB-CHANGES: NEW-FIRM (NONE) NAME ADDRESS OWNERSHIP SIZE PROD-CODE
OTHER EST-TYPE O/B INACTIVE NOT-OEI AUX-FIRM REGISTRATION

PAC	PROCESS (PRODUCT) CODE	EST TYP	INSP BASIS	EMPL1 PC:2 NO:211 HD:Ø	EMPL2 PC:3 NO:553 HD:H	EMPL3 PC: NO: HD:	PRODUCT	PR IT Y	RESC HED DATE	INSP CONG	DIST DCSN
5 06	64XCS	M	2	72	56		ADAPALENE	2		A	E

SAMPLES COLLECTED: NONE
SAMPLE# PRODUCT:

HEADQUARTERS UNIT REFERRED: HFC-134 FD 483 ISSUED: (YES) NO

REASON REFERRED OTHER FED GOVT INSP OR GRADING:

INSPECTOR'S NAME/SIGNATURE: SUPERVISOR'S NAME/SIGNATURE:

[illegible] A. Erickson Janet L. Burke Salvatore J. Comado, SDWT

FORM FDA 481(A)-CG (09/84)

PRODUCTS COVERED

CFN: [redacted] EMPL NO.: [redacted]

ESTABLISHMENT NAME: [redacted]

DATE INSPECTED: 11/9-14/95 DATE ASSIGNED : 11/95

DATE COVERED	PRODUCT CODE	EST TYP	EST TYP	EST TYP	PRODUCT DESCRIPTION
95/11/14	64XCS99	M			[redacted]
PHARMACEUTICAL: [redacted]					
/ /					
/ /					
/ /					
/ /					
/					
/ /					
/ /					
/ /					
/ /					
/ /					

FORM FDA 481(C)-CG (09/84)

PROFILE DATA SHEET

CENTRAL FILE NO: [redacted]
FIRM NAME: [redacted]
ADDRESS: [redacted]

PROFILE DATA SHEET NO:
COVER SHEET NO :

EMPL NO: [redacted] SUPV GROUP:

PRO CLS	NEW STATUS M	NEW STATUS R	CURRENT STATUS M	CURRENT STATUS R	GMP DATE	REMARKS
CCS	(A) N	A N	A		11/14/95	
	A N	A N				
	A N	A N				
	A N	A N				
	A N	A N				
	A N	A N				
	A N	A N				
	A N	A N				
	A N	A N				
	A N	A N				
	A N	A N				
	A N	A N				
	A N	A N				
	A N	A N				

SIGN OFF SIGNATURE: 451
DATE OF SIGNATURE: 12/19/95

DISTRIBUTION:

FORM FDA 2860-CG (01/85)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER ITOB, HFC-134, Room 12-18 5600 Fishers Lane Rockville, MD 20857 USA 301-443-1855
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO:	PERIOD OF INSPECTION November 9-14/95 / C. F. NUMBER
TITLE OF INDIVIDUAL	TYPE ESTABLISHMENT INSPECTED BPC Manufacturer
FIRM NAME	NAME OF FIRM, BRANCH OR UNIT INSPECTED Same
STREET ADDRESS	STREET ADDRESS OF PREMISES INSPECTED Same
CITY AND STATE *(Zip Code)*	CITY AND STATE *(Zip Code)* Same

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

1 The [redacted] used for the analysis of raw material [redacted] which is manufactured by the firm, has not been validated.

2 The [redacted] used for the analysis of the intermediate [redacted] has not been validated.

3 The original analysis of Lot No. AG 710 of product Adapalene [redacted] failed due to a residue on ignition result above the [redacted] limit. No documentation was prepared by the original analyst showing verification of the use of the correct control method, suitable equipment, and adequate reagents and solvents.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE [redacted]	EMPLOYEE(S) NAME AND TITLE *(Print or Type)* [redacted]	DATE ISSUED Nov 14, 95

Food and Drug Administration
St Louis Branch
808 North Collins
Laclede's Landing
St. Louis, MO 63102
USA

attn. Mr Ralph A. Erickson

O/Ref. : MNC/MC/98-95

November 21, 1995

Dear Mr Erickson,

You will find enclosed copy of the letter sent to the FDA in reply to your FDA form 483.

May we take this opportunity to thank you for the agreeable, courteous and professional manner in which Mrs Burke and you conducted your inspection.

Yours sincerely.

9611996

Quality Assurance Director

FOOD AND DRUG ADMINISTRATION
International and Technical Operations
Branch, HFC-134 - Room 12 to 18
5600 Fishers Lane
ROCKVILLE MD 20857
U.S.A.

O/Ref : FM/FM/97.95

November 14th, 1995

RE : Inspection of : concerning the New Drug Applications :
20-338 - ADAPALENE Topical Solution 0.1 %
20-380 - ADAPALENE Topical Gel 0.1 %

Dear Sir or Madam :

was inspected by Ralph A. Erickson and Janet L. Burke the 9th, 10th, 13th and 14th of November. A form FDA 483 was issued (see Appendix # 1) which mentions three observations.

OBSERVATIONS # 1 AND 2

Observations # 1 and 2 concerned analytical methods used respectively for the analysis of starting materials , which have not been validated.

hereby undertakes to validate these methods prior to subsequent use for the control of the next batches of these compounds. This is expected, at the latest, by the end of the first quarter of 1996.

OBSERVATION #3

The third observation concerned the standard operating procedure [redacted] specification results" (reference number [redacted]). The verification of the control method, equipment, etc. was not documented.

This procedure will be revised in the near future in order to take into account the Inspector's observations.

Yours faithfully,

[redacted]

Managing Director

[redacted]

Quality Assurance Director

cc. : Ralph A. Erickson,
Janet L. Burke

SUMMARY OF FINDINGS

The inspection of this Bulk Pharmaceutical Chemical manufacturer was conducted in response to several concerns expressed by HFD-322 in memorandums dated May 19, 1994; February 9, 1995; and August 4, 1995. This was the third inspection of [redacted] to cover the drug substance Adapalene (CD 271). Adapalene is the active ingredient for two pending NDAs (20-380 and 20-338) filed by Galderma, Fort Worth, TX.

The current inspection determined that [redacted] manufactured [redacted] Adapalene [redacted] batches in 1989/90. An additional [redacted] batches were manufactured in 1994/95 using essentially the same equipment and procedures as the [redacted] batches. At this time [redacted] intends to manufacture commercial size batches of approximately [redacted] in the [redacted] plant. [redacted] management acknowledged that if larger batch sizes were to be manufactured additional equipment, validation, and approval would be required.

HFD-322's memo of May 19, 1994 expressed concern over discrepancies found during stability testing. Impurity [redacted] was initially reported at levels up to [redacted] and subsequent levels were in the range of [redacted] The current inspection found that the discrepancies were a result of stability testing conducted at [redacted] versus stability testing conducted at the customer, Galderma, Fort Worth, TX. Differences in the [redacted] used at [redacted] and Galderma resulted in the variation in the reported levels of impurity [redacted]. [redacted] and Galderma now use the same specific [redacted] and both labs report impurities at levels less than [redacted]

[redacted] stores stability samples in an [redacted] warehouse. This did not appear to be an objectional condition since the labeling of the finished Adapalene does not specify [redacted] The official stability samples for the [redacted] batches were stored and analyzed by Galderma. The stability samples at [redacted] were reported for informational purposes.

[redacted] continues to rely on [redacted] to determine the adequacy of cleaning of the [redacted] The current inspection determined that for each batch of product (Adapalene as well as other products) manufactured in the [redacted] charges the [redacted] with an appropriate [redacted] the [redacted] to [redacted] and samples the [redacted] for residual drug product. This procedure appears adequate for verification of the cleaning of the [redacted].

In response to the February 9, 1995 memo from HFD-322 additional information was obtained regarding the identity of various drug intermediates shipped to the United States and the circumstances surrounding [redacted] manufacture of [redacted] for [redacted]

Three items were listed on the FD Form 483 for the current inspection:

1 The [redacted] method [redacted] used for the analysis of raw material [redacted] which is manufactured by the firm, has not been validated.

2 The [redacted] method [redacted] used for the analysis of the intermediate [redacted] has not been validated.

3 The original analysis of Lot No. AG 710 of product Adapalene [redacted] failed due to a residue on ignition result above the [redacted] limit. No documentation was prepared by the original analyst showing verification of the use of the correct control method, suitable equipment, and adequate reagents and solvents.

[redacted] made a verbal commitment during the discussion of the FD Form 483 to correct these observations and stated that a written response would be submitted to ITOB.

HISTORY OF BUSINESS OPERATIONS

At the initiation of the inspection [redacted] provided an overview of the corporate structure of [redacted] Exhibit No. 1 shows that [redacted] is primarily owned by [redacted]

The [redacted] was merged into [redacted] in 1995 as shown in Exhibit No. 2. [redacted] reported that the [redacted] plant has been covered by FDA's foreign inspection program.

PERSONS INTERVIEWED

Upon arrival in [redacted]. I telephoned [redacted] and was directed to [redacted] Mr. [redacted] picked us up at the [redacted] at 8:30 am each morning of the inspection. [redacted] provided prepaid taxi transportation back to the hotel each evening.

At the initiation of the inspection the following individuals were present:

[redacted]

[redacted] Division was present at various times during the inspection including the initiation and discussion of the FD Form 483. Oliver Watts, Director, Research and Development for Galderma arrived later in the day on November 9, 1995 and was present at [redacted] during the inspection to provide information regarding Galderma's involvement in this project. All individuals listed above were present for the Discussion of the FD Form 483.

Exhibit No. 3 is an organization chart for [redacted] and [redacted] facility. [redacted] is the top corporate official at the [redacted] plant. [redacted] Chairman of the Board is located in [redacted]

PHYSICAL PLANT

Exhibit No. 4 is a diagram of the [redacted] facility. The following locations were of interest during the current inspection. Building [redacted] is the administration building where the majority of the record review was conducted as well as the opening and FD 483 discussions. [redacted] (building) [redacted] is the [redacted] plant were the 1989/90 [redacted] batches and the 1994/95 [redacted] batches were manufactured. The current raw material (Matieres Premeres) and finished goods (Produits Finis) warehouse was visited. The Adapalene stability samples are stored on a [redacted] in the finished goods area. This area is [redacted]

[redacted] monitored but not [redacted] at [redacted]

The [redacted] laboratory currently located in the Laboratoier building was inspected by Chemist Janet Burke. [redacted] expects to [redacted] the warehouse and laboratory [redacted] of the current laboratory early in [redacted]

[redacted] operates [redacted] shifts per day from [redacted] for manufacturing operations. A [redacted] shift is in place to monitor in process operations but no [redacted] such as [redacted] is performed during the [redacted] shift.

US DISTRIBUTION OF DRUG SUBSTANCES AND DRUG INTERMEDIATES

HFD-322 requested information on the drug intermediates shipped to the United States and [redacted] involvement with the drug substance [redacted] provided information on [redacted] products distributed to the United States. [redacted] reported at this time the [redacted] facility manufactures [redacted] bulk pharmaceutical chemical for distribution to the U.S., [redacted]. We requested information on the chemical structure and chemical names for [redacted] and the drug intermediates shipped to the United States. Exhibit 5, page 1, is the information sheet for [redacted] and Exhibit 5, page 2, lists the distribution of [redacted] for the years 1992/95.

Exhibit 6, page 1, lists the drug intermediates shipped to the U.S. in 1995. Exhibit 6, pages 2-9, are the information sheets for the drug intermediates. Distribution of drug intermediates in 1994 is covered by Exhibit 7 and 1993 by Exhibit 8.

Dr. [redacted] was requested to provide information on [redacted] or [redacted] manufactured for [redacted] since 1990. Dr. [redacted] determined that [redacted] sold [redacted] batches of [redacted] to [redacted] These batches were sold to [redacted] in November 1990 and no additional [redacted] has been manufactured. Dr. [redacted] provided a statement (Exhibit 9) of [redacted] regarding the sale of these batches. Dr. [redacted] stated that [redacted] provided a service to help [redacted] while they were experiencing a technical problem.

BATCH NUMBERING SYSTEM

For [redacted] plant production [redacted] uses a batch numbering system consisting of the [redacted] followed by a [redacted] from the [redacted] For example batch number [redacted] would be the [redacted] project for [redacted] Each step in the [redacted] is assigned a [redacted] and [redacted] are assigned a [redacted]

[redacted] BATCHES - 1989/1990

The basic process for the synthesis of Adapalene was provided to [redacted] by Galderma. Exhibit No. 18 is the Development Report for Adapalene showing the development history from 1985 to 1990. This development report documents the [redacted] plant batches ([redacted] batches).

HFD-322 expressed concern in their memorandum of May 19, 1994 regarding the feasibility of [redacted] using [redacted] in the range of [redacted] to manufacture [redacted] batch sizes. In addition they were concerned that the batch records for the [redacted] batches had not been submitted so that the equipment used in the manufacture of the [redacted] batches could be verified.

The manufacture of the [redacted] batches was reviewed with [redacted] Exhibit No. 10 is a flow sheet showing the progression of the intermediate batches leading to the [redacted] batches PIC 2288, PIC 2295, AG 189, AND AG 201. [redacted] translated the batch records for my review. The identification of equipment (as reported in the batch records) was entered on the flow sheet for the [redacted] batches. Equipment identification for [redacted] batch [redacted] and subsequent [redacted] into [redacted] was inadvertently not recorded during the inspection. Batch AG 195 was out of specification for [redacted] and the lot was [redacted] and assigned lot number AG 201. Exhibit 11 is a listing of equipment in the [redacted] plant from [redacted] annual update dated December 12, 1992.

The manufacturing process for the [redacted] batches was compared with the synthesis summary contained in the April 24, 1995 [redacted] DMF for Adapalene (pages 29-49/124). The process for the [redacted] batches was identical to the synthesis summary except the [redacted] batches used a separate [redacted] and a separate [redacted] for the completion of Step [redacted] The [redacted] batches used a [redacted] for Step [redacted]

Exhibit 12 is a flow chart listing the process and equipment identification for the commercial manufacture of Adapalene.

[redacted] has developed a master production and control record for the manufacture of commercial batches of Adapalene. The master production and control record for commercial production was essentially the same as the batch production and control records for the 1994/1995 [redacted] batches. The [redacted] batch production records did include additional instructions for the collection of [redacted] data. The requirement for collection of [redacted] data was deleted from the master production and control record for commercial production.

[redacted] BATCHES - 1994/1995

[redacted] intended to manufacture [redacted] batches starting in 1994. Exhibit No. 13 is [redacted] flow sheet. A manufacturing problem reduced the number of [redacted] batches to [redacted] The 1989/1990 [redacted] batches used [redacted] for Step [redacted] For batch AG 701 [redacted] used a [redacted] which was unsuitable due to chemical and physical reasons. [redacted] undertook a study to find a suitable [redacted] determined that a [redacted] could be used and the [redacted] was used for lots AG 702, AG 709, and AG 714. An explanation of the failure of the [redacted] is contained on page 22 of the 30 page [redacted] report prepared at the completion of the [redacted] batches.

The Adapalene [redacted] Flow Sheet lists [redacted] batches AG 697, AG 698, AG 699, and AG 700 as meeting specifications but they were [redacted] into batches AG 705/AG 708 and AG 711. Mr. [redacted] stated that at the time of manufacture Step [redacted] batches (AG 693 through AG 700) met the pre-defined specification limits and acceptable amounts of residual solvents were found. A study of the first batch of [redacted] (Batch 703) showed that the impurity [redacted] is not removed in Steps [redacted] A discussion of impurity [redacted] as it relates to the [redacted] lots is documented on pages 19 and 20 of the 30 page [redacted] report. These pages and the analytical results for step [redacted] are submitted as Exhibit No. 14. Since batches AG 697 - AG 700 had already been manufactured, [redacted] decided to [redacted] the lots AG 697 - AG 700 to reduce the level of [redacted] impurity to less than [redacted]. Batch AG 697 and AG 698 were [redacted] into batch AG 705. This [redacted] resulted in a [redacted] level of [redacted] which was still out of specification. Batch AG 705 was [redacted] again resulting in a [redacted] level of [redacted] for batch AG 708%. Batches AG 699 and AG 799 were [redacted] into batch AG 711 which had a [redacted] level of [redacted] The [redacted] of Step [redacted] material for batches AG 697 - AG 700 consisted of dissolving the material in [redacted]

Batch AG 710 was reworked into batch 723 due to a residue on ignition result of [redacted] (specification ROI less than [redacted]) and foreign material [redacted] The laboratory could not find enough of the foreign material in the batch to conduct an investigation. [redacted] felt that the [redacted] may be [redacted] due to the abrasive nature of the material. Investigation of the out of specification result for residue on ignition determined that the [redacted] was not sufficiently [redacted] with [redacted] Exhibit 15 documents the out of specification result and the explanation of the investigation. The batch was reworked according to the flow chart submitted as Exhibit 12, page 4.

STABILITY SAMPLES

In HFD-322 memorandum of May 19, 1994, concern was expressed regarding the storage of stability samples. At this time stability samples are stored on a [redacted] in the finished goods warehouse (Produits Finis). This area is monitored for [redacted] but is not [redacted]

The Adapalene stability samples were stored in a [redacted] The [redacted] was labeled [redacted] Lots AG 189, PIC 2295, PIC 2288, AG 703/C, AG 716, AG 723". These lots were the first [redacted] of the [redacted] 1989/1990 [redacted] batches and the 1994/1995 [redacted] batches. The [redacted] contained [redacted] containing the [redacted] stability samples.

The label for the finished product did not state recommended storage conditions (temperature and humidity). [redacted] reported that the official stability data for the [redacted] batches was generated by Galderma. Stability studies on Adapalene conducted at [redacted] for the [redacted] batches represented ancillary data to the official stability studies conducted at Galderma. [redacted] is conducting the official stability studies on the [redacted] batches. It appears that the storage conditions are appropriate in that the finished goods warehouse [redacted] represent the labeled storage conditions.

Galderma has conducted stability studies on the [redacted] Adapalene [redacted] batches under stressed conditions. Exhibit No. 17C documents Galderma's stability testing under ambient and stressed conditions.

CLEANING VALIDATION - CLEANING VERIFICATION

[redacted] uses [redacted] to verify the cleaning of the

[redacted] HFD-322 objected to this procedure in their memorandum of May 19, 1994, and indicated that [redacted] sampling was required to verify the cleaning process. At this time [redacted] continues to use [redacted] verification of the cleaning process for the [redacted] At the conclusion of a manufacturing campaign for a specific product the [redacted] is [redacted] with a [redacted] specific for the previous drug product. The [redacted] is [redacted] to ensure coverage throughout the [redacted] At the conclusion of the cleaning operation a sample of the [redacted] is collected for [redacted] analysis. A [redacted] of the [redacted] results filed with the subsequent product batch record. If the [redacted] results indicate incomplete cleaning the cleaning operation is repeated.

[redacted] stated that he remains opposed to [redacted] the [redacted] of the [redacted] due to safety concerns. Inspection of the [redacted] found that they were small compared to a normal production facility. The safety concerns dealt with the inhalation of toxic solvents.

[redacted] has completed cleaning validation of the [redacted] This validation was conducted by [redacted] the equipment to determine drug residue.

Exhibits 16 and 17 cover [redacted] validation of cleaning for Adapalene and their rational for establishment maximum value of (w/w).

LABORATORY FAILURE INVESTIGATIONS

[redacted] submitted an SOP for the investigation and tracking of Laboratory failures following the January 1994 inspection. One deficiency was observed regarding the investigation of laboratory failures. The original analysis of Batch No. AG 710 of product Adapalene [redacted] failed due to a residue on ignition result above the [redacted] limit. No documentation was prepared by the original analyst showing verification of the use of the correct control method, suitable equipment, and adequate reagents and solvents. Following this review the assay was repeated and the second assay confirmed the Residue on Ignition failure. Appropriate records were maintained of the second assay and rework of lot AG 710.

COMPLAINTS AND EMPLOYEE TRAINING

The [redacted] complaint handling procedures were reviewed and appeared satisfactory. The firm received [redacted] complaints on finished bulk pharmaceutical chemicals and drug intermediates in

1995. None of the complaints dealt with [redacted] finished bulk pharmaceutical chemical shipped to the U.S.

CHEMISTRY SECTION OF [redacted] EIR
Janet L. Burke (553) Seattle, Chemist

GENERAL INFORMATION

The quality control laboratory is located in a separate building at the [redacted] facility. The working area of the laboratory is approximately [redacted] total area is [redacted] The existing building is [redacted] There are also various [redacted] in the building. All laboratories and instrument rooms were clean, orderly, and appropriately equipped. A [redacted] separate [redacted] laboratory is located near the quality control laboratory. Since no analysis pertaining to this product was conducted in the [redacted] lab it was not inspected.

The analytical instruments are calibrated [redacted] and the majority are routinely calibrated and/or serviced by [redacted] During the inspection I suggested that a record be maintained of the daily calibration of the [redacted]

The sample receipt, generation of analytical documentation and the sample flow through the [redacted] laboratory was explained and found satisfactory. After analysis, the data results and record(s) of the data check are entered into a [redacted] report at computer terminals. Upon satisfactory analysis of the raw materials, [redacted] labels are printed and sent to the warehouse for attachment to the appropriate raw materials. Only raw materials with the [redacted] sticker attached to them are used in production. The firm uses both [redacted] and maintains [redacted]

The [redacted] laboratory runs [redacted] from approximately [redacted] Additionally, the laboratory is staffed by [redacted] who [redacted] and people who [redacted]

[redacted] is the [redacted] of the QC laboratory and is responsible for [redacted] His assistant is [redacted] an [redacted]

[redacted] Those individuals with release authority are [redacted] Mr [redacted] who is responsible for [redacted] and Mr [redacted] who is the [redacted]
The laboratory inspection was found satisfactory.

INSPECTIONAL FINDINGS OF DATA INTEGRITY ISSUES:

I asked Mr. [redacted] and Ms. [redacted] about the apparent discrepancies between stability impurities reported for the 1989-1990 batches and those found under "Impurity Profile" in Section XI titled HISTORICAL BATCH DATA. (see Exhibit 17A). The firm responded that data on page 13, Section XI HISTORICAL BATCH DATA actually contains data from both [redacted] and Galderma; the impurity profile reported at the bottom of the page is Galderma's time zero data. The firm stated that the stability information gathered at [redacted] for the first [redacted] batches of product (1989-1990) is ancillary to Galderma's stability data. The firm considers that Galderma's analytical data represents the "official" results for these earlier batches.

Although informative, this information did not explain the differences noted between the impurity results reported for [redacted]. The firm explained that [redacted] and Galderma were aware of these differences and had a number of discussions about this issue.

In attempts to correlate/duplicate the [redacted] results from the two cites, the [redacted] method used at [redacted] underwent a number of minor revisions; [redacted] (see Exhibit 17G the 1990 method, and Exhibit 17B the 1995 method) The [redacted] being used by the two firms was not producing consistent results with the [redacted] procedure. The problem has been satisfactorily resolved as both firms now use [redacted] of the same [redacted] that are produced in the United States. This [redacted] produces consistent impurity separations and comparable results using the current specified [redacted] procedure. **NOTE:** There is no alternative (or equivalent) [redacted] stated on the official methods [redacted] (see Exhibit 17B)

I asked Mr. [redacted] about the following high area percent impurity values:

1.) [redacted] area percent reported for [redacted] in batch 2295 and [redacted] for [redacted] in batch AG189 both in March of 1990.
2.) [redacted] area percent reported for [redacted] in batch PIC

2295 and [redacted] for [redacted] in AG 189 both in December of 1992.

The firm replied that the raw data was checked for accuracy, as per their procedures, and was evaluated [for trend] at the next stability time point. No trend was observed. As mentioned above, raw data supported the values reported. I was given a report of the "official" stability results for the [redacted] 1989-1990 batches analyzed by Galderma, the report shows no impurities above (see Exhibit 17C)

During my review of Galderma's results (Exhibit 17C) I noted two values were reported for a number of assay and chromatographic purity time periods for all [redacted] batches. I asked the firm what the two values represented as a number of the results were below the [redacted] minimum specification. The firm was unable to definitively explain the reason for the two results, even after contacting Galderma.

CLEANING VALIDATION: [redacted] ANALYSIS OF [redacted]

The [redacted] for the detection of residues was reviewed. The limit of detection of this method is [redacted] from a [redacted] application of [redacted] Data were reviewed and found satisfactory. The firm's practice is to [redacted] of the [redacted] If a [redacted] is detected at the same R_f as the reference standard ([redacted] for a [redacted] application) it would indicate that the equipment contained residues over the limit. I asked the firm what they would do if they detected a [redacted] at the [redacted] or elsewhere on the [redacted] They replied that the [redacted]

The firm uses a [redacted] The [redacted] are [redacted] and the [redacted] viewed under [redacted] and a [redacted] of the [redacted] is taken and placed in the record. [I am of the opinion that any substance (former or impurity) that would [redacted] would be detected at the [redacted] or somewhere else on the [redacted] using this method.] The limit of detection using their [redacted] method, however, has only been established for current product.

I asked the firm how they validated their [redacted] technique. As described, the firm determined the [redacted] off the [redacted] correctly. When asked if they had determined the [redacted] of [redacted] from the [redacted] to the [redacted] they responded that no such [redacted] study [redacted] had been

done. I stated that determining the [redacted] from the was an integral part of a [redacted] cleaning validation.

STABILITY ISSUES WITH THE 1995 BATCHES

The firm stated that the "official" stability analysis for the 1995 validation batches would be conducted by [redacted] During our walk through of the facility, we inspected the stability area. The [redacted] of material are located on the [redacted] of the warehouse. This area is [redacted] from the remainder of the warehouse and is not [redacted] The area is automatically monitored for [redacted] I reviewed the monthly graphs of temperature and relative humidity for 1995. The temperature ranged from [redacted] degrees centigrade. (see Exhibit 17D: a summary table) All of the stability batches were [redacted] in [redacted] and kept in the same [redacted] container. There appeared to be enough material of each batch to conduct the required analysis.

I reviewed selected raw data for the six month time point for the [redacted] batches; it was satisfactory. (see Exhibit 17E)

DATA REVIEW

[redacted] performs a variety of analysis on the raw materials, intermediates and finished product. As this inspection was "for cause", I did not review the methods that are compendial (European and French) in nature. [redacted] methods developed in-house were reviewed.

I reviewed raw data associated with the validation of the analytical methods [redacted] which on Exhibit 17F means both the assay and the stability method. The raw data and results of the validation, as translated by [redacted], an [redacted] were satisfactory. I asked Mr. [redacted] where the information regarding robustness was documented. [Robustness is a 1995 USP 23rd edition and ICH requirement that, in general, describes what small changes in the mobile solvent, pH, flow, column length, etc., have on the analytical results. In the 1995 USP 23rd edition, robustness replaces the test for ruggedness.] Mr. [redacted] explained that the robustness information was collected and documented during the [redacted] stages of the method. I suggested that for completeness, a reference to that information should be placed in the validation package. He agreed to do so.

During an initial review of the specifications of the [redacted] method, I asked to see a chromatogram showing the drug substance separated from impurity [redacted] at, or near, the [redacted] area specification. The firm explained that [redacted] is not found in the finished product. I stated that since there was a specification for this impurity, found or not found, I needed to confirm that the impurities could be detected at the specification limits. Since [redacted] was very close to the drug substance, I had some concerns if low levels could be seen so close to the peak tail of the drug substance. The firm produced a chromatogram of the drug substance with the impurities in question. (see Exhibit 17H) The impurity separations at/near the specifications are satisfactory.

CURRENT INSPECTIONAL OBSERVATIONS AND DISCUSSION WITH MANAGEMENT:

I asked Mr. [redacted] and his staff to prepare a list of the analytical techniques used for raw material, intermediates and the finished product and indicate if the methods had been validated; he did so. (see Exhibit 17F)

The methods used for most of the raw materials [redacted] are compendial in nature. The [redacted] is obtained from a commercial supplier, [redacted] It is identified at [redacted] by [redacted] and assayed by [redacted] The [redacted] is also commercially supplied. One of the [redacted] lots, (lot# 63186) of [redacted] used in the [redacted] batches had an original analysis dated February 19, 1990. The firm's reanalysis schedule is [redacted] I reviewed the reanalysis of this lot prior to use in the validation batches; it was satisfactory.

The [redacted] raw material is manufactured by [redacted] The [redacted] method has not been validated. I told Mr. [redacted] and Ms. [redacted] that this method should be validated. The firm indicated the would do so.

FDA-483 item #1: The [redacted] analytical method [redacted] used for the analysis of raw material [redacted] which is manufactured by the firm, has not been validated.

I reviewed the [redacted] method for the intermediate [redacted] and stated to Mr. [redacted] and Ms. [redacted] that this method should also be validated. The firm indicated they would do so.

FDA-483 item #2: The [redacted] analytical method [redacted] used for the

analysis of the intermediate [redacted] has not been validated.

DDITIONAL OBSERVATIONS

reviewed the firm's training procedures and Mr. [redacted] raining record. Both procedures and record were satisfactory.

ERSONS INTERVIEWED:

[redacted]

ISCUSSION WITH MANAGEMENT

t the conclusion of the inspection the FD Form 483 was issued to [redacted] Personnel attending the iscussion of the FD Form 483 are listed in the Persons ıterviewed heading. Each item on the FD Form 483 was read out ɔud. [redacted] did not make a formal response to the FD Form 483 ıt Mr. [redacted] stated that the analytical methods for [redacted] and [redacted] would be validated. [redacted] dicated that a written response to the FD Form 483 would be bmitted to ITOB.

ST OF EXHIBITS

[redacted] Ownership Chart
[redacted] History
[redacted] Organization Charts
[redacted] Layout
[redacted] Identification and Distribution
1995 Drug Intermediates Identification
1994 Drug Intermediates Identification
1993 Drug Intermediates Identification
1990 [redacted] Distribution
1989/1990 Adapalene [redacted] Batches Flow Chart
[redacted] Plant Equipment List (Dec. 12, 1992)
Commercial Batch Adapalene Manufacturing Flow Chart

WITHHOLD 2 PAGE (S)

WITHHOLD 1 PAGE (S)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **NDA 20748/000**
Priority: **3S**
Org Code: **540**
Stamp: **17-JUL-1997** Regulatory Due: **08-MAR-2000**
Action Goal:
District Goal: **17-MAR-1998**
Applicant: **GALDERMA**
331329
FORT WORTH, TX 76133
Brand Name: **DIFFERIN (ADAPALENE) TOPICAL CREAM 0.1%**
Established Name:
Generic Name: **ADAPALENE**
Dosage Form: **CRM (CREAM)**
Strength: **0.1%**

FDA Contacts:

O. CINTRON	**(HFD-540)**	**301-827-2023**	**, Project Manager**
W. TIMMER	**(HFD-540)**	**301-827-2048**	**, Review Chemist**
W. DECAMP II	**(HFD-540)**	**301-827-2041**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 18-JAN-2000 by M. EGAS (HFD-322) 301-594-0095
ACCEPTABLE on 12-AUG-1997 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: **1628114**
DPT LABORATORIES INC
307 EAST JOSEPHINE
SAN ANTONIO, TX 78215
DMF No:
AADA No:

Profile: **OIN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **04-OCT-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment. [redacted]
DMF No: [redacted]
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **18-JAN-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: [redacted]

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*U.S.GPO:1997-517-038/86093

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION

Division (Office)		FROM:	
HFD-160 Dr. Greenman		Olga Cintron HFD-540	
DATE: 2/5/98	IND NO.	NDA NO. 20-748	TYPE OF DOCUMENT: BE
DATE OF DOCUMENT: 2-2-98	NAME OF DRUG: Diflorasone Cream	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG
DESIRED COMPLETION DATE: 4-2-98	NAME OF FIRM: Galderma		

REASON FOR REQUEST

I. GENERAL

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

micro amendment

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*

Please find Galderma's response to the micro differences listed in the review of original submission.

to V. Greenman

LS 2/12/98

CENTER FOR DRUG REC'D FEB 09 1998 HFD-160 EVALUATION AND RESEARCH

SIGNATURE OF RECEIVER LS

METHOD OF DELIVERY *(Check one)* ☐ MAIL ☐ HAND

SIGNATURE OF DELIVERER

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

REQUEST FOR CONSULTATION

(Division/Office)		FROM:	
HFD-160 Paul Stinivasan / Peter Lurie		C. Center 540	
DATE: 3/9/98	IND NO.	NDA NO. 20-934	TYPE OF DOCUMENT: New Dos.	DATE OF DOCUMENT: 12/16/97
NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG: 3S	DESIRED COMPLETION DATE: —

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

- ☐ SOLUTION
- ☐ OAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES
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- ☐ IN–VIVO WAIVER REQUEST

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- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)*
- ☐ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*

NDA review.

CENTER FOR DRUG
REC'D
MAR 1 0 1998
HFD-160
EVALUATION AND RESEARCH

SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)*
	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER: 3/10/98	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	REQUEST FOR CONSULTATION

TO (Division/Office)		FROM:	
Vivian Greenman HFD-160		Olga Gintzen HFD-540	
IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
	20-748	Original NDA	July 18, 1997
NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Differin (adapalene) Cream	S	3S	—

NAME OF FIRM
Galderma Labs.

REASON FOR REQUEST

I. GENERAL

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

Original NDA

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

- ☐ SOLUTION
- ☐)AVAILABILITY STUDIES
- ☐ ıASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL– BIOPHARMACEUTICS
- ☐ IN–VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*

Original submission for review.

Sent 7.29.97 Anita

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

FORM FDA 3291 (7/83)

SPONSOR: GALDERMA LABS INC

DRUG: DIFFERIN (ADAPALENE) TOPICAL CREAM 0.1% (1mg/g)

INDICATION: FOR THE TOPICAL TREATMENT OF ACNE VULGARIS

NDA NUMBER: 20748 DIVISION: 540 FORM 5: _____

DATE REC: 17 Jul 97 DATE SENT: 18 Jul 97 NEW REG. NDA: _____

PRE ASSIGNED: 20 PE-SUBM: _____ FOLLOW-UP SHIPMENT: _____

"COPIES RECEIVED, STORED AND SENT"

X	BLUE Archival - 2626 (1.1 Copy Sent HFD-092 Nicholson Lane to Division, Form 1706)	RECV: 1.1 — 1.32 SENT: 1.1 — 132 STOR:
P	Orange Pharmacokinetics Review (2626C all copies sent to HFD870 Rm 13-B-31, For 1706	RECV: 1.1, 1.13 — 1.15 SENT: 1.1, 1.13 — 1.15 STOR:
S	Green Statistical Review - 2626F (Summary sent to HFD-713 Rm 18-B-45, Form 1706	RECV: 1.1, 1.16 — 1.28 SENT: 1.1, 1.16 — 1.28 STOR:
T	Tan Clinical Review - 2626E (All copies sent to Division Form 2817)	RECV: 1.1, 1.16 — 1.28 SENT: 1.1, 1.16 — 1.28 STOR:
B	Red Chemists Review - 2626A (All copies sent to Division)	RECV: 1.1 — 1.7 SENT: 1.1 — 1.7 STOR:
C	Yellow Pharmacology Review (2626B all copies sent to Division)	RECV: 1.1, 1.8 — 1.12 SENT: 1.1, 1.8 — 1.12 STOR:
W	White Microbiology Review - 2626D (All copies sent to Division)	RECV: 1.1 — 1.4 SENT: 1.1 — 1.4 STOR:

COMMENTS: ARCHIVAL 1.1 — 1.7, 1.16 SENT TO HFD 092

WITHHOLD 2 PAGE (S)

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

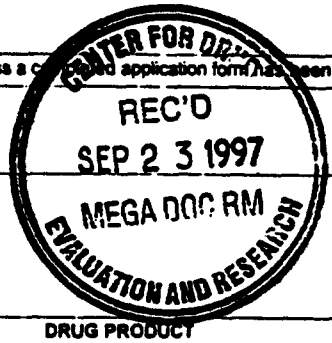
APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: April 30, 1994
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.



NOTE: No application may be filed unless a completed application form has been received (*21 CFR Part 314*).

NAME OF APPLICANT	DATE OF SUBMISSION
Galderma Laboratories, Inc.	September 19, 1997
ADDRESS (*Number, Street, City, State and Zip Code*)	TELEPHONE NO. (*Include Area Code*)
Post Office Box 331329 Fort Worth, Texas 76163	(817) 263-2676
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (*If previously issued*)
	NDA 20-748

DRUG PRODUCT

ESTABLISHED NAME (*e.g., USP/USAN*)	PROPRIETARY NAME (*If any*)
adapalene cream	DIFFERIN
CODE NAME (If any)	CHEMICAL NAME
CD 271; ALO2866	6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
cream	topical to the skin	0.1% (1 mg/g)

PROPOSED INDICATIONS FOR USE

For the topical treatment of acne vulgaris

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (*21 CFR Part 312*), NEW DRUG OR ANTIBIOTIC APPLICATIONS (*21 CFR Part 314*), AND DRUG MASTER FILES (*21 CFR 314.420*) REFERRED TO IN THIS APPLICATION:

INFORMATION ON APPLICATION

TYPE OF APPLICATION (*Check one*)

☐ THIS SUBMISSION IS A FULL APPLICATION (*21 CFR 314.50*) ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (*21 CFR 314.55*)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE OF SUBMISSION (*Check one*)

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION

☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (*e.g., Part 314.70(b)(2)(iv)*)

PROPOSED MARKETING STATUS (*Check one*)

☐ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (*Rx*) ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (*OTC*)

Public reporting burden for this collection of information is estimated to average 20 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Reports Clearance Officer, PHS
Hubert H. Humphrey Building, Room 721-B
200 Independence Avenue, S.W.
Washington, DC 20201
Attn: PRA

and to:

Office of Management and Budget
Paperwork Reduction Project (0910-0001)
Washington, DC 20503

Please DO NOT RETURN this application to either of these addresses.

ITEM 3.C. - ENVIRONMENTAL ASSESSMENT

Pursuant to 21 CFR 314.50(d)(1)(iii) the application is required to contain either a claim for categorical exclusion under §25.30 or §25.31 or an environmental assessment under §25.40.

The applicant, Galderma Laboratories, Inc., hereby claims categorical exclusion from preparation of an environmental assessment pursuant to the provisions of 21 CFR 25.31(b). To the applicant's knowledge no extraordinary circumstances exist that would warrant the preparation of an environmental assessment.

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

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

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: April 30, 1994
See OMB Statement on Page 3

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
17 Jul 97	
DIVISION ASSIGNED	**NDA/ANDA NO. ASS.**
540	20748

NOTE: No application may be filed unless a completed application form has been received (*21 CFR Part 314*).

NAME OF APPLICANT	DATE OF SUBMISSION
Galderma Laboratories, Inc.	July 16, 1997
ADDRESS (*Number, Street, City, State and Zip Code*)	**TELEPHONE NO.** (*Include Area Code*)
Post Office Box 331329 Fort Worth, Texas 76163	(817) 263-2600
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
	20-748

DRUG PRODUCT

ESTABLISHED NAME (*e.g., USP/USAN*)	PROPRIETARY NAME (*If any*)
Adapalene	DIFFERIN

CODE NAME (If any)	CHEMICAL NAME
CD 271; AL02866	6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
cream	Topical to the skin	0.1% (1mg/g)

PROPOSED INDICATIONS FOR USE

For the topical treatment of acne vulgaris.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (*21 CFR Part 312*), NEW DRUG OR ANTIBIOTIC APPLICATIONS (*21 CFR Part 314*), AND DRUG MASTER FILES (*21 CFR 314.420*) REFERRED TO IN THIS APPLICATION:

See attached listing.

INFORMATION ON APPLICATION

TYPE OF APPLICATION (*Check one*)

☒ THIS SUBMISSION IS A FULL APPLICATION (*21 CFR 314.50*) ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (*21 CFR 314.55*)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE OF SUBMISSION (*Check one*)

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION

☒ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (*e.g., Part 314.70(b)(2)(iv)*)

PROPOSED MARKETING STATUS (*Check one*)

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

CONTENTS OF APPLICATION

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

X	1. Index
X	2. Summary (21 CFR 314.50 (c))
X	3. Chemistry, manufacturing, and control section (21CFR 314.50 (d)(1))
X	4. a. Samples (21 CFR 314.50 (e)(1)) (Submit only upon FDA's request)
X	b. Methods Validation Package (21 CFR 314.50 (e)(2)(i))
	c. Labeling (21 CFR 314.50 (e)(2)(ii))
X	i. draft labeling (4 copies)
	ii. final printed labeling (12 copies)
X	5. Nonclinical pharmacology and toxicology section (21CFR 314.50 (d)(2))
X	6. Human pharmacokinetics and bioavailability section (21 CFR314.50 (d)(3))
	7. Microbiology section (21 CFR 314.50 (d)(4))
X	8. Clinical data section (21 CFR 314.50 (d)(5))
	9. Safety update report (21 CFR 314.50 (d)(5)(vi)(b))
X	10. Statistical section (21 CFR 314.50 (d)(6))
X	11. Case report tabulations (21 CFR 314.50 (f)(1))
X	12. Case reports forms (21 CFR 314.50 (f)(1))
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
	15. OTHER *(Specify)*

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit thee safety update reports as follows: (1) 4 months after the initial submission (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 34.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

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

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Christine Shank, Director, Regulatory Affairs	Christine Shank	7/16/97

ADDRESS (*Street, City, State, Zip Code*)	TELEPHONE NO. (*Include Area Code*)
Post Office Box 331329, Fort Worth, Texas 76163	(817) 263-2676

WARNING: A willfully false statement is a criminal offense U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 20 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Reports Clearance Officer, PHS
Hubert H. Humphrey Building, Room 721-B
200 Independence Avenue, S.W.
Washington, DC 20201
Attn: PRA

and to:

Office of Management and Budget
Paperwork Reduction Project (0910-0001)
Washington, DC 20503

Please DO NOT RETURN this application to either of these addresses.

LIST OF NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS, NEW DRUG OR ANTIBIOTIC APPLICATIONS, AND DRUG MASTER FILES REFERRED TO IN THIS APPLICATION:

Document Type	Sponsor	Subject
[redacted]	Galderma Laboratories, Inc. Fort Worth, Texas 76133	CD 271 Topical Solution (adapalene)
[redacted]	Galderma Laboratories, Inc. Fort Worth, Texas 76133	CD 271 Topical Gel (adapalene)
[redacted]	Galderma Laboratories, Inc. Fort Worth, Texas 76133	CD 271 Topical Cream (adapalene)
[redacted]		
NDA 20-338	Galderma Laboratories, Inc. Fort Worth, Texas 76133	DIFFERIN™ (adapalene solution) Solution, 0.1%
NDA 20-380	Galderma Laboratories, Inc. Fort Worth, Texas 76133	DIFFERIN™ (adapalene gel) Gel, 0.1%
DMF # [redacted]		
DMF # [redacted]		
DMF [redacted]		

Copies of Drug Master File reference authorization letters are provided on the following pages and also appear in the **ITEM 3.** Chemistry, Manufacturing, and Controls Section of the application.

WITHHOLD 2 PAGE (S)

STATISTICAL REVIEW AND EVALUATION: 45 DAY MEETING REVIEW
(COMPLETED REVIEW FOR INTERNAL DISTRIBUTION ONLY)

AUG 28 1997

NDA:	20-748
DRUG CLASS:	3S
NAME OF DRUG:	Differin (Adapolene) Topical Cream 0.1%
APPLICANT:	Galderma Laboratories, Incorporated
SUBMISSION DATE:	July 17, 1997
INDICATION(S):	Treatment of Acne Vulgaris
NUMBER AND TYPE OF CONTROLLED CLINICAL STUDIES:	Two Randomized, Double-Blind, Parallel, Multi-Center, one of which is Vehicle-Controlled & the second study is Reference Controlled
STATISTICAL REVIEWER:	Shahla S. Farr, M.S.
CLINICAL REVIEWER:	Phyllis Huene , M.D.
PROJECT MANAGER:	Olga Cintron
45 DAY MEETING DATE:	August 28, 1997
WAS THE NDA FILED:	Yes
IF YES, DUE DATE:	August 28, 1997
USER FEE DATE:	July 17 , 1998

I. ORGANIZATION AND DATA PRESENTATION	YES	NO	N/A
***A. Is there a comprehensive table of contents with adequate indexing and pagination?**	✓		
@B. Are the original protocols, protocol amendments and proposed label provided?	✓		
*C. Are the following tables/listings provided in each study report?			
1. Patient profile listings by center(includes all enrolled patients).		✓	
At this point, I don't need them.			
2. Lost subject tables by center which includes reason and time of loss.	✓		
3. Intermediate analysis summary tables (gender, age, race/ethnic, etc.).	✓		
4. Pathogen listings.			✓

		YES	NO	N/A
@D.	Adverse event listings by center and time of occurrence relative to enrollment date.	✓		
*1.	Are adverse events from cited sources(foreign and domestic) provided?	✓		
#E.	Is a CANDAR or an electronic submission of the data necessary?	✓		

The data will be provided by the sponsor.

@F.	If the data have been submitted electronically, has adequate documentation of the data sets been provided?			✓
G.	Are inclusion/exclusion (evaluability) criteria adequately coded and described:			✓
*H.	Are there discrepancies between CRF information and CANDAR/Jacket data?			✓
I.	If the data have been submitted electronically, can laboratory data be easily merged across studies and indications?			✓

II. STATISTICAL METHODOLOGY

		YES	NO	N/A
*A.	Are all primary efficacy studies of appropriate design to meet basic approvability requirements, within current Divisional policy statements or to the extent agreed upon previously with the sponsor by the Division?	✓		
*B.	For each study, is there a comprehensive statistical summary of the efficacy analyses which covers the intent-to-treat population, evaluable subject population and other applicable sub populations (age, gender, race/ethnicity, etc.)?	✓		
C.	Based on the summary analyses of each study, do you believe:			
*1.	The analyses are appropriate for the type data			

	collected, the study design, and the study objectives(based on protocol and proposed label claims)?	✓		
*2.	Intent-to-treat (ITT and MITT) analyses are properly performed?	✓		
3.	Sufficient and appropriate references were included for novel statistical approaches?			✓
*D.	If interim analyses were performed, were they planned in the protocol and were appropriate significance level adjustments made?			✓
*E.	Are there studies which are incomplete or ongoing?		✓	
*F.	Is there a comprehensive, adequate analysis of safety data as recommended in the Clinical/Statistical Guideline?		✓	

No statistical analysis was performed to compare the adverse events in each arm.

III. FILEABILITY CONCLUSIONS

From a statistical perspective is this submission, or indications therein, reviewable with only minor further input from the sponsor?

Yes, but we need the data and the data dictionary to be able to perform the statistical analyses.

Shahla S. Farr
Biomedical Statistician, DOB IV

5/1

Concur: R. Srinivasan, Ph.D.
Team Leader, DOB IV

cc:
Archival: NDA 20-748
HFD-540
HFD-540/Dr. Wilkin
HFD-540/Dr. Walker
HFD-540/Dr. Huene
HFD-540/Mr. Cintron
HFD-725/Dr. Harkins
HFD-725/Dr. Srinivasan
HFD-725/Ms. Farr
HFD-344/Dr. Lepay
Chron.

* These items, if not included or if incorrect, are justifiable reasons for not filing the NDA.

@ These items, if not acceptable, are reason to consider not filing.

It is the Agency's intent that all submissions be CANDARs or electronic in format in 1995. Clearly, we do not need CANDARs for every submission, but, just as clearly, we need data on disks if we are to do an expeditious review. Since the company, in all likelihood, used computers to do their evaluations, all data should be readily available to us on disk, at least, for our use in the review action.

NDA 20-748

45 DAY MEETING CHECKLIST

FILEABILITY:

On initial overview of the NDA application:	YES	NO

CLINICAL:

(1)	On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?	X
(2)	Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X
(3)	On its face, is the clinical section of the NDA legible so that substantive review can begin?	X
(4)	If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	NA
(5)	On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application?	X
(6)	Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	X
(6)	Are all data sets for pivotal efficacy studies complete for all indications (infections) requested?	X
(7)	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X
(8)	Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division?	X

(9) Has the application submitted a rationale for assuming the applicability of foreign data in the submission to the US population? NA

(10) Has the applicant submitted all additional required case record forms (beyond deaths and drop-outs) previously requested by the Division? NA

(11) Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division? X

(12) Has the applicant presented a safety assessment based on <u>all</u> current world-wide knowledge regarding this product? NA

(13) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package? X

(14) Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? NA

(15) From a clinical perspective, is this NDA fileable? If "no", please state below why it is not. X

LSI 8/27/97
Reviewing Medical Officer

Supervisory Medical Officer

CHEMISTRY

7. Estimated date of completion of the initial chemistry review is *March 1998*.

CMC SECTION CHECKLIST:

		YES	NO
(1)	Is the CMC section organized in a manner to allow substantive review to begin?	-X-	
(2)	Is the CMC section indexed and paginated in a manner to allow substantive review to begin?	-X-	
(3)	Is the CMC section legible so that substantive review can begin?	-X-	
(4)	Are all the facilities (manufacturing, packaging, testing, sterilization, etc.) appropriately delineated with full street addresses?	-X-	
(5)	Has the sponsor submitted an environmental impact assessment or a categorical exclusion?	-X-	
(6)	Has the sponsor developed appropriate controls assessment procedures that are currently ready for FDA verification?	-X-	
(7)	For an antibiotic, has the sponsor submitted an appropriate validation package and committed to the readiness of exhibit samples?	-X-	
(8)	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	-X-	
(9)	Has the sponsor submitted draft labeling consistent with 21 CFR 201.56 and 201.57, current Division labeling policies, and the design of the development package?	-X-	
(10)	Has the sponsor submitted stability data to support and justify the proposed expiry?	-X-	
(11)	Has the sponsor submitted a summary which lists the batch size, formulation, and site of production, for all pivotal clinical batches manufactured in support of the NDA?	-X-	
(12)	Is this NDA fileable from a CMC perpsective? If "No," please explain.	-X-	

LSI

Reviewing Chemist

LSI

Chemistry Team Leader

FORWARD PLANNING MEETING CHECKLIST
August 6, 1997.

NDA 20-748 Differin (adapalene cream) Cream, 0.1%

Indication: Treatment of acne vulgaris.
Galderama Laboratories, Inc.
Type 3S
Filing Date: 9/15/97.
User Fee Date: 9/17/98.
Regulatory Due Date: 1/13/98.
FILEABILITY:

On initial overview of the NDA application:

PROJECT MANAGEMENT:

(1) Do any of the following apply to this application (i.e., if YES , the application MUST BE REFUSED TO FILE under 314.101 (e) and there is no filing over protest):

(a) Is the drug product already covered by an approved application?
NO.
(b) Does the submission purport to be an abbreviated application under 314.55; however the drug product is not one for which FDA has made a finding that an abbreviated application is acceptable under 314.55(b)?
NO.
(c) Is the drug product subject to licensing by FDA under the Public Service Act and Subchapter F of Chapter I of Title 21 of the CFR?
NO.

(2) Do any of the following apply to this application (i.e., if NO, the application MAY BE REFUSED TO FILE under 314.101(d) and there is the potential for filing over protest):

(a) Does the application contain a completed application form as required under 314.50 or 314.55?
YES.
(b) On its face, does the application contain the sections of an application required by regulation and Center guidelines?
YES. (Clinical, Biopharm, Statistics, Microbiology, Pharm/Tox, Chemistry)

(c) Has the applicant submitted a complete environmental assessment which addresses each of the items specified in the applicable format under 25.31 or has the applicant submitted evidence to establish that the product is under 25.24 of the CFR?
YES. APPLICANT SUBMITTED ENVIRONMENTAL ASSESSMENT. LOCATED IN VOLUME 1.4, PAGE 3 0601.

(d) On its face, is the NDA formatted in compliance with Center guidelines including integrated efficacy and safety summaries?

YES. BOTH EFFICACY AND SAFETY SUMMARIES ARE LOCATED IN VOLUME 1.28.

(e) Is the NDA indexed and paginated?

YES.

(f) On its face, is the NDA legible?

YES.

(g) Has the applicant submitted all required copies of the submission and various sections of the submission?

YES.

(h) Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?

YES. HOWEVER, THE SPONSOR STATES THAT NO SPECIFIC MEETINGS NOR SPECIAL CORRESPONDENCE HAVE BEEN CONDUCTED REGARDING THE DEVELOPMENT OF THE CREAM. THE CREAM FOLLOWS THE SAME DEVELOPMENT PROGRAM AS FOR THE GEL AND SOLUTION.

(i) Does the application contain a statement that all nonclinical laboratory studies were conducted in compliance with the requirements set forth in Part 58 or a statement why a study was not conducted in compliance with those requirements?

YES. STATEMENT LOCATED IN VOLUME 1.1, PAGE 2 0088.

(j) If required, has the applicant submitted carcinogenicity studies?

YES. TWO CARCINOGENICITY STUDIES WERE PERFORMED. ONE WAS IN CD RATS BY DIETARY ADMINISTRATION OF ADAPALENE AND THE OTHER IN CD-1 MICE BY TOPICAL APPLICATION OF ADAPALENE AQUEOUS GEL. SUMMARY TABLES ARE PROVIDED IN VOLUME 1.1, PAGE 2 0136.

(k) On its face, does the application contain at least two adequate and well-controlled clinical trials?

YES. THESE ARE: CLINICAL REPORT 9111-CD271C-EV AND CLINICAL REPORT CR 90087.

(l) Does the application contain a statement that all clinical trials were conducted in accord with the IRB/Declaration of Helsinki provisions of the CFR?

YES. STATEMENT LOCATED IN VOLUME 1.28, PAGE 8 5187 AND IN VOLUME 1.1, PAGE 2 0299.

(m) Have all articles/study reports been submitted whether in English or translated into English?
YES.

(n) Has the applicant submitted draft labeling in compliance with 210.56 and 210.57 of the CFR?
YES, LOCATED IN VOL. 1.1, PAGE 1 0015.

(o) Has the applicant submitted the required FRAUD POLICY notice?
YES. LOCATED IN VOLUME 1.1.

(p) Has the applicant submitted copies of all package inserts (or their equivalent) from all countries in which this product has been previously approved for marketing? Have all non-English package inserts been translated?
NOT APPLICABLE.

(q) Has the applicant stated that the integrated summary of safety includes all safety data for this product of which they are aware from all sources, domestic and foreign? What is the cut-off date for the preparation of the ISS?
THE SPONSOR STATES THAT THE INTEGRATED SUMMARY OF SAFETY INCLUDES ALL THE EVALUABLE DATA OBTAINED DURING THE CLINICAL PROGRAMS RUN IN THE U.S., CANADA, AND EUROPE. ALL CLINICAL STUDIES REPORTED IN THE APPLICATION HAVE BEEN COMPLETED. THE CUT-OFF DATE FOR THE PREPARATION OF THE INTEGRATED SUMMARY OF SAFETY IS MAY 1, 1997.

(r) If this is a CANDA submission, has the applicant submitted a statement to the archival NDA that the text, tables, and data in the CANDA and the archival hardcopy NDA are identical? If they are not identical, is there a letter to the archival NDA that specifies distinctly ALL of the differences in the two submissions?
NO.

(3) From a project management perspective, is this NDA fileable? If "no". please state on the reverse why it is not.
THIS APPLICATION IS FILEABLE FROM A PROJECT MANAGEMENT PERSPECTIVE.

LST

Project Manager

LST

Supervisory Project Manager

Pharm Tox

45 DAY MEETING CHECKLIST

FILEABILITY: DRUG: ADAPLENE (DIFFERIN)
NDA 20-748

On initial overview of the NDA application: YES NO

PHARMACOLOGY:

(1) On its face, is the pharmacology section of the NDA organized in a manner to allow substantive review to begin? ✓

(2) Is the pharmacology section of the NDA indexed and paginated in a manner to allow substantive review begin? ✓

(3) On its face, is the pharmacology section of the NDA legible so that substantive review can begin? ✓

(4) Are all required(*) and requested IND studies completed and submitted in this NDA ✓carcinogenicity, ✓mutagenicity, ✓teratogenicity*, effects on fertility*, ✓juvenile studies, acute adult studies*, ✓chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)? ✓

(5) If the formulation to be marketed is different from the formulation used in the toxicology studies, has the sponsor made an appropriate effort to either repeat the studies using the to be marketed product or to explain why such repetition should not be required? Formulation proposed for marketing has been clinically tested

(6) Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57? ✓

(7) Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? N/A

(8) On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route? ✓

(9) Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? ✓

(10) Has the sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns? ✓

(11) From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not. ✓

LT

Reviewing Pharmacology Officer

LT

Supervisory Pharmacology Officer

45 DAY MEETING CHECKLIST

FILEABILITY:

On initial overview of the NDA application: (YES) NO

BIOPHARMACEUTICAL:

(1) On its face, is the biopharmaceutics section of the NDA organized in a manner to allow substantive review to begin? — yes

(2) Is the biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin? — yes

(3) On its face, is the biopharmaceutics section of the NDA legible so that substantive review can begin? — yes

(4) Are the Phase 1 studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? — yes

(5) If several formulations of the product were used in the clinical development of the product, has the sponsor submitted biopharmaceutics data to allow comparison between the product to be marketed and the product(s) used in the clinical development? — See Comment # 4 in review.

(6) From a biopharmaceutic perspective, is the NDA fileable? If "no", please state below why it is not? — yes

VI
Reviewing Biopharmaceutics Officer

VI
Supervisory Biopharmaceutics Officer

SEP 2 1997

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

45 DAY MEETING **DATE: 08/28/97**

NDA: 20-748 **SUBMISSION DATE:** 07/16/97
PRODUCT: Differin (adapalene) Cream, 0.1%
SPONSOR: Galderma Laboratories, Inc.
3000 Alta Mesa Blvd., Suite 300
Fort Worth, Texas 76163
TYPE OF SUBMISSION: Original NDA **REVIEWER:** Sue-Chih Lee, Ph.D.

I. BACKGROUND:

Adapalene, a naphthoic acid derivative, possesses retinoid-like activities, i.e., modulation of cellular differentiation, keratinization and inflammatory processes. The proposed product, Differin Cream 0.1%, is intended for the treatment of acne vulgaris. The adapalene solution and gel dosage forms were approved in 1996. The sponsor indicated that this formulation incorporates emollient and moisturizing characteristics and may be more appealing to certain group of patients.

II. FORMULATIONS AND DOSAGE REGIMEN:

The cream is to be applied to affected areas of the skin once daily at nighttime. Several formulations were tested during the drug development phases (see attachment). The following formulations are of importance:

- Proposed formulation: Formulations CDP
- Formulation used in PK study: C2 (clinical study #CR 90087)
- Formulation used in tape-stripping study: C4, C7 and C9
- Formulation used in in vitro percutaneous absorption study: C3
- Clinical safety and efficacy studies: C1 and C2

Comment:

a. Formulation used in systemic absorption study, C2:
#C2 differs from the proposed formulation in that the former contains [redacted]
Whether this difference will result in different study outcome is not clear.

b. Formulation used in tape-stripping study, C4, C7 and C9:
#C4 contains [redacted] carbomer while the proposed formulation has [redacted] carbomer. It is not clear whether this difference has impact on the study results. (There are also differences in preservative concentration and alkalizing agent used. These differences are not expected to affect thestudy outcome.)
#C7 and C9 have the same vehicle as #C4 but have higher content of the active ingredient.

c. Formulations used in clinical trials, C1 and C2:

#C1 is identical to the proposed formulation except that it contains — overage of the active ingredient. This is acceptable.
#C2 differs from the proposed formulation in that the former contains ——— Whether this difference will result in different clinical outcome is not clear.

III. PK STUDIES:

Besides the various studies previously submitted to the gel and solution NDAs, the following new studies are provided in the Clinical Pharmacology and Human Pharmacokinetic section:

Cream formulations:

a) PK study using cream formulation C2 (Clinical study #CR 90087).
b) Tape-stripping study comparing three strengths of adapalene in a cream formulations (Formulation C4) (Study #1.CG.03.SRE.2042)

Gel formulation (to address the potential teratogenic risk):

c) PK study with 0.1% gel to examine adapalene distribution into adipose tissue (Study #1.CG.03.SRE.2019)
d) PK study using ^{14}C-adapalene in 0.1% gel to characterize the extent of absorption (Study #1.CG.03.SRE.4529)
e) Absorption and Excretion under maximized exposure conditions using 0.1% gel (Study #1.CG.03.SRE.2005)

Oral administration (to address the potential teratogenic risk)::

f) Oral ADME study with single dose of 10 mg or 25 mg of adapalene in sesame oil (Study #1.CG.03.SRE.4515)

IV. OTHER STUDIES:

Among the studies previously submitted to the gel and solution NDAs, one study considered pertinent to this NDA is the in vitro percutaneous absorption study (PK Study #91005) which compared the three dosage forms.

V. COMMENTS:

1. The only PK study that addresses the systemic absorption of the cream formulation was conducted as part of a clinical study (Clinical study #CR 90087). This formulation (#C2) differs from the proposed formulation in that it contains ——— Whether this difference will result in different study outcome is not clear. In addition, only one blood sample per subject was collected in this study. There appear no records of sampling time as related to dosing time. The sponsor is required to conduct a multiple-dose study to determine full plasma concentration-time profiles in patients under maximal exposure conditions using the proposed cream formulation.

2. The formulation used in tape-stripping study (C4) contains —— carbomer while the proposed formulation has —— carbomer. This difference may have impact on the study results.

3. The new studies conducted using topical gel formulation were conducted in healthy subjects. Because the diseased skin can enhance the systemic absorption, studies in patients with maximal surface area of the involved skin are most desirable.

4. Regarding the formulations used in clinical trials (Formulations C1 and C2):
#C1 is identical to the proposed formulation except that it contains — overage of the active ingredient. This is acceptable.
#C2 differs from the proposed formulation in that the former contains ——
Whether this difference will result in different clinical outcome is not clear.

VI. RECOMMENDATION:

From the biopharmaceutics standpoint, the application is fileable. Please convey Comments #1, 2 and 3 to the sponsor. Comment #4 should be communicated to the Medical Officer.

Sue-Chih Lee, Ph.D.
Pharmacokinetics Evaluation Branch III

RD/FT Initialed by Dennis Bashaw, Pharm.D. 9/2/97

CC:
NDA 20-748
HFD-540 (Div.File)
HFD-540 (CSO/Cintron)
HFD-880 (Bashaw)
HFD-880 (Lazor)
HFD-880 (Lee)
HFD-870 (attn: CDR. Barbara Murphy)
HFD-344 (Viswanathan)

TABLE I

	Commercial Drug Product (Proposed Formulation)	Adapalene Cream Investigational Formulations				
Formulation Code **Strength - w/w%**	**CDP** **0.1**	**C1** **0.1**	**C2** **0.1**	**C3** **0.1**	**C4** **0.1**	**C5**
INGREDIENTS = w/w%						
ACTIVE INGREDIENT: Adapalene	0.1	0.1[1]	0.1[2]	0.1	0.1	
INACTIVE INGREDIENTS: Carbomer 934P, NF Carbomer 934P Propylparaben, NF Phenoxyethanol, BP Methylparaben, NF Edetate Disodium, USP Glycerin, USP PEG-20 Methyl Glucose Sesquistearate Methyl Glucose Sesquistearate Cyclomethicone Squalane, NF Trolamine, NF Purified Water						
Lot (Batch) No. - used in clinical and human biopharmaceutic studies		ELDP-2	AKEI-0054	524.827/F1 [^{14}C]-524.827/R11	553.109/2F1	524.894/E1

1 Includes excess to compensate for loss during production. Subsequent evaluation of batch records and analysis revealed no significant losses occurred, thus the excess was dropped from the proposed commercial formulation.

2 Includes excess to compensate for loss during production.

mulasum
y 28, 1997

TABLE I (continued)

Formulation Code Strength - w/w%	Adapalene Cream Investigational Formulations				Cream Vehicle Formulations	
	C6	C7	C8	C9	CV1	CV2
INGREDIENTS = w/w%						
ACTIVE INGREDIENT:						
Adapalene					--	--
INACTIVE INGREDIENTS:						
Carbomer 934P, NF						
Carbomer 934P						
Propylparaben, NF						
Phenoxyethanol,						
Methylparaben, NF						
Edetate Disodium, USP						
Glycerin, USP						
PEG-20 Methyl Glucose Sesquistearate						
Methyl Glucose Sesquistearate						
Cyclomethicone						
Squalane, NF						
Trolamine, NF						
Purified Water						
Lot (Batch) No. - used in clinical and human biopharmaceutic studies	524.865/E2	553.112/2F1	524.864/F1	553.113/2F1	524.827/P/F1	ELDN-2

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