CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-502

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-502 SUPPL # N/A HFD # 540

Trade Name Differin Lotion, 0.1%

Generic Name adapalene

Applicant Name Galderma Research and Development

Approval Date, If Known PDUFA Date 4-2-2010

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

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 ☒ 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.

N/A

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:

N/A

d) Did the applicant request exclusivity?

YES ☒ 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?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 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 ☒ NO ☐

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

NDA#	21-753	Differin (adapalene) Gel, 0.3%
NDA#	20-748	Differin (adapalene) Cream 0.1%
NDA#	20-380	Differin (adapalene) Gel, 0.1%
	NDA # 20-338	Differin (adapalene) Solution, 0.1% (discontinued)
	NDA # 22-320	Epiduo (adapalene 0.1%; benzoyl peroxide, 2.5%) Gel

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 ☐

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. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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 ☒ 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 ☒ 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 ☒

(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:

N/A

(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 ☒

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:

RD.06.SPR.18113
RD.06.SPR.18114

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 ☒

Investigation #2 YES ☐ NO ☒

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

N/A

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 ☒

Investigation #2 YES ☐ NO ☒

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

N/A

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"):

RD.06.SPR.18113
RD.06.SPR.18114

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 # 76,057 YES ☒ ! NO ☐
! Explain:

Investigation #2 !
!
IND # 76,057 YES ☒ ! 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 ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! 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 ☒

If yes, explain:

==========

Name of person completing form: Kelisha C. Turner
Title: Regulatory Health Project Manager
Date: 3-16-2010

Name of Office/Division Director signing form: Susan J. Walker, M.D., F.A.A.D.
Title: Director

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22502	ORIG-1	GALDERMA RESEARCH AND DEVELOPMENT INC	DIFFERIN LOTION

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

/s/

KELISHA C TURNER
03/17/2010

MARGO L OWENS
03/17/2010

DAVID L KETTL
03/17/2010

SUSAN J WALKER
03/17/2010

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

DA/BLA#: NDA 22-502 Supplement Number: N/A NDA Supplement Type (e.g. SE5): _____

Division Name: Division of Dermatology and Dental Products PDUFA Goal Date: 1-2-2010 Stamp Date: 3-2-2009

Proprietary Name: Differin

Established/Generic Name: adapalene

Dosage Form: Lotion, 0.1%

Applicant/Sponsor: Galderma Research and Development, Inc.

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) N/A. Differin Cream and Differin Gel have been previously approved for Acne Vulgaris.
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Acne Vulgaris

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☒ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☒ No: Please check all that apply:
  - ☒ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☒ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☒	Neonate	0 wk. 0 mo.	__ wk. 11 mo.	☒	☐	☐	☐
☒	Other	1 yr. 0 mo.	11 yr. 11 mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☒ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☒ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

ediatric subpopulation(s) in which studies have been completed (check below):

	Population	minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__wk. __mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__yr. __mo.	__yr. __mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

ldditional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☒	Other	12 yr. __ mo.	16 yr. 11 mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

'ote: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other ediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

MEMORANDUM OF TELECON

DATE: December 22, 2009

APPLICATION NUMBER: NDA 022502 Differin® (adapalene) Lotion, 0.1%.

BETWEEN:

Name: ***Galderma Research and Development, Inc.***

A. Fields, M.S., M.Ed., DrPH, Director of Regulatory Submissions
M. Keegan, M.S., Global Project Manager

Phone: 1-877-409-7700 Ext. 200 (call-in)

Representing: Galderma Research and Development, Inc.

AND

Name: ***Office of New Drug Quality Assessment***
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead

Division of Dermatology and Dental Products
Susan J. Walker, M.D., F.A.A.D., Director
David Kettl, M.D., Clinical Team Leader
Margo Owens, Project Management Team Leader
Kelisha C. Turner, B.S., Regulatory Health Project Manager

SUBJECT: NDA 022502 Differin (adapalene) Lotion, 0.1% - Facilities Withhold recommendation.

Background:
The Agency initiated a teleconference with the applicant to inform them of the facility recommendation of Withhold for the (b) (4) Site for NDA 022502 Differin (adapalene) Lotion, 0.1%.

The Agency informed the applicant of the overall withhold recommendation received. The applicant indicated that the (b) (4) site was only a back-up testing site, and would like to withdraw the site from the application. The Agency informed the applicant that if this is the applicant's decision, they must submit the withdrawal as soon as possible to the application as the review cycle continues. Additionally, a submission of this type would trigger a major amendment and extend the review clock by 90 days.

The call ended amicably.

David Kettl, M.D.
Clinical Team Leader
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22502	ORIG-1	GALDERMA RESEARCH AND DEVELOPMENT INC	DIFFERIN LOTION

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/s/

KELISHA C TURNER
02/01/2010

DAVID L KETTL
02/01/2010

MEMORANDUM OF TELECON

DATE: January 28, 2010

APPLICATION NUMBER: NDA 022502 Differin® (adapalene) Lotion, 0.1%.

BETWEEN:

Name: ***Galderma Research and Development, Inc.***
Allen Fields, DrPH, Director of Regulatory Submissions
Denis Gross, Ph.D., Global Regulatory Affairs Director
Vasant Manna, M.D., Senior Medical Advisor/Project Team Leader
Maureen Keegan, Global Project Manager
Isabelle Preuilh, Ph.D, Pharmaceutical Project Team Representative
Jean-Pierre Etchegaray, Pharmaceutical Development Expert
Paul Clark, Director of Regulatory Affairs (Galderma Laboratories, Inc.)

Phone: 1-877-409-7700 Ext. 200 (call-in)

Representing: Galderma Research and Development, Inc.

AND

Name: ***Office of New Drug Quality Assessment***
Rajiv Agarwal, Ph.D., Chemistry Reviewer
Jeannie David, M.S., Regulatory Health Project Manager

Division of Dermatology and Dental Products
David Kettl, M.D., Clinical Team Leader
Amy Woitach, D.O. Clinical Reviewer
Margo Owens, Project Management Team Leader
Kelisha C. Turner, B.S., Regulatory Health Project Manager

SUBJECT: Packaging Configuration for NDA 022502 Differin (adapalene) Lotion, 0.1%.

Background:
The Agency initiated a teleconference with the applicant to discuss the packaging configuration for NDA 022502 Differin (adapalene) Lotion, 0.1%.

The Agency informed the applicant that as the clinical trial was performed with the pump inserted in the bottle, (b) (4) The applicant will send the amendment as an

email to the OND and ONDQA Regulatory Project Managers and officially to the application on Monday, February 1, 2010.

_____

David Kettl, M.D.
Clinical Team Leader
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22502	ORIG-1	GALDERMA RESEARCH AND DEVELOPMENT INC	DIFFERIN LOTION

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/s/

KELISHA C TURNER
02/01/2010

DAVID L KETTL
02/01/2010

MEMORANDUM OF TELECON

DATE: November 30, 2009

APPLICATION NUMBER: NDA 22-502 Differin® (adapalene) Lotion, 0.1%.

BETWEEN:

Name: ***Galderma, Fort Worth, Texas***
M.-L. Abou-Chacra, Ph.D., Pharm D., Regulatory Affairs Project Manager
A. Fields, M.S., M.Ed., DrPH, Director of Regulatory Submissions
D. Gross, Ph.D., Global Regulatory Affairs Director
M. Keegan, M.S., Global Project Manager
V. Manna, M.D., Senior Medical Advisor/Project Team Leader
I. Preuilh, Ph.D., Pharmaceutical Development Project Manager
O. Watts, Ph.D., Vice President, Regulatory and Technical Affairs, Galderma Laboratories

Phone: 1-888-287-5336 (call-in)

Representing: Galderma Research and Development, Inc.

AND

Name: ***Office of New Drug Quality Assessment***
Rajiv Agarwal, Ph.D., Chemistry Reviewer

Division of Dermatology and Dental Products
David Kettl, M.D., Clinical Team Leader
Amy Woitach, D.O. Clinical Reviewer
Kelisha C. Turner, B.S., Regulatory Health Project Manager

SUBJECT: Package Configuration in Studies 18113 and 18114 for NDA 22-502 Differin (adapalene) Lotion, 0.1%

Background:
The Agency initiated a teleconference with the sponsor to confirm the package configuration used in studies 18113 and 18114.

The Agency informed the sponsor that it was unclear in their original NDA submission whether they are referring to a product (b) (4)

The sponsor confirmed that the product will be marketed with the pump on the bottle. In addition, (b) (4)

The Agency requested that the sponsor submit color mock ups of both the 2oz and 4oz carton and container labels to include NDC numbers and instructions to the pharmacist. The sponsor agreed to submit this information by close of business, December 1, 2009.

Addendum:

The sponsor submitted the requested information on December 1, 2009 as discussed.

David Kettl, M.D.
Clinical Team Leader
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22502	ORIG-1	GALDERMA RESEARCH AND DEVELOPMENT INC	DIFFERIN LOTION

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/s/

KELISHA C TURNER
01/19/2010

DAVID L KETTL
01/20/2010

MEMORANDUM OF TELECON

DATE: October 20, 2009

APPLICATION NUMBER: NDA 22-502 Differin® (adapalene) Lotion, 0.1%.

BETWEEN:

Name: **Galderma Research and Development's Attendees:**

A. Fields, M.S., M.Ed., DrPH, Director of Regulatory Submissions
M.-L. Abou-Chacra, Ph.D., Pharm D., Regulatory Affairs Project Manager
M. Keegan, M.S., Global Project Manager
Y. Liu, Ph.D., Head of US Biometrics
V. Manna, M.D., Senior Medical Advisor/Project Team Leader

Consultants:

(b) (4)

Phone: 1-888-287-5336 (call-in)

Representing: Galderma Research and Development, Inc.

AND

Name: David Kettl, M.D., Clinical Team Leader, DDDP
Amy Woitach, D.O., Clinical Reviewer, DDDP
Mat Soukup, Ph.D., Biostatistics Reviewer, DB III
Kelisha C. Turner, B.S., Regulatory Health Project Manager, DDDP

SUBJECT: Biostatistics concerns regarding the reproduction of results in the label for NDA 22-502 Differin (adapalene) Lotion, 0.1%.

Background:
The Agency initiated a teleconference with the sponsor to confirm their SAS code and data input information to understand how they derived their data set.

The Agency informed the sponsor that we are not able to reproduce the results provided in Table 2 of the label. The Agency further stated that the data will be presented in Table 2 by the Agency as we deem to be representative and will be reflected during labeling negotiations.

David Kettl, M.D.
Clinical Team Leader
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22502	ORIG-1	GALDERMA RESEARCH AND DEVELOPMENT INC	DIFFERIN LOTION

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/s/

KELISHA C TURNER
01/14/2010

DAVID L KETTL
01/14/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022502

PDUFA GOAL DATE EXTENSION

Galderma Research and Development, Inc.
Attention: Allen E. Fields, DrPH
Director of Regulatory Submissions
5 Cedar Brook Drive, Suite 1
Cranbury, NJ 08512

Dear Dr. Fields:

Please refer to your February 27, 2009 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Differin (adapalene) Lotion, 0.1%.

On December 29, 2009, we received your December 23, 2009, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is April 2, 2010.

If you have any questions, call Kelisha C. Turner, Regulatory Project Manager, at (301) 796-0766.

Sincerely yours,

{See appended electronic signature page}

Barbara Gould, M.B.A.H.C.M.
Chief, Project Management Staff
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22502	ORIG-1	GALDERMA RESEARCH AND DEVELOPMENT INC	DIFFERIN LOTION

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/s/

BARBARA J GOULD
12/30/2009

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: December 16, 2009

To: Allen E. Fields, DrPH **Director of Regulatory Submissions**	**From:** Kelisha Turner Regulatory Project Manager
Company: Galderma Research & Development, Inc.	Division of Dermatology & Dental Drug Products
Fax number: (682) 831-9191	**Fax number:** (301) 796-9894
Phone number: (817) 961-5227	**Phone number:** (301) 796-0766

Subject: NDA 22-502 Differin (adapalene) Lotion, 0.1%

Total no. of pages including cover: 3

Comments:
Please review and respond to the postmarketing requests.

Document to be mailed: ☐ YES ☑ NO

Please refer to your February 27, 2009, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Differin (adapalene) Lotion, 0.1%.

The Agency has the following informational need which could be provided post-approval:

Conduct a post-marketing study to obtain pharmacokinetic data for adolescents aged 12 years to 17 years who have acne vulgaris treated with adapalene lotion under maximal use conditions.

Final study protocol submitted:	by June 2010
Protocol initiated:	by November 2010
Final study results submitted:	by June 2011

You are encouraged to submit a protocol to the Agency for review prior to initiation of the study to assure that the proper design elements of a maximal usage trial are incorporated.

Send a letter stating the commitments as outlined above, and your agreement to those commitments and timelines. We request receipt of your written response no later than 3:00 p.m. on December 17, 2009.

If you have any questions, call Kelisha Turner, Regulatory Project Manager, at 301-796-0766.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22502	ORIG-1	GALDERMA RESEARCH AND DEVELOPMENT INC	DIFFERIN LOTION

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/s/

KELISHA C TURNER
12/16/2009

MEMORANDUM OF TELECON

DATE: November 23, 2009

APPLICATION NUMBER: NDA 22-502 Differin® (adapalene) Lotion, 0.1%.

BETWEEN:

Name: ***Galderma, Fort Worth, Texas***
Allen E. Fields, DrPH, Director of Regulatory Submissions
O. Watts, PhD - Vice President, Regulatory and Technical Affairs

Galderma, Sophia Antipolis, France
M.-L. Abou-Chacra, PhD, Pharm D., Reg Affairs Project Manager
I. Preuilh, PhD Pharmaceutical Development Project Manager

Galderma, Princeton (Cranbury), New Jersey
M. Keegan, M.S., Global Project Manager
V. Manna, MD, Senior Medical Advisor/Project Team Leader

Phone: 1-888-287-5336 (call-in)

Representing: Galderma Research and Development, Inc.

AND

Name: ***Office of New Drug Quality Assessment***
Rajiv Agarwal, Ph.D., Chemistry Reviewer
Jeannie David, M.S., Regulatory Health Project Manager

Division of Dermatology and Dental Products
David Kettl, M.D., Clinical Team Leader
Kelisha C. Turner, Regulatory Health Project Manager
Margo Owens, Team Leader, Project Management Staff

SUBJECT:

Background:
Galderma submitted an original NDA on March 2, 2009. A labeling amendment was submitted on October 22, 2009, which refers to a label for a "2 Ounce Carton (b) (4) Draft Carton and Container Labels. Galderma also submitted an amendment on July 28, 2009, to inform the Agency that (b) (4) will be relocating to a new facility.

The following two points were provided to Galderma from Jeannie David, Project Manager for the FDA/ONDQA, to Allen Fields, Galderma, by email on November 20, 2009, in preparation for the November 23, 2009, teleconference:

1. You have proposed carton and container labels for product with a pump (b) (4) for NDA 22-502 Differin (adapalene) Lotion, 0.1%. However, Phase 3 studies were done with only pump containers. The FDA requests that we discuss this.

2. With the update of site address for (b) (4), please state whether or not the former address will still be used or withdrawn from the NDA.

Discussion:
Point 2 was discussed. Galderma agreed to submit an amendment stating that they will withdraw the former address for (b) (4) from the NDA.

Point 1 was discussed. FDA stated that the Agency would not consider information provided to the NDA for product (b) (4) The Agency will continue its review and action based only on the product described for use with the pump, because this was the drug product design used in the pivotal Phase 3 studies. (b) (4)

FDA also stated that NDA 22-502 is still pending resolution of inspections.

Galderma agreed to submit timelines for submission to address these two points, as well as the amendments themselves, to the NDA. Informal copies will be sent to Kelisha Turner, FDA/DDDP, and Jeannie David, FDA/ONDQA.

The call ended.

David Kettl, M.D.
Clinical Team Leader
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22502	ORIG-1	GALDERMA RESEARCH AND DEVELOPMENT INC	DIFFERIN LOTION

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/s/

KELISHA C TURNER
12/07/2009

DAVID L KETTL
12/08/2009

Turner, Kelisha C
From: Greeley, George
Sent: Tuesday, November 10, 2009 8:54 AM
To: Turner, Kelisha C
Cc: Stowe, Ginneh D.
Subject: NDA 22-502 Differin

Importance: High

Hi Kelisha,

The Differin (adapalene) partial waiver/appropriately labeled application was reviewed by the PeRC PREA Subcommittee on November 4, 2009. The Division recommended a partial waiver in 0-11 years because the disease/condition does not exist in children and that the product is appropriately labeled from 12-16 years of age.

The PeRC agreed with the Division to grant a partial waiver and that the product is appropriately labeled.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: October 30, 2009

To: Kelisha Turner, DDDP
Amy Woitach, MD, DDDP
David Kettl, MD, DDDP

From: Andrew Haffer, PharmD, DDMAC

Re: NDA# 22-502
Differin (adapalene) Lotion 0.1%

As requested in your consult dated October 2, 2009, DDMAC has reviewed the draft PI for Differin (adapalene) Lotion 0.1%. DDMAC's comments are based on the proposed substantially complete, mark-up, version of the label located in the DDDP eRoom.

DDMAC's comments are provided directly in the attached document.

If you have any questions about DDMAC's comments please call.

11 Pages of Draft Labeling has been withheld in full immediately following this page as B4 (CCI/TS)

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/s/

ANDREW S HAFFER
10/30/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-502

INFORMATION REQUEST LETTER

Galderma Research and Development, Inc.
Attention: Allen E. Fields, DrPH
Director of Regulatory Submissions
5 Cedar Brook Drive, Suite 1
Cranbury, NJ 08512

Dear Dr. Fields:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Differin (adapalene) Lotion, 0.1%.

We are reviewing the CMC section of your submission and have the following comment and information request. We request a prompt written response in order to continue our evaluation of your NDA.

> Amend the presentation of your tradename, established name, dosage form and strength in all container/closure systems as follows and provide colored mock ups of the container/closure systems.
>
> Differin®
> (adapalene) Lotion
> 0.1%

If you have any questions, call Kelisha Turner, Regulatory Project Manager, at (301) 796-0766.

Sincerely,

{See appended electronic signature page}

Margo Owens
Project Management Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22502	ORIG-1	GALDERMA RESEARCH AND DEVELOPMENT INC	DIFFERIN LOTION

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/s/

MARGO L OWENS
10/05/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-502

INFORMATION REQUEST LETTER

Galderma Research and Development, Inc.
Attention: Allen E. Fields, DrPH
Director of Regulatory Submissions
5 Cedar Brook Drive, Suite 1
Cranbury, NJ 08512

Dear Dr. Fields:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Differin (adapalene) Lotion, 0.1%.

We also refer to your submissions dated June 14, June 29, July 2, and July 3, 2009.

We are reviewing your submission and have the following comment and information request. We request a prompt written response in order to continue our evaluation of your NDA.

Clarify the description and function of the medium chain triglycerides in the formulation. If claims for emollient are being made, you will need to adequately support such a claim with clinical data. Alternatively, a different description/function based on physicochemical properties of this excipient should be amended in the application with justification.

If you have any questions, call Kelisha Turner, Regulatory Project Manager, at (301) 796-0766.

Sincerely,

{See appended electronic signature page}

Margo Owens
Project Management Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margo Owens
7/10/2009 04:56:27 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-502

INFORMATION REQUEST LETTER

Galderma Research and Development, Inc.
Attention: Allen E. Fields, DrPH
Director of Regulatory Submissions
5 Cedar Brook Drive, Suite 1
Cranbury, NJ 08512

Dear Dr. Fields:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Differin (adapalene) Lotion, 0.1%.

We are reviewing your submission and have the following comment and information request. We request written response by close of business, July 10, 2009 in order to continue our evaluation of your NDA.

The following literature reference located in **Clinical Overview: Dose Regimen and Dose Selection** section 2.5.3.1 is written in French:

Alirezai M, Meynadier J, Jablonska S, Czernielewski J, Verschoore M. Comparative study of the efficacy and tolerability of 0.1 and 0.03 percent adapalene gel and 0.025 percent tretinoin gel in the treatment of acne. Ann Dermatol Venereol 123(3):165-70, 1996.

Provide a translated copy in English.

If you have any questions, call Kelisha Turner, Regulatory Project Manager, at (301) 796-0766.

Sincerely,

{See appended electronic signature page}

Margo Owens
Project Management Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margo Owens
7/2/2009 07:47:52 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-502

Galderma Research and Development
Attention: Allen E. Fields, DrPH
Director of Regulatory Submissions
5 Cedar Brook Drive, Suite 1
Cranbury, New Jersey 08512

Dear Dr. Fields:

Please refer to your new drug application (NDA) dated February 27, 2009, received March 2, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Differin (adapalene) Lotion, 0.1% for the treatment of acne vulgaris.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is January 2, 2010.

During our filing review of your application, we identified the following potential review issues and requests for information:

CMC:

1. Provide representative samples (3 units for each size) in the to-be-marketed container/closure system to the NDA with rheograms (viscosity versus shear rate and shear stress versus shear rate) to assist the assessment of dosage form.

2. Provide an updated letter of authorization for Polyolprepolymer-02 DMF with the proper DMF#.

3. Provide the Establishment Registration number for [redacted] (b) (4)

Clinical:

4. Submit your waiver request with accompanying rationale for phototoxicity and photoallergenicity studies along with the UV absorption spectrum of your final to-be

marketed drug formulation and other approved topical adapalene products for comparison.

Clinical Pharmacology:

5. We could not locate the bioanalytical method validation report RDS.03.VRE.34016. Please identify the sections where it is located, or submit the report if omitted.

6. Incorrect references and/or hyperlinks were found. For example, the study in section 2.7.2 on page 8, RDS.03.SRE.4789 is incorrectly referenced. Please confirm the entire document for the accuracy of references and appropriate hyperlinks.

7. The application states that "lower systemic exposure is seen with Adapalene Lotion, 0.1% than that observed with Adapalene 0.3% Gel (...NDA 021753)...". Please provide appropriate information support this comparison, including a complete report on PK studies of Adapalene 0.3% Gel.

8. The application states that "systemic exposure to Adapalene from Adapalene Lotion, 0.1% and Epiduo Gel with the same adapalene 0.1% concentration are not different from one another". Please submit the complete PK study report on Epiduo Gel with individual data and identify the appropriate section

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Upon review of the draft labeling submitted in Physician Labeling Rule (PLR) format, we have identified the following formatting issues in the proposed label:

Highlights Section:

1. The revision date should be the month/year that the application is approved.

Full Prescribing Information (FPI) Section:

2. According to 21 CFR 201.1, manufacturing information should be located at the end of the label, after the Patient Counseling Information section. The manufacturing information should be included for this product according to regulations.

Address the identified labeling deficiencies/issues and re-submit labeling by June 15, 2009.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We note that you have submitted pediatric studies with this application for pediatric patients 12 years old to 17 years old. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this age group.

If you have any questions, call Catherine Carr, Regulatory Project Manager, at (301) 796-2311.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Susan Walker
5/15/2009 02:32:33 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-502

NDA ACKNOWLEDGMENT

Galderma Research and Development, Inc.
Attention: Allen E. Fields, DrPH
Director of Regulatory Submissions
5 Cedar Brook Drive
Suite 1
Cranbury, NJ 08512

Dear Mr. Fields:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Differin (Adapalene) Lotion, 0.1%

Date of Application: February 27, 2009

Date of Receipt: March 2, 2009

Our Reference Number: NDA 22-502

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 1, 2009 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatology and Dental Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call me, at (301) 796-2311.

Sincerely,

{See appended electronic signature page}

Catherine Carr, MSc.
Regulatory Health project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Catherine Carr
3/18/2009 11:28:36 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 76,057

Dow Pharmaceutical Sciences, Inc
Attention: Barry M. Calvarese, MS
Vice President, Regulatory and Clinical Affairs
1330 Redwood Way
Petaluma, CA 94954

Dear Calvarese:

Please refer to your New Drug Application (NDA) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Adapalene Lotion, 0.1% for the treatment of acne vulgaris.

We also refer to the meeting between representatives of your firm and the FDA on August 7, 2007. The purpose of the meeting was to seek FDA concurrence that the development plan, as propose, will support opening a 505(b)(1) New Drug Application(NDA) for an acne indication.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Vickey Lutwak, Regulatory Project Manager, at (301) 769-2445.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	**August 7, 2007**
TIME:	**3:00 PM EST**
LOCATION:	**WO 22 Room 1315**
APPLICATION:	**IND 76,057**
DRUG NAME:	**Adapalene Lotion, 0.1%**
TYPE OF MEETING:	**505(b)(1)**

MEETING CHAIR: Susan J. Walker, M.D./Division Director, DDDP, HFD-540

MEETING RECORDER: Vickey Lutwak, Regulatory Project Manager, DDDP, HFD-540

FDA ATTENDEES:

Susan Walker, M.D./Division Director, DDDP, HFD-540
Markham Luke, M.D., Ph.D./Team Leader, Clinical, Dermatology, DDDP, HFD-540
Mohamed Al-Osh, Ph.D./Team Leader, Biostatistics, DBIII, HFD-725
Clara Kim, Ph.D./Reviewer, Division of Biometrics III, HFD-725
Shulin Ding, Ph.D./Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment
Bogdan Kurtyka, Ph.D./Reviewer, Office of New Drug Quality Assessment
Paul Brown, Ph.D./Supervisory Pharmacologist, DDDP, HFD-540
Tien Mien (Albert) Chen, Ph.D./Pharmacokinetics Reviewer, DCPIII, HFD-880
Vickey Lutwak/Regulatory Project Manager, DDDP, HFD-540

EXTERNAL CONSTITUENT ATTENDEES:

Dow Pharmaceutical Sciences:
Barry M. Calvarese, MS/ VP, Regulatory and Clinical Affairs

Galderma:
Paul Clark/US Regulatory Affairs Director
Michael Graeber/MD/Head of US Clinical Development
Vasant Manna, M.D./Clinical Development - Project Leader
Isabelle Preuilh, Pharm D./Manager, Pharmaceutical Development
Florence Bistuer, Pharm D./Project Manager
Michael Graeber/Development

MEETING OBJECTIVES:

Purpose of the Meeting: Purpose: To seek FDA concurrence that the development plan, as propose, will support opening a 505(b)(1) New Drug Application(NDA) for an acne indication.

Chemistry, Manufacturing and Controls (CMC):

CMC Question:
The Sponsor has optimized the Lotion's manufacturing process during scale-up operations. Does the Agency concur that the formulation now meets all the characteristics of CDER's thinking of a lotion, including pourability and flowability (samples provided) with rheological properties discussed in section 3.3.2.1.2?

FDA Response:

Yes, we agree that the two scale-up samples (Lot # 031-07 and 032-07) which were submitted to us on June 5, 2007 meet CDER's thinking of a lotion.

Additional Comments:

1. The formulation contains (b) (4) non-compendial excipients:
   - Polyoxyl 6 & Polyoxyl 32 Palmitostearate,
   - PPG-12/SMDI Copolymer, and
   - (b) (4)

   For each non-compendial excipient please provide manufacturer's name and address, manufacturer's Certificate of Analysis, and your incoming specification.

2. We cannot verify your claim that there are no novel excipients used in the formulation of Adapalene Lotion, 0.1% (section 3.3.4.5 on page 33 of the End-of-Phase 2 Briefing Book). Our review indicates that the substance (polyoxyl 6 & polyoxyl 32 palmitostearate) listed in FDA's Inactive Ingredients Database may be (b) (4) used in your formulation. Please provide information to support that (b) (4) has been used in FDA approved drug products.

3. PPG-12/SMDI can contain up to (b) (4). Please provide the information on the origin of (b) (4) in the excipient and its chemical form (b) (4)

4. Please include product homogeneity as an in-process control.

5. Please address the issues of container extractables and weight loss in the registration stability program.

6. We would like to reiterate our comments which were conveyed to you in the pre-IND meeting on February 26, 2007 regarding polymorphs, product homogeneity within container, and manufacturing site of commercial batches.

Pharmacology/Toxicology:

Question:
Does the Agency agree that the information provided in section 4.0 and the proposed minipig studies are sufficient to support the NDA filing for Adapalene Lotion, 0.1%?

Agency Response:
Yes

Clinical Pharmacology/Biopharmaceutics:

Your protocol for a pharmacokinetic study to determine the systemic exposure in patients following topical application of adapalene lotion 0.1% once daily for 30 days (Protocol # RD.06.SPR.18108; submitted on 04/06/07) was reviewed by the Agency and was found acceptable. [Post-meeting note: Comments for the protocol are added.]

- The number of evaluable subjects should be at least 12. Seven subjects are too low to make any meaningful conclusion.
- Record should be maintained for each patient in terms of % BSA involved in the application and the amount of medication applied, at least during the first and last treatment.

Clinical & Biostatistics:

Sponsor's Question:

It is the sponsor's opinion that a single pivotal efficacy study should be sufficient to support the new adapalene lotion, 0.1%, NDA filing.

Does the Agency agree with the sponsor based on the rationale presented in Section 5.1.5.7 at the End of Phase 2 (EOP2) meeting briefing package?

Agency Response:

Yes, a single successful adequate, blinded, randomized study demonstrating the superiority of adapalene lotion 0.1% to vehicle and providing a comparison of the adapalene lotion to a currently marketed adapalene formulation may be sufficient to provide evidence of efficacy to support approval of adapalene lotion 0.1%. Additional studies to support dermal safety and PK exposure are needed as discussed. Study design and statistical analysis plans for such a protocol have not yet been agreed upon.

Sponsor's Question:

The phase 3 pivotal study protocol is provided in Appendix 1 of the briefing package. The sponsor intends to implement the protocol to generate the required evidence to support the claim of adapalene lotion 0.1% being safe and effective in the indication acne vulgaris.

The applicant proposes a phase 3 program with the primary efficacy analyses intended to show adapalene lotion 0.1% significantly superior to corresponding vehicle in Success Rate (defined as the percentage of subjects who achieve at least a 2 point reduction at week 12 in the

Investigator's Global Severity Score from baseline) and absolute changes in inflammatory, non-inflammatory and total lesion counts at week 12 (LOCF) in the ITT population. The trial will be claimed positive for the indication acne vulgaris if (1) Success Rate and (2) at least two of the three lesion counts absolute changes are significant, each at the 0.05 level for the week 12 (LOCF) data. The secondary efficacy analyses will include the percent changes in inflammatory, non-inflammatory and total lesions counts at week 12 (LOCF) in the ITT population. Additional sensitivity analyses will be performed.

Does the Agency agree that the design and endpoints of the pivotal study fully support sponsor's intention?

Agency Response:

The sponsor should provide evidence demonstrating that the product is superior to vehicle in global evaluation and in counts of acne lesions. Various scenarios were discussed at the meeting and the sponsor will present their study plan in a future protocol with sufficient time for review by the Agency prior to conduct.

Specifically, the Agency agrees that absolute change in lesion counts should be used together with success for the Investigator's Global Severity Score as co-primary evaluations. There was discussion of addressing the multiplicity issue to control the type I error rate, if they define success on the co-primary endpoint, lesion count, as winning on 2 out of 3 lesions (inflammatory, non-inflammatory, and total lesions). The sponsor might propose any scientifically correct methodology to control the Type I error, including a nested approach; pre-specifying success criteria based on certain lesion types; or carrying out multiplicity adjustment after taking the correlation between the lesion types into account.

The Agency agreed that the Investigator's Global Severity Score described may be acceptable, but that specifics, such as any instructional materials to be used for investigators should be provided to the Agency together with the proposed protocol.

General Question:

Would the Agency concur with the sponsor that there would be no need for a subsequent Special Protocol Assessment if the comments from the Agency on the draft phase 3 protocol and statistical plan are fully incorporated?

Agency Response:

The decision to submit the revised final phase 3 protocol for a special protocol assessment rests with the sponsor. We support a mutual understanding of endpoints and statistical plan prior to the initiation of clinical trials conducted to demonstrate safety and efficacy. During the meeting it was agreed that the sponsor will submit a more finalized protocol and statistical plan for review and the Agency will review and provide comments.

The Agency cannot grant a waiver for long term studies at this time for this new formulation. Data from the pharmacokinetic exposure and shorter term efficacy studies will need to be reviewed so that a determination of the need for long term studies can be made.

Project Management:

1. Comments shared today with the sponsor are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of the information submitted to the IND might identify additional comments or information requests.

2. The sponsor is reminded of the Pediatric Research Equity Act of 2003 which requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain and assessment of the safety and effectiveness of the pediatric patients unless this requirement is waived or deferred. Please request the appropriate action.

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

4. You are reminded that all new NDAs/BLAs and efficacy supplements submitted on or after June 30, 2006 must include content and format of prescribing information based on the new Physicians Labeling Rule at the time of submission (see attached website http://www.fda.gov/cder/regulatory/physLabel/default.htm for additional details).

5. The sponsor is reminded to please submit appropriate patent certification at the time of NDA submission.

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/s/

Susan Walker
9/7/2007 04:14:55 PM