

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207917Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 207917

SUPPL #

HFD # 540

Trade Name Epiduo Forte®

Generic Name adapalene and benzoyl peroxide gel,0.3%/2.5%

Applicant Name Galderma Research and Development LLC

Approval Date, If Known July 17, 2015 (PDUFA Date)

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)(2)

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.

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 NO

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

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?

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).

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# 022320	Epiduo (adapalene and benzoyl peroxide) gel, 0.1%/2.5%
NDA# 021753	Differin (adapalene) gel, 0.3%
NDA# 020748	adapalene cream, 0.1%
NDA# 050819	benzoyl peroxide/clindamycin phosphate gel, 2.5%/1.2%
NDA# 050756	benzoyl peroxide/clindamycin phosphate gel, 5%/EQ 1%
NDA# 050741	benzoyl peroxide/clindamycin phosphate gel, 5%/EQ 1%
NDA# 050557	benzoyl peroxide/erythromycin gel, 5%/3%
NDA# 050769	benzoyl peroxide/erythromycin gel, 5%/3%
NDA# 065112	benzoyl peroxide/erythromycin gel, 5%/3%

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:

(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:

18242: *Evaluation of the Cutaneous Cumulative Irritancy Potential of CD0271 0.3%/CD1579 2.5% Gel and Corresponding Vehicle Gel Following Repeated Applications to the Skin of Healthy Subjects*

18229: *A Pharmacokinetic Study to Determine the Systemic Exposure to CD0271 During Dermal Application of Either a Fixed-Dose Combination of CD0271 0.3%/ CD1579 2.5% Gel or Differin 0.3% Gel for 4 weeks in Adolescent and Adult Subjects with Acne Vulgaris*

18240: *A Multi-center, Randomized, Double-blind, Parallel-group Vehicle and Active Controlled Study to Compare the Efficacy and Safety of CD0271 0.3% / CD1579 2.5% Topical Gel Versus Topical Gel Vehicle in Subjects with Acne Vulgaris*

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

Investigation #3 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:

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

Investigation #3 YES NO

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"):

18242: *Evaluation of the Cutaneous Cumulative Irritancy Potential of CD0271 0.3%/CD1579 2.5% Gel and Corresponding Vehicle Gel Following Repeated Applications to the Skin of Healthy Subjects*

18229: *A Pharmacokinetic Study to Determine the Systemic Exposure to CD0271 During Dermal Application of Either a Fixed-Dose Combination of CD0271 0.3%/ CD1579 2.5% Gel or Differin 0.3% Gel for 4 weeks in Adolescent and Adult Subjects with Acne Vulgaris*

18240: *A Multi-center, Randomized, Double-blind, Parallel-group Vehicle and Active Controlled Study to Compare the Efficacy and Safety of CD0271 0.3% / CD1579 2.5% Topical Gel Versus Topical Gel Vehicle in Subjects with Acne Vulgaris*

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 # 067801 YES ! NO
! Explain:

Investigation #2 !
IND # 067801 YES ! NO

! Explain:

Investigation #3

!

IND # 067801

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?

(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: Belainesh Robnett

Title: Regulatory Health Project Manager

Date: June 17, 2015

Name of Office/Division Director signing form: Jill A. Lindstrom, MD, FAAD

Title: Acting Deputy Director, Division of Dermatology and Dental Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

BELAINESH ROBNETT
06/26/2015

JILL A LINDSTROM
06/26/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹		
NDA # 207917 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Epiduo Forte Established/Proper Name: (adapalene and benzoyl peroxide) Dosage Form: gel, 0.3%/2.5%		Applicant: Galderma Research and Development LLC Agent for Applicant (if applicable): N/A
RPM: Belainesh Robnett		Division: Dermatology and Dental Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		For ALL 505(b)(2) applications, two months prior to EVERY action: <ul style="list-style-type: none"> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <ul style="list-style-type: none"> <input type="checkbox"/> No changes <input checked="" type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: 7/15/15 <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>July 17, 2015</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Acne Agents (4029041)
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) 7/15/15
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included 6/16/15
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included 9/17/14
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included 6/16/15
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included 9/17/14
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included 6/16/15
❖ Proprietary Name	Granted letter 2/4/15 Acceptable Review 2/3/15
• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i>	
• Review(s) <i>(indicate date(s))</i>	
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input type="checkbox"/> None 5/26/15 DMEPA: <input type="checkbox"/> None 3/26/15 DMPP/PLT (DRISK): <input type="checkbox"/> None 5/15/15 OPDP: <input type="checkbox"/> None 5/19/15 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	7/7/15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 5/28/15
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo <i>(indicate date)</i> ○ If yes, OC clearance for approval <i>(indicate date of clearance communication)</i> 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics <i>(approvals only)</i> <ul style="list-style-type: none"> • Date reviewed by PeRC <u>6/10/15</u> If PeRC review not necessary, explain: _____ 	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) <i>(do not include previous action letters, as these are located elsewhere in package)</i> 	12/26/13 Advice 10/9/14 Acknowledge NDA 10/17/14 Information Request 11/21/14 No Filing Review Issues Identified 2/4/15 Information Request 2/4/15 Proprietary Name Granted 3/31/15 Information Request 5/27/15; 6/10/15 Labeling Discussion Comments 6/26/15 Advice
<ul style="list-style-type: none"> ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) 	N/A
<ul style="list-style-type: none"> ❖ Minutes of Meetings <ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i> • Pre-NDA/BLA meeting <i>(indicate date of mtg)</i> • EOP2 meeting <i>(indicate date of mtg)</i> • Mid-cycle Communication <i>(indicate date of mtg)</i> • Late-cycle Meeting <i>(indicate date of mtg)</i> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) <i>(indicate dates of mtgs)</i> 	<input checked="" type="checkbox"/> N/A or no mtg <input type="checkbox"/> No mtg 12/19/12 (Pre-Phase 3) 6/26/14 (Pre-NDA) <input type="checkbox"/> No mtg 1/11/06 <input checked="" type="checkbox"/> N/A <input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
<ul style="list-style-type: none"> ❖ Office Director Decisional Memo <i>(indicate date for each review)</i> 	<input type="checkbox"/> None
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None 7/15/15
PMR/PMC Development Templates <i>(indicate total number)</i>	<input checked="" type="checkbox"/> None
Clinical	
<ul style="list-style-type: none"> ❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) <i>(indicate date for each review)</i> • Clinical review(s) <i>(indicate date for each review)</i> • Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i> 	<input checked="" type="checkbox"/> No separate review 11/5/14; 6/2/15 <input type="checkbox"/> None N/A

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (indicate date of review/memo)	Under clinical review 6/2/15
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) REMS Memo(s) and letter(s) (indicate date(s)) Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 11/5/14; 5/14/15
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 11/5/14; 5/5/15
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 11/3/14; 5/13/15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review (<i>indicate date for each review</i>)	<input type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/1/14; 11/3/14; 5/11/15; 6/29/15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable 6/29/15 Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input checked="" type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the "preferred" name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

**PeRC Meeting Minutes
June 10, 2015**

PeRC Members Attending:

Wiley Chambers
George Greeley
Freeda Crooner
Kristiana Brugger
Tom Smith
Daiva Shetty
Peter Starke
Lily Mulugeta
Robert "Skip" Nelson
Kevin Krudys
Shrikant Pagay
Rosemary Addy
Greg Reaman
Linda Lewis

Agenda

Non Responsive

10:50	NDA	207917	Epiduo Forte (adapalene/benzoyl peroxide) Gel (Partial Waiver/Assessment) w/Agreed iPSP	Acne vulgaris
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Non Responsive

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immediately following this page.

Non Responsive

Epiduo forte (adapalene/benzoyl peroxide) Partial Waiver/Assessment

- Proposed Indication: Acne vulgaris
- The PeRC noted that the plan to support approval of this product is the same as the one agreed upon in the Agreed iPSP for this product.
- PeRC agreed with the plan as established in the Agreed iPSP.

- *PeRC Recommendations:*
 - The PeRC agreed to the partial waiver in patients less than 12 years of age and to the assessment presented in patients 12 years of age and above.

Non Responsive



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/s/

GETTIE AUDAIN
06/23/2015

From: Robnett, Belainesh
To: "CLARK Elaine"
Cc: Gould, Barbara; Williams, Dawn; WINTER Stacie
Subject: RE: Agency-Proposed Labeling: NDA 207917 Epiduo Forte (adapalene and benzoyl peroxide) Gel, 0.3%/2.5%
Date: Tuesday, June 09, 2015 3:58:00 PM
Attachments: [NDA 207917 draft Agency-proposed PI label 6-9-15.docx](#)
[NDA 207917 Epiduo Forte draft Agency-proposed PPI labeling 6-9-15.docx](#)

Good Morning Ms. Clark,

Attached please find the draft prescribing information (PI) and patient information (PPI) labeling for Epiduo Forte with Agency-proposed changes. Also, address the following comment for the draft carton (15 g, 30 g, 45 g, 60 g, 70 g) labeling:

- Relocate the route of administration statement "Not for ophthalmic, oral or intravaginal use" to appear **on a single line** under the statement "For Topical Use Only".

Please confirm receipt and provide your feedback by close of business Friday, June 12, 2015.

Thank you,

Belai

From: CLARK Elaine [<mailto:Elaine.CLARK@galderma.com>]
Sent: Tuesday, June 02, 2015 6:44 PM
To: Robnett, Belainesh
Cc: Gould, Barbara; Williams, Dawn; WINTER Stacie
Subject: RE: Agency-Proposed Labeling: NDA 207917 Epiduo Forte (adapalene and benzoyl peroxide) Gel, 0.3%/2.5%

Hello Belai,

Attached please find Galderma counterproposal to FDA-proposed PI and PPI, inclusive of comments explaining Galderma position and requesting FDA clarification on a few of the calculations related to nonclinical data. I have attached redline MS word files of the Galderma counterproposals for the PI and PPI and these will be formally submitted to the NDA shortly as requested by COB today, June 2, 2015. Note that we have accepted the majority of FDA's proposed revisions except for those specifically discussed during our teleconference of May 19, 2015. We have provided our rationale for not combining the PI for Epiduo Forte with that of Epiduo within the enclosed cover letter.

In addition, we have made nearly all of the FDA-requested changes to the container and carton labeling, except that we did not reduce the size of the curved graphic as we were able to implement FDA comments on proprietary and established name presentations without doing so; and we did not change the orientation of the text to run in one direction on the (b) (4) packaging as doing so would cause such text to be obscured/illegible. We have depicted the tube outline on the card to illustrate this point. Finally, the lot and expiry for the sample tubes is crimped into the end of the tube, not placed directly on the label, which is why this does not appear on the artwork. Due to email file size constraints, I am unable to send you courtesy copies of the artwork mockups, but

these presentations will be shown in the formal NDA amendment to be submitted shortly.

We appreciate FDA consideration of our counterproposal and look forward to additional discussions. I am presently in our Princeton NJ office and available by mobile with full email access all week; I will be traveling next week for business [REDACTED] (b) (4)

[REDACTED] I will have access to email but cannot read encrypted email on my mobile device. Stacie Winter, Regulatory Submission Manager (copied on this email) is an alternate point of contact for email related to this submission and you may include her in copy if you anticipate submission of further comments next week. Please do not hesitate to contact me if you have any questions or comments regarding this submission.

Best regards,
Elaine

Elaine M. Clark

Sr. Director, Global Prescription Regulatory Affairs & US Submissions
Galderma Laboratories, L.P.
14501 North Freeway
Fort Worth, TX 76177
phone (817) 961-5492
fax (817) 720-1040
mobile [REDACTED] (b) (6)
e-mail Elaine.clark@galderma.com

From: Robnett, Belainesh [<mailto:Belainesh.Robnett@fda.hhs.gov>]
Sent: Tuesday, May 26, 2015 3:08 PM
To: CLARK Elaine
Cc: Gould, Barbara; Williams, Dawn
Subject: Agency-Proposed Labeling: NDA 207917 Epiduo Forte (adapalene and benzoyl peroxide) Gel, 0.3%/2.5%

Good Afternoon Ms. Clark,

Attached please find the Agency-proposed prescribing information (PI), patient information (PPI) and a document containing comments on the carton and container labeling, for Epiduo Forte. In addition, we request that you consider one combined PI for both the approved Epiduo and the pending Epiduo Forte, for the reasons stated during the May 19, 2015, teleconference. Although these combination products have different strengths of one of the active moieties (adapalene), Epiduo and Epiduo Forte would have the same indication and the same prescriber audience. We are sending you an example of a combined PI with different proprietary names (Zomig/Zomig-ZMT) and slightly different population. You may refer to this PI for an example in your revision.

Please propose a combined PI or response with your rationale for not combining the PI. Provide your feedback by COB June 2, 2015.

Thank you,

Belai

Belainesh Robnett, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food and Drug Administration

E-mail: belainesh.robnett@fda.hhs.gov

Phone: 240-402-4236

Fax: 301.796.9895

10 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page.

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/s/

BELAINESH ROBNETT
06/10/2015

From: Robnett, Belainesh
To: ["CLARK Elaine"](#)
Cc: [Gould, Barbara](#); [Williams, Dawn](#)
Subject: Agency-Proposed Labeling: NDA 207917 Epiduo Forte (adapalene and benzoyl peroxide) Gel, 0.3%/2.5%
Date: Tuesday, May 26, 2015 4:08:00 PM
Attachments: [NDA 207917 Epiduo Forte draft Agency-proposed PI labeling 5-26.docx](#)
[NDA 207917 Epiduo Forte draft Agency-proposed PPI labeling 5-26.docx](#)
[NDA 207917 Epiduo Forte Agency-proposed comments for draft Carton and Container labeling 5-21.docx](#)
[Zomig zolmitriptan multiple combinations revised 2012.pdf](#)

Good Afternoon Ms. Clark,

Attached please find the Agency-proposed prescribing information (PI), patient information (PPI) and a document containing comments on the carton and container labeling, for Epiduo Forte. In addition, we request that you consider one combined PI for both the approved Epiduo and the pending Epiduo Forte, for the reasons stated during the May 19, 2015, teleconference. Although these combination products have different strengths of one of the active moieties (adapalene), Epiduo and Epiduo Forte would have the same indication and the same prescriber audience. We are sending you an example of a combined PI with different proprietary names (Zomig/Zomig-ZMT) and slightly different population. You may refer to this PI for an example in your revision.

Please propose a combined PI or response with your rationale for not combining the PI. Provide your feedback by COB June 2, 2015.

Thank you,

Belai

Belainesh Robnett, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food and Drug Administration
E-mail: belainesh.robnett@fda.hhs.gov
Phone: 240-402-4236
Fax: 301.796.9895

11 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page.

A. General Comments (all container labels, (b) (4) and carton labeling; 2 g, 5 g, 15 g, 30 g, 45 g, 60 g, 70 g)

1. Consider revising the presentation of the proprietary name from all-caps (i.e., EPIDUO FORTE) to title case (i.e., Epiduo Forte) to improve readability of the name. Refer to the guidance for industry, *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*.
2. Revise the presentation of the established name to ensure that it is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2). As currently presented, the typography used for the proprietary name (all caps) versus the typography used for the established name (lower case and condensed font), we find they are not commensurate in prominence.
3. To implement comment 2 above, consider relocating the dosage form and strength statement “Gel, 0.3%/2.5%” to appear below the established name to help increase the readability of information.
4. Consider reducing the size or deleting the curved graphic presented to the right of the proprietary name, established name, dosage form, and strength to allow for implementation of comments 2 and 3 above.

B. Sample container labels (2 g and 5 g tubes)

Ensure the lot number and expiration date are present on the container labels. From the images provided it is not evident where this information will be presented.

(b) (4)

D. Carton labeling (15 g, 30 g, 45 g, 60 g, 70 g)

1. Relocate the route of administration statement “Not for ophthalmic, oral or intravaginal use” to appear on a single line under the statement “For Topical Use Only”.
2. Increase the prominence of the net quantity statement to facilitate differentiation between the multiple package sizes.

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/s/

BELAINESH ROBNETT
05/27/2015

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND

Please check all that apply: Full Waiver Partial Waiver Pediatric Assessment Deferral/Pediatric Plan

BLA/NDA#: NDA 207917

PRODUCT PROPRIETARY NAME: Epiduo Forte **ESTABLISHED/GENERIC NAME:** adapalene and benzoyl peroxide Gel, 0.3%/2.5%

APPLICANT/SPONSOR: Galderma Laboratories LP

PREVIOUSLY APPROVED INDICATION/S:

- (1) none
- (2) _____
- (3) _____
- (4) _____

PROPOSED INDICATION/S:

- (1) acne vulgaris (b) (4) _____
- (2) _____
- (3) _____
- (4) _____

BLA/NDA STAMP DATE: Sept 17, 2014

PDUFA GOAL DATE: July 17, 2015

SUPPLEMENT TYPE: not a supplement

SUPPLEMENT NUMBER: not a supplement

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

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

Did the sponsor submit an Agreed iPSP? Yes ***No***

Did FDA confirm its agreement to the sponsor's Agreed iPSP? Yes ***No***

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes ***No***

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes ***No***

If Yes, PMR # _____ NDA # _____

Does the division agree that this is a complete response to the PMR? Yes ***No***

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

- Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.*
- Pediatric Record*

1. Pediatric age group(s) to be waived.
Under the age of twelve (12) years.

2. Reason(s) for waiving pediatric assessment requirements (*Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.*)

- Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.
- The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information **MUST** be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.
- The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
- Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. (*This reason is for Partial Waivers Only*)

3. Provide justification for Waiver:

There are multiple other products available for ages 9-11 years (the population to be waived). Acne in the population aged 9-11 is more likely to be mild and comedonal and the currently approved dosage form Epiduo is sufficient (in addition to other approved products) for this age group. This had already been agreed upon with PERC and there is an agreed PSP.

4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:

Safety and effectiveness of EPIDUO FORTE gel in pediatric patients under the age of 12 have not been established.

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/s/

BELAINESH ROBNETT

04/14/2015



NDA 207917

INFORMATION REQUEST

Galderma Research and Development LLC
Attention: Elaine Clark
Senior Director, US Regulatory Submissions
14501 North Freeway
Fort Worth, TX 76177

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for adapalene and benzoyl peroxide gel, 0.3%/2.5%.

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

1. Letters of Authorization

- Your letter of authorization to reference (b) (4) DMF (b) (4) with respect to their (b) (4) cannot be located. Please submit a copy.

2. Benzoyl Peroxide Drug Substance

- Neither of the tests for identity are considered specific since they provide no structural information (Sections 3.2.S.4.1 Specification). Add a specific identity test to the drug substance specification (ICH Q6A 3.2.1.b).

3. Regional Information

- Create separate files for the batch record documents and methods validation documents.

Please respond by April 10, 2015.

If you have any questions, please contact Olga Simakova, Regulatory Business Process Manager, at (240) 402-3814.

Sincerely,

Moojhong Rhee -S

Digitally signed by Moojhong Rhee -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Moojhong Rhee -S,
0.9.2342.19200300.100.1.1=1300041261
Date: 2015.03.31 13:33:27 -04'00'

Moo-Jhong Rhee, PhD
Branch Chief, Branch V
Division of New Drug Products II
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207917

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Galderma Research and Development, LLC
Attention: Elaine Clark
Senior Director, US Regulatory Submissions
14501 North Freeway
Fort Worth, TX 76177

Dear Ms. Clark:

Please refer to your New Drug Application (NDA), dated and received September 17, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Adapalene and Benzoyl Peroxide Gel, 0.3%/2.5%.

We also refer to your correspondence, dated and received November 25, 2014, requesting review of your proposed proprietary name, Epiduo Forte.

We have completed our review of the proposed proprietary name, Epiduo Forte and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your November 25, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact Belainesh Robnett, Regulatory Project Manager in the Office of New Drugs, at (240) 402-4236.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk
Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
02/04/2015

For the record, please note that the email correspondence below was sent to the sponsor on 10/31/14 and not on 11/7/14 as indicated in their 11/25/14 PNR correspondence.

From: Anderson, Janet
Sent: Friday, October 31, 2014 3:41 PM
To: Elaine.clark@galderma.com
Subject: NDA 207917 Request for Proprietary Name Review

Dear Ms. Clark,

We are in receipt of your new submission, dated September 18, 2014, for Adapalene 0.3%/Benzoyl Peroxide 2.5% gel. We note that you have listed Epiduo Forte as the proposed proprietary name on the labels and labeling for this submission but a request for review of this proposed proprietary name has not been submitted.

The proposed proprietary name request for review has a separate PDUFA goal date of 90 days, which is independent from the application (NDA) PDUFA goal date. You can submit your request for a proposed proprietary name for review at any time during the NDA review cycle but please keep in mind that if your primary proposed proprietary name is denied, additional names submitted for review will each have a 90-day review cycle. We, therefore, encourage you to submit your proposed proprietary name for review as early in the review cycle as possible.

In your request for review of a proposed proprietary name, please provide a link to the labels/labeling or reference in the request where the labels/labeling can be found in the submission.

Please refer to the following link for FDA Guidance for Industry: Contents of a Complete Submission for the Evaluation of Proprietary Names.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>

Sincerely,

Janet

*Janet L. Anderson, Pharm.D.
Safety Regulatory Project Manager - OSE
FDA CDER OSE, WO Bldg. 22, Rm 4484
10903 New Hampshire Ave
Silver Spring, Maryland 20993-0002
301-796-0675*

APPEARS THIS WAY ON ORIGINAL.

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/s/

JANET L ANDERSON
02/04/2015



NDA 207917

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Galderma Research and Development, LLC
Attention: Elaine Clark
Senior Director, US Regulatory Submissions
14501 North Freeway
Fort Worth, TX 76177

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) dated September 17, 2014, received September 17, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for adapalene and benzoyl peroxide gel, 0.3%/2.5%.

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**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 19, 2015.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. Provide representative samples (3 units for each fill size) to the NDA to assist the verification of dosage form.
2. Provide stability update for all registration stability batches.

3. It is noted that [REDACTED] (b) (4) is assigned as the function for glycerin and propylene glycol. [REDACTED] (b) (4) Assign a function for glycerin and propylene glycol according to their physicochemical properties.
4. Submit the raw plasma adapalene concentrations from maximal use PK trial (RD.06.SRE.18240) in SAS transport format.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for 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.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We reference the partial waiver granted on December 26, 2013, for the pediatric study requirement for this application for pediatric patients 0 years to 11 years.

If you have any questions, call Belainesh Robnett, Regulatory Project Manager, at (240) 402-4236.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

KENDALL A MARCUS
11/21/2014



NDA 207917

INFORMATION REQUEST

Galderma Research and Development LLC
Attention: Elaine Clark
Senior Director, US Regulatory Submissions
14501 North Freeway
Fort Worth, TX 76177

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for adapalene and benzoyl peroxide gel, 0.3%/2.5%.

We are reviewing the Chemistry, Manufacturing and Controls (CMC) sections of your submission and have the following information requests. We request a written response by close of business, October 23, 2014, in order to continue our evaluation of your NDA.

1. Update the establishment attachment to Form 356h by (1) adding all testing facilities that are involved in this NDA for the release/stability of drug substance and/or drug product, and (2) providing all information (including function and readiness for inspection or not) as instructed by Form 356h for each facility.
2. Provide Master Batch Record (with English translation) for the drug product, or identify its location in the submission.
3. Provide information that clearly indicates that analytical samples for the pump configurations were taken from the pumped out formulation, as agreed to in the pre-NDA meeting in June 2014.

If you have any questions, please contact Belainesh Robnett, Regulatory Project Manager, at (240) 402-4236.

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, MD, FAAD
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JILL A LINDSTROM
10/17/2014



NDA 207917

NDA ACKNOWLEDGMENT

Galderma Research and Development LLC
Attention: Elaine Clark
Senior Director, US Regulatory Submissions
14501 North Freeway
Fort Worth, TX 76177

Dear Ms. Clark:

We have received your New Drug Application (NDA) submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: adapalene and benzoyl peroxide gel, 0.3%/2.5%

Date of Application: September 17, 2014

Date of Receipt: September 17, 2014

Our Reference Number: NDA 207917

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 November 16, 2014, 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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. 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.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

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/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me, at (240) 402-4236.

Sincerely,

{See appended electronic signature page}

Belainesh Robnett, MS
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/

BELAINESH ROBNETT
10/09/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 067801

ADVICE

Galderma Laboratories, LP
Attention: Elaine Clark
Senior Director, US Regulatory Submissions
14501 North Freeway
Fort Worth, TX 76177

Dear Ms. Clark:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (adapalene and benzoyl peroxide) Gel, 0.3%/2.5%.

We also refer to your amendment dated February 28, 2013, containing a new clinical protocol.

We have the following comments and recommendations:

1. For Trial RD.06.SPR.18229, we recommend that your drug product be applied in a sufficient quantity to cover the entire area of the face, shoulders, upper chest and upper back. A dose of (b) (4) does not appear to be sufficient to cover the entire target area of the face, shoulders, upper chest and upper back (which is usually considered to be approximately 15% body surface area). You should consider applying a larger amount.
2. Ensure that there is adequate number of subjects in the lowest age range (e.g., 12-13 years of age).
3. We note that Epiduo[®] (adapalene and benzoyl peroxide) Gel, 0.1%/2.5% is approved for the treatment of acne vulgaris down to 9 years of age. If you decide to pursue an indication for subjects down to 9 years of age, then the proposed maximal use PK trial (RD.06.SPR.18229) will not be adequate to support such an indication.

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>. Your responsibilities include:

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/s/

KENDALL A MARCUS
06/26/2014

Reference ID: 3532844



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 067801

MEETING MINUTES

Galderma Research & Development LLC
Attention: Elaine Clark
Senior Director, US Regulatory Submissions
14501 North Freeway
Fort Worth, TX 76177

Dear Ms. Clark:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (adapalene and benzoyl peroxide) gel, 0.3%/2.5%.

We also refer to the teleconference between representatives of your firm and the FDA on June 25, 2014. The purpose of the meeting was to discuss the content and format of Galderma's planned NDA submission for (adapalene and benzoyl peroxide) gel, 0.3%/2.5%.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Dawn Williams, Regulatory Project Manager at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Acting Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA Meeting

Meeting Date and Time: June 25, 2014; 11:00am
Meeting Location: Teleconference

Application Number: IND 067801
Product Name: (adapalene and benzoyl peroxide) gel, 0.3%/2.5%
Proposed Indication: Treatment of acne vulgaris (b) (4)
Sponsor Name: Galderma Research and Development, LLC

Meeting Chair: Kendall A. Marcus, MD
Meeting Recorder: Dawn Williams, BSN

FDA ATTENDEES

Julie Beitz, MD, Director, ODE III
Amy Egan, MD, MPH, Acting Deputy Director, ODE III
Kendall A. Marcus, MD, Acting Director, DDDP
Jane Liedtka, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Kumar Mainigi, PhD, Pharmacology Reviewer, DDDP
Shulin Ding, PhD, Pharmaceutical Assessment Lead, DNDQA II
Mohamed Alesh, PhD, Biostatistics Team Leader, DB III
Matthew Guerra, PhD, Biostatistics Reviewer, DB III
Chinmay Shukla, PhD, Clinical Pharmacology Reviewer, DCP III
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
Dawn Williams, BSN, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Elaine Clark, US Senior Director Regulatory Submissions
Martine Ortega, Regulatory Affairs Project Group Manager
Marie-Line Abou Chacra, Regulatory Affairs Project Manager
Matthew Leoni, Project Leader
Oliver Galley, Pharmaceutical Development Coordinator
Beatrice Gauthier, Pre-clinical Development Coordinator
Vasant Mann, MD, Senior Medical Advisor
Michael Graber, MD, Clinical Science Director
Jesse Kooker, Head of Global Biometrics

Mi Yao, Senior Statistical Manager
Khaled Benkali, Clinical Pharmacokinetics

Regulatory Correspondence History

We have had the following teleconferences:

- December 5, 2012 Pre-Phase 3
- May 30, 2014 Pre-IND (under PIND (b) (4))

We have sent the following correspondences:

- December 26, 2013 Advice
- September 13, 2013 Advice
- July 3, 2013 Advice
- March 11, 2013 Special Protocol Agreement

Chemistry, Manufacturing and Controls (CMC)

Question 1:

The sponsor will describe in Module 3 the two suppliers for adapalene and the two suppliers for benzoyl peroxide Drug Substances as approved in the fixed-dose combination Epiduo[®] gel (NDA 022320).

In the Drug Product Module 3, the Sponsor will describe the composition of the fixed-dose combination, which is precisely the same as the currently approved fixed-dose combination Epiduo[®] gel (NDA 022320) except for the higher dose of adapalene (0.3% w/w).

Does the Agency concur that the drug substance suppliers described in the approved fixed-dose combination Epiduo[®] gel (NDA 022320) can be registered for this new fixed-dose combination dosage strength in consideration of the stability data that will be available at the time of submission?

Response:

Yes, we concur provided that a letter of authorization will be provided for each of the four DMF listed in Table 4 Drug Substance Manufacturer Information.

Question 2:

A supportive batch and two campaigns of 3 registration batches each of the fixed-dose combination were manufactured with adapalene and BPO sourced from two suppliers each. The supportive batch and the 3 registration batches from the first campaign were packaged in the same (b) (4) pump bottle of 45 g and (b) (4) tube of 2 g as the approved Epiduo[®] gel (NDA 022320); stability results of respectively 18 months for the supportive batch and 12 months for the first campaign will be reported at time of submission. Three registration batches from a second campaign were packaged in 15 g and 45 g sizes of the same (b) (4) pump bottle and 2 g (b) (4) tube; stability results of 3 months will be reported at the time of submission.

Stability results with the current Drug Substances and Packaging, reported in the approved Epiduo[®] gel (NDA 022320), will also be shown.

Does the Agency concur that the proposed stability package will be adequate to support submission of the 15 g (b) (4) pump bottle?

Response:

Yes, we concur provided that you will conduct an in-use stability study for each pump configuration, and the in-use stability studies and registration stability studies for pumps will include the following tests: pump functionality (number of prime, amount dispensed per actuation, and total deliverable), weight loss, and package integrity (interior, exterior, and leakage).

The analytical samples for a pump configuration should be taken from the pumped-out formulation.

Meeting Discussion:

The applicant stated that they plan to use 2 different pump designs. The (b) (4) pump is the (b) (4) type, and the (b) (4) pump is the (b) (4) type. The 15 g pump will have its own data set. The (b) (4) type pump has a variety of sizes (b) (4) therefore, the applicant plans to apply bracketing design (b) (4) The FDA requested that the applicant provide a rationale for bracketing in the planned NDA submission.

Question 3:

Does the Agency concur with the proposed format and contents of Module 3 of the proposed NDA for the new fixed-dose combination dosage strength?

Response:

Yes, we concur. You should also include drug product Master Batch Records, drug product Executed Batch Records, and Method Validation Package in the Regional Information section.

Pharmacology/Toxicology

Question 4:

The sponsor proposes to submit to the NDA the nonclinical studies that were reviewed within the context of the previously approved NDA 021753 Differin[®] 0.3% gel and NDA 022320 Epiduo[®] gel, in addition to the studies that were conducted specifically on the new fixed-dose combination. A detailed Table of Contents of non-clinical sections of Module 2 is presented in Table 12.

Does the Agency concur with the proposed format and contents of non-clinical sections of Module 2 and Module 4 of the proposed NDA for the new fixed-dose combination dosage strength?

Response:

Yes, we concur.

Clinical Pharmacology/Biopharmaceutics**Question 5:**

The sponsor conducted a maximal use PK trial in adult and adolescent acne subjects, implementing advice received from the Agency (pre-IND meeting held 30 May 2012 and advice letter of 03 July 2013). The study assessed the systemic exposure of adapalene after repeated topical applications during 4 weeks on face, shoulders, upper chest and upper back of either the new fixed-dose combination Adapalene 0.3%/Benzoyl Peroxide 2.5% product or Differin[®] 0.3%. The draft CSR synopsis is presented in Appendix 2 and results are discussed in this briefing package.

Does the Agency agree that PK data are adequate to support NDA submission?

Response:

The overall design of the maximal use pharmacokinetic (PK) trial (RD.06.SRE.18229) appears reasonable to support the filing of your NDA and we remind you to submit the raw and PK analysis electronic data sets in SAS transport format. You should also provide statistical analysis by calculating the 90% confidence interval (CI) on the ratio of the geometric means of C_{max} , AUC_{0-24} and $AUC_{0-\infty}$ following administration of your test product versus Differin Gel 0.3% in your NDA. We recommend you to perform the 90% CI analysis in two ways by: (1) Excluding subjects with AUC not calculated or C_{max} value below the limit of quantification (BLQ) (i.e., set those values as missing) and (2) Including all subjects with a specified way to handle concentrations that are BLQ. The same approach should also be applied to calculations of the descriptive statistics. The adequacy of the data will be determined following a detailed review at the time of your NDA submission.

Question 6:

As discussed during the Pre-IND meeting on 30 May 2012: to support the request of a waiver from the requirement to conduct a thorough QT/QTc study with the new fixed-dose combination product, the Sponsor has generated data demonstrating that systemic exposure under maximal use in acne patients with the new fixed dose combination of Adapalene 0.3%/Benzoyl Peroxide 2.5% is comparable to that of Differin[®] (adapalene) 0.3%. A waiver request and full supportive rationale will be provided to the Agency in section 1.12.5 of the proposed NDA.

Does the Agency agree that the request for a waiver to conduct a thorough QT/QTc study with the to-be-marketed fixed-dose combination of Adapalene 0.3%/Benzoyl Peroxide 2.5% gel is acceptable?

Response:

The waiver request for conducting a thorough QT/QTc trial appears reasonable. However, final determination will be made during the review of your NDA submission. Submit statistical analysis of PK parameters from your maximal use PK trial as indicated in the response to Question 5.

Clinical/Biostatistics

Question 7:

Topline results of the single pivotal SPA-agreed Phase 3 study conducted with the new fixed-dose combination are included in the Briefing Package.

Does the Agency concur that the Phase 3 study results support submission of the new proposed NDA for the acne vulgaris indication?

Response:

It appears that the Phase 3 study results would support filing.

Question 8a:

As previously discussed with the Agency during the Pre-IND meeting of 30 May 2012 and in subsequent IND submission (SN 0097, 18 June 2013), the Sponsor intends to request waivers from the requirement to conduct specific clinical trials with the new fixed-dose combination product. Waiver requests with supportive rationales will be provided to the Agency in Section 1.12.5 of the proposed NDA.

In addition, the Pediatric Study Plan (PSP) in adolescents aged 12 years and above was submitted to the IND (above-mentioned SN 0097). The PSP was discussed by FDA (13 September 2013). Additional nonclinical data was submitted (SN 0100, 10 October 2013) and further agreed by the Agency (01 November 2013). This agreed initial PSP (IND Section 1.9.6) will be re-submitted to the future NDA in Section 1.9.6.

Clinical waivers will be presented in module 1 (Section 1.12.5) of the NDA and will be justified on the basis of the Written and Tabulated summaries (integrated in Module 2.7.4) of studies referenced from previously approved Epiduo[®] gel and Differin[®] 0.3% NDAs. These waivers will also indicate how the label is informed, as per prior FDA request.

In follow-up of the discussion at the Pre-IND meeting of 30 May 2012: Long-term safety studies and corresponding safety databases from the previously approved Differin[®] 0.3% gel and Epiduo[®] gel products support the request for a waiver for the long term safety study requirement with the new fixed-dose combination (Adapalene 0.3%/Benzoyl Peroxide 2.5% gel). PK data showing that the adapalene systemic exposure from the new fixed-dose combination is comparable to that from Differin[®] 0.3% gel, further support the request for a waiver of a long term safety study for Adapalene 0.3%/Benzoyl Peroxide 2.5% gel.

Does the Agency agree to waive the requirement for a long term safety study for Adapalene 0.3%/Benzoyl Peroxide 2.5% gel?

Response:

We agree that an additional long-term safety study is not needed at this time.

Question 8b:

In follow-up of the discussion at the Pre-IND meeting of 30 May 2012: both active compounds have been studied in previous development programs for Epiduo[®] gel and Differin[®] 0.3% gel where Dermal Safety studies have been performed. Further, there are no new excipients in the

new fixed-dose combination formulation in comparison to Epiduo[®] gel. Existing data from these products will be used to inform the labeling of the new fixed-dose combination product; the proposed labeling is depicted in the draft TPP as shown in Appendix 4. The sponsor will therefore request a waiver from the requirement to conduct sensitization (RIPT), photoallergy and phototoxicity studies and will detail the rationale in Section 1.12.5 of the NDA.

Does the Agency agree to waive the requirement for sensitization (RIPT), photoallergy and phototoxicity studies for Adapalane 0.3%/Benzoyl Peroxide 2.5% gel?

Response:

We agree that additional sensitization, photoallergy and phototoxicity studies are not needed.

Question 9:

The sponsor proposes to include in Module 5 selected clinical studies that were reviewed within the context of the previously approved NDA 022320 Epiduo[®] gel and NDA 021753 Differin[®] 0.3% gel, in addition to the studies that were conducted specifically on the new dosage strength of the fixed-dose combination. A detailed Table of Contents of Module 5 is included in the meeting Briefing Package for easy reference.

Does the Agency concur with the proposed format and contents of Module 5 of the NDA for the fixed-combination dosage strength?

Response:

Your proposed format and contents of Module 5 appear reasonable.

Question 10:

In accordance with the Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (April 2009), the Sponsor proposes to provide the Agency with Sections 2.7.3 Summary of Clinical Efficacy (SCE) and 2.7.4 Summary of Clinical Safety (SCS) that are sufficiently detailed to also serve as the full narrative portions of the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS), respectively, while remaining within the suggested size limitations for Module 2 (i.e., maximum 400 pages for Section 2.7 Clinical Summaries). ISE and ISS appendices (tables, figures, and datasets) in Section 5.3.5.3 Reports of Analyses of Data from More than One Study will not be generated as there is only one new efficacy and safety study in the proposed NDA. Draft Tables of Contents for Sections 2.7.3 SCE (Table 16) and 2.7.4 SCS (Table 17) are provided in the meeting briefing package, to demonstrate the planned analyses to be presented in the proposed NDA.

Based on the Draft Tables of Contents provided for Sections 2.7.3 and 2.7.4, does the Agency agree that separate ISE and ISS narratives are not required in the proposed NDA?

Response:

This seems reasonable at this time.

Question 11:

The Sponsor intends to submit study datasets in accordance with the current Study Data Tabulation Model (SDTM) Implementation Guide, version 3.1.2, amendment 1, with the accompanying Define.xml.

Does the Agency agree with the proposed dataset submission plan?

Response:

Your proposal to submit study datasets in accordance with the current Study Data Tabulation Model (SDTM) Implementation Guide, version 3.1.2, amendment 1 is acceptable.

The primary method for handling missing efficacy data in your trial is the Multiple Imputation (MI) approach, which involves generating multiple datasets. Instead of submitting the multiple imputed datasets, submit the SAS code used to implement MI. In addition, submit the SAS code used to analyze these datasets.

For the analysis datasets, we have the following general comments:

- Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.
- The analysis dataset documentation (Define.xml) should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables. For ease of viewing by the reviewer and printing, submit corresponding Define.pdf files in addition to the Define.xml files.

In addition to the electronic datasets, you should submit study protocols including the statistical analysis plan, all protocol amendments (with dates), generated treatment assignment lists, and the actual treatment allocations (along with the date of enrollment).

Question 12:

The Sponsor does not intend to submit patient data listings (i.e., no Appendix 16.2 of the final clinical study report), as the SDTMs are submitted for all patient data to facilitate review.

Does the Agency agree with the proposal?

Response:

Your proposal appears reasonable.

Regulatory

Question 13:

The Sponsor's current proposal for the prescribing information (package insert) to be submitted with the NDA is reflected in the Target Product Profile (TPP) for the Adapalene 0.3%/Benzoyl Peroxide 2.5% gel, which is appended to the meeting Briefing Package. The proposed package

insert is based primarily on that approved for Epiduo[®] (adapalene and benzoyl peroxide) gel, 0.1%/2.5%. Considering the reliance upon data generated for the currently approved product Epiduo[®] gel (NDA 022320) and Differin[®] 0.3% (NDA 021753), the Sponsor seeks Agency agreement on the annotation and cross reference plan for the new product's package insert as shown in the TPP. Reports to be included in the NDA and those which will be incorporated by reference are described as above under Clinical Question 9.

Does the Agency agree with the plan for cross-referencing and annotation to inform labeling for the new Adapalene 0.3%/Benzoyl Peroxide 2.5% gel product?

Response:

It appears that you propose a separate package insert for the higher-concentration product. Clarify why you do not plan to include both products in combined labeling.

Your plan for cross-referencing and annotation to inform the labeling otherwise appears reasonable.

Meeting Discussion:

The sponsor noted that for business reasons they plan to keep the 2 labels separate.

Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND or NDA might identify additional comments or information requests.
2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21 CFR 54 and 21CFR 314.50(k).
3. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

PREA REQUIREMENTS

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information website including:

The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products Regulations and related guidance documents A sample tool illustrating the format for Highlights and Contents, and The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify in a single location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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/s/

KENDALL A MARCUS
06/26/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 067801

ADVICE

Galderma Laboratories, L.P.
Attention: Elaine Clark
Senior Director, U.S. Regulatory Submissions
14501 North Freeway
Fort Worth, TX 76177

Dear Ms. Clark:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (adapalene and benzoyl peroxide) Gel, 0.3%/2.5%.

We also refer to your amendment dated November 26, 2013, containing your Agreed Initial Pediatric Study Plan (iPSP).

We acknowledge your plan to study pharmacokinetics, safety and efficacy of (adapalene and benzoyl peroxide) Gel, 0.3%/2.5% in pediatric subjects with severe acne vulgaris aged 12 years to 17 years. We have completed our review of the submission and have no further comments at this time. We confirm our agreement to your Agreed iPSP. A clean copy of the Agreed iPSP is attached for your reference.

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

If your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

If your IND is not in eCTD format:

- you should submit 7-day reports by a rapid means of communication, preferably by facsimile or email. You should address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;
- if you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter);
- if you also send copies of these reports to your IND, the submission should have the same date as your facsimile or email submission and be clearly marked as "Duplicate."
- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and
- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/>.

If you have any questions, contact Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Galderma Agreed iPSP

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

/s/

SUSAN J WALKER
12/26/2013

**PeRC BPCA/Pediatric Study Plan Subcommittee Meeting Minutes
December 11, 2013**

PeRC Members Attending:

Lynne Yao

Hari Cheryl Sachs

George Greeley

Jane Inglese

Wiley Chambers

Tom Smith

Karen Davis-Bruno

Peter Starke

Patricia Dinndorf

Non Responsive

Gregory Reaman

Daiva Shetty

Non Responsive

Julia Pinto

Ruthanna Davi

(only reviewed Adapalene/Benzoyl Peroxide,

Non Responsive

Lisa Kammerman

(only reviewed Adapalene/Benzoyl Peroxide and

Non Responsive

Lily Mulugeta

Nisha Jain

Non Responsive

Barbara Buch

Adrienne Hornatko-Munoz

Non Responsive

Rachel Witten

(only reviewed Adapalene/Benzoyl Peroxide,

Non Responsive

Dianne Murphy

(only reviewed Adapalene/Benzoyl Peroxide,

Non Responsive

William J. Rodriguez

Dianne Murphy

Agenda

9:00	IND	067801	Adapalene/Benzoyl Peroxide Agreed iPSP (Partial Waiver/Deferral)	Treatment of acne vulgaris
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Non Responsive

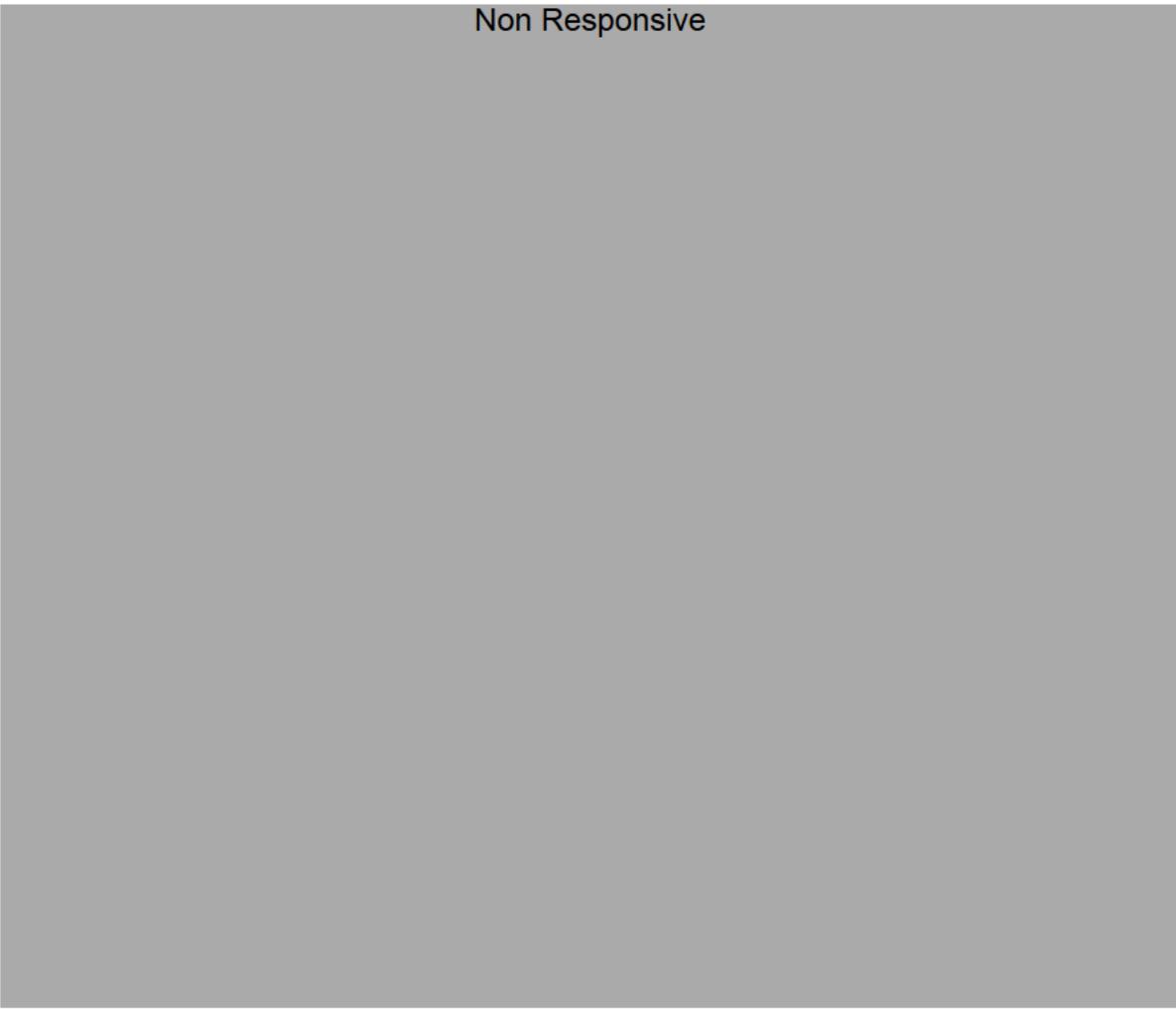
Adapalene/Benzoyl Peroxide Agreed iPSP (Partial Waiver/Deferral)

- Proposed Indication: treatment of acne vulgaris
- *PeRC Recommendations:*
 - The PeRC noted that waiver of any pediatric age group would have to be granted for one of four reasons. The appropriate reason to waive studies for pediatric patients aged 9 to 11 should be determined and justified by

the Division. The PeRC advised the Division to obtain use data on Epiduo in pediatric patients aged 9 to 11 to support a waiver based on the grounds that the product does not represent a meaningful therapeutic benefit over existing therapies and would not likely be used by a substantial number of pediatric patients age 9 to 11

- The PeRC voted unanimously that patients down to 9 years should be included in studies unless use data demonstrate that the product would not likely be used by a substantial number of patients aged 9 to 11.
- The PeRC strongly recommended that studies for pediatric patients less than 9 years of age be waived and that the iPSP could be amended later to waiver patients less than 11 based on use data.
- The PeRC chair reminded the Division that the PeRC is advisory and that the decision to agree to the iPSP should be made by the Division. The PeRC chair also reminded the Division that the sponsor or the FDA can request an amendment to an agreed iPSP.
- The PeRC chair will follow up with the Division director regarding future pediatric study plans for topical acne products.

Non Responsive



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/s/

JANE E INGLESE
12/20/2013



IND 067801

ADVICE

Galderma Laboratories, L.P.
Attention: Elaine Clark
Senior Director, Regulatory Submissions
14501 North Freeway
Fort Worth, TX 76177

Dear Ms. Clark:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (adapalene and benzoyl peroxide) Gel, 0.3%/2.5%.

We also refer to your amendment dated June 18, 2013, containing your initial Pediatric Study Plan (iPSP).

Your iPSP has been discussed with the Pediatric Review Committee (PeRC). Our comments and recommendations are provided in your enclosed iPSP. You must submit a revised iPSP within 30 days of the date of this letter addressing our comments.

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

If your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

If your IND is not in eCTD format:

- you should submit 7-day reports by a rapid means of communication, preferably by facsimile or email. You should address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;

- if you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter);
- if you also send copies of these reports to your IND, the submission should have the same date as your facsimile or email submission and be clearly marked as “Duplicate.”
- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and
- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/>.

If you have any questions, contact Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

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

Enclosure:

Galderma Laboratories iPSP with FDA comments and recommendations

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/s/

SUSAN J WALKER
09/13/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 067801

ADVICE

Galderma Laboratories, LP
Attention: Elaine Clark
Senior Director, US Regulatory Submissions
14501 North Freeway
Fort Worth, TX 76177

Dear Ms. Clark:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (adapalene and benzoyl peroxide) Gel, 0.3%/2.5%.

We also refer to your amendment dated February 28, 2013, containing a new clinical protocol.

We have the following comments and recommendations:

1. For Trial RD.06.SPR.18229, we recommend that your drug product be applied in a sufficient quantity to cover the entire area of the face, shoulders, upper chest and upper back. A dose of (b) (4) does not appear to be sufficient to cover the entire target area of the face, shoulders, upper chest and upper back (which is usually considered to be approximately 15% body surface area). You should consider applying a larger amount.
2. Ensure that there is adequate number of subjects in the lowest age range (e.g., 12-13 years of age).
3. We note that Epiduo[®] (adapalene and benzoyl peroxide) Gel, 0.1%/2.5% is approved for the treatment of acne vulgaris down to 9 years of age. If you decide to pursue an indication for subjects down to 9 years of age, then the proposed maximal use PK trial (RD.06.SPR.18229) will not be adequate to support such an indication.

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfeft/CFRSearch.cfm>. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)].

If your IND is in eCTD format, submit 7-day reports electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). To obtain an ESG account, see information at the end of this letter.

If your IND is not in eCTD format:

- you should submit 7-day reports by a rapid means of communication, preferably by facsimile or email. You should address each submission to the Regulatory Project Manager and/or to the Chief, Project Management Staff;
 - if you intend to submit 7-day reports by email, you should obtain a secure email account with FDA (see information at the end of this letter);
 - if you also send copies of these reports to your IND, the submission should have the same date as your facsimile or email submission and be clearly marked as “Duplicate.”
- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and
 - Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. If your IND is in eCTD format, you should obtain an ESG account. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/>.

IND 067801
Page 3

If you have any questions, contact Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Stanka Kukich, MD
Deputy Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

STANKA KUKICH
07/03/2013



IND 067801

SPECIAL PROTOCOL - AGREEMENT

Galderma Laboratories, LP
Attention: Elaine Clark
Senior Director, US Regulatory Submissions
14501 North Freeway
Fort Worth, TX 76177

Dear Ms. Clark:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for (adapalene and benzoyl peroxide) Gel, 0.3%/2.5%.

We acknowledge your request dated and received on January 25, 2013, for a special protocol assessment of a clinical protocol. The protocol, number RD.06.SPR.18240, is titled "A Multi-center, Randomized, Double-blind, Parallel-group Vehicle and Active Controlled Study to Compare the Efficacy and Safety of CD0271 0.3%/CD1579 2.5% Topical Gel Versus Topical Gel Vehicle in Subjects with Acne Vulgaris".

We have completed our review and, based on the information submitted, agree that the design and planned analysis of your study adequately address the objectives necessary to support a regulatory submission. We advise you that, if you make any changes to this protocol, this agreement may be invalidated. If you choose to revise this protocol, submit your modifications as "**Special Protocol Assessment - Amendment**". This agreement is subject to modification only as outlined in section 505(b)(4)(C) of the Act.

As stated on page 9 in the "Guidance for Industry: Special Protocol Assessment," a special protocol assessment documents our agreement that the design and planned analysis of a study can adequately address objectives in support of a regulatory submission. However, final determinations for marketing application approval are made after a complete review of a marketing application and are based on the entire data in the application.

I. Agreements

1. The general design of your phase 3 study entitled "A Multi-center, Randomized, Double-blind, Parallel-group Vehicle and Active Controlled Study to Compare the Efficacy and Safety of CD0271 0.3%/CD1579 2.5% Topical Gel Versus Topical Gel Vehicle in Subjects with Acne Vulgaris" is acceptable.
2. The proposed dose regimen is acceptable.

3. The proposed entry criteria of subjects age 12 years and older with facial acne vulgaris of at least moderate severity on the proposed Investigator's Global Assessment (IGA) scale with 20-100 inflammatory lesions and 30-150 non-inflammatory lesions and no more than 2 nodules is acceptable.
4. The proposed safety assessments are acceptable.
5. The proposed co-primary efficacy endpoints of success in IGA, defined as the proportion of subjects with an IGA score of 0 (clear) or 1 (almost clear) at Week 12 and therefore at least 2-grade reduction, and absolute change in inflammatory and non-inflammatory lesion counts from baseline to Week 12 are acceptable.
6. The proposed secondary efficacy endpoints of percent change in inflammatory and non-inflammatory lesion counts from baseline to Week 12 are acceptable.
7. The proposed definition of the intent-to-treat (ITT) population as all subjects randomized is acceptable.
8. Your proposal to analyze success in IGA with the Cochran-Mantel-Haenszel (CMH) test is acceptable.
9. Your proposal to analyze absolute change in inflammatory and non-inflammatory lesion counts from baseline to Week 12 with ANCOVA models with terms for the respective baseline lesion count, treatment, and the variables that will be used to stratify the randomization is acceptable.

II. Questions

"In particular, does the Agency agree with the entry criteria, endpoints, proposed statistical analysis, and overall design to support the stated indication?"

Response: See the agreements above and comments below.

III. Additional Comments

1. You stated that the trial efficacy outcome will be considered positive if superiority of the new formulation over vehicle gel is demonstrated in the total population and in the subgroup with severe acne. It should be noted that you expect the treatment effect in the severe population will be similar to the treatment effect in the total population. Generally, once superiority is demonstrated in the total population, subgroup analyses could be used to identify subgroups that would benefit more from treatment; however, this is not consistent with your expectation. In addition, the Agency reiterates the previous comment that establishment of a superiority claim in a subgroup of subject with severe disease would need replication in two studies.
2. You stated that the trial efficacy outcome will be considered positive if superiority of the new formulation over vehicle gel is demonstrated in the total population and in the subgroup with severe acne. You also expect the treatment effect in the severe population will be similar to the treatment effect in the total population. It should be noted that for clinical trials designed for a targeted subgroup, it is expected that the efficacy results for

the subgroup is higher than that of the total population. Thus, under your assumption, you take a risk that the subgroup does not demonstrate superiority. You can claim the trial is positive by limiting your criteria to establishing efficacy in the total population. Analysis by severity can be conducted as a subgroup analysis without the requirement of formal hypothesis testing.

3. You proposed to “assess the superiority” of the new formulation versus Epiduo[®] (adapalene and benzoyl peroxide) Gel, 0.1%/2.5% in the subgroup of subjects with severe acne using confidence intervals. You should provide your regulatory intent of such an assessment.
4. You proposed to stratify the randomization by baseline disease severity (IGA) and country/region, where country/region will have 5 groups (Canada, Russia, and 3 groups for US). The utility of randomly assigning US subjects to 3 groups is not clear. If you expect efficacy to vary across regions of the US, then randomly assigning US subjects to 3 groups could mask regional effects. To investigate potential regional effects, you could define the groups based on geographical location. However, as the Agency is still interested in assessing the center-to-center variability, we still recommend reducing the number of centers to enroll a sufficient number of subjects per center, and stratifying the randomization by center. For randomization stratified by center, the analysis should follow the randomization and be stratified by center as well.
5. You stated that last observation carried forward (LOCF) was chosen as the primary imputation method for missing data because it would allow comparison to historical data obtained on Epiduo[®] (adapalene and benzoyl peroxide) Gel, 0.1%/2.5% and it would be conservative; however, it should be noted that whether LOCF is conservative would depend on the proportion of missing data in each treatment arm. As your proposed justification does not provide a convincing scientific rationale for LOCF, you are encouraged to select a more scientifically appropriate method (e.g. multiple imputation) as the primary imputation method.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

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

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/s/

TATIANA OUSSOVA

03/11/2013

Signing on behalf of Dr. Susan Walker



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 067801

MEETING MINUTES

Galderma Laboratories, LP
Attention: Elaine Clark
Senior Manager, Regulatory Affairs
14501 North Freeway
Fort Worth, TX 76177

Dear Ms. Clark:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (adapalene and benzoyl peroxide) Gel, 0.3%/2.5%.

We also refer to the teleconference between representatives of your firm and the FDA on December 5, 2012. The purpose of the meeting was to discuss the late development program for (adapalene and benzoyl peroxide) Gel, 0.3%/2.5%.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, MD
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Pre-Phase 3

Meeting Date and Time: December 5, 2012; 9:00 am
Meeting Location: Teleconference

Application Number: IND 067801
Product Name: (adapalene and benzoyl peroxide) Gel, 0.3%/2.5%
Indication: Treatment of acne vulgaris [REDACTED] (b) (4)

Sponsor Name: Galderma Laboratories, LP

Meeting Chair: Jill Lindstrom, MD
Meeting Recorder: Dawn Williams, BSN

FDA ATTENDEES

Jill Lindstrom, MD, Clinical Team Leader, DDDP
Jane Liedtka, MD, Clinical Reviewer, DDDP
Chinmay Shukla, PhD, Clinical Pharmacology Reviewer, DCP III
Kathleen Fritsch, PhD, Acting Biostatistics Team Leader, DB III
Matthew Guerra, PhD, Biostatistics Reviewer, DB III
Dawn Williams, BSN, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Elaine Clark, Senior Manger, Regulatory Affairs
[REDACTED] (b) (4)
Jean-Danial Doutremepuich, Full Development Project Leader
Vasant Manna, MD, Medical Advisor
Michel Poncet, Senior Statistical Expert
Martine Ortega, Regulatory Affairs Project Group Manager

Regulatory Correspondence History

We have had the following teleconference with you:

- May 30, 2012; Pre-IND Meeting (conducted under PIND (b) (4))

Regulatory

Question 1:

Following FDA recommendation on May 30, 2012, the sponsor intends to conduct a 3-arm study with the new fixed dose combination (Adapalene 0.3% / BPO 2.5% Gel), the approved fixed dose combination (Epiduo®: Adapalene 0.1% / BPO 2.5% Gel), and the vehicle.

The primary objective of the proposed study will be to demonstrate the superior efficacy of the new fixed-dose combination over the vehicle in the entire study population, which consists of 50% of patients with moderate acne (IGA=3) and 50% with severe acne (IGA=4), and if this is met, to also demonstrate the same within the severe subgroup (IGA=4) only. The co-primary efficacy endpoints will be:

- IGA success rate defined as Clear / Almost clear and at least 2 grades improvement
- Change in inflammatory lesion counts at Week 12.
- And change in non-inflammatory lesion counts at Week 12

The relative efficacy of the new fixed dose combination will be estimated versus Epiduo® in severe patients. The point estimate of the difference between the two fixed dose combinations with its 95% confidence interval will be provided for each of the three co-primary efficacy endpoints (Re. Statistical questions below).

- Does the Agency agree that the proposed clinical development program, including the single pivotal Phase 3 study as outlined above, supports the approval of the new fixed dose combination in the treatment of acne vulgaris?

Response:

You propose a development plan comprised of (1) a 21-day cumulative irritancy study, (2) a Maximal Use Systemic Exposure PK study in subjects aged 12 years and older and (3) a single pivotal active- and vehicle-controlled 3-arm Phase 3 study. We anticipate that the development program you outline could be sufficient for filing if you adequately address the comments that follow. Approval of an application will rest on the adequacy of the data submitted. As noted at the Pre-IND meeting held on May 30, 2012 you must provide adequate data to inform labeling.

- Would the demonstration of efficacy in the subgroup of severe acne patients in the Phase 3 study be reflected in section 14 of the labeling?

Response:

Establishment of a superiority claim relative to a comparator product or in a subgroup of subjects with severe disease would need replication in two studies. The single 3-arm study you propose

would not provide adequate information for the proposed subgroup of subjects with severe disease nor did you provide any other information that could be used for this claim. For establishment of a claim for patients with severe disease, we would need additional information.

Meeting Discussion:

The sponsor stated that they do not plan to claim superiority to the approved Epiduo, and that they do not plan to include “severe” acne in the indication.

Clinical/Biostatistics

Question 2:

Following the FDA recommendation on May 30, 2012, the sponsor intends to conduct a 3-arm study with the new fixed dose combination (Adapalene 0.3%/ BPO 2.5% Gel), the approved fixed dose combination (Epiduo: Adapalene 0.1%/ BPO 2.5% Gel), and the vehicle.

The primary objective of the proposed study will be to demonstrate the superior efficacy of the new fixed-dose combination over the vehicle in the entire study population, which consists of 50% of patients with moderate acne (IGA=3) and 50% with severe acne (IGA=4), and if this is met, to also demonstrate the same within the severe subgroup (IGA=4) only. The co-primary efficacy endpoints will be:

- IGA success rate defined as Clear/Almost clear and at least 2 grades improvement
- Change in inflammatory lesion counts at Week 12.
- And change in non-inflammatory lesion counts at Week 12

The relative efficacy of the new fixed dose combination will be estimated versus Epiduo in severe patients. The point estimate of the difference between the two fixed dose combinations with its 95% confidence interval will be provided for each of the three co-primary efficacy endpoints (Re. Statistical questions below).

- Does the Agency agree that the proposed study design is adequate to support approval of the new fixed dose combination (Adapalene 0.3%/ BPO 2.5%) in the treatment of patients with Acne vulgaris?

Response:

For the proposed 3-arm study, you propose the following co-primary efficacy endpoints:

- Success Rate, the percentage of subjects with an IGA of clear or almost clear (and therefore at least a 2-grade improvement from Baseline at Week 12 Intent-to-treat [ITT]);
- Change in Inflammatory Lesion Count from Baseline to Week 12 (ITT);
- Change in Non-inflammatory Lesion Count from Baseline to Week 12 (ITT);

We note that your enrollment criteria allow enrollment of subjects

(b) (4)

We encourage you to revise your enrollment criteria to reduce the number of nodules permitted at baseline to qualify for enrollment (such as was done in the Epiduo pivotal study 18087 which allowed “no more than one nodule”).

Meeting Discussion:

The sponsor clarified that nodular acne is not their target population. The sponsor stated that they will amend their inclusion/exclusion criteria to exclude nodular acne and to limit the number of nodules to 2 or fewer.

You plan to use the Interactive Response Technology (IRT) to randomize subjects stratified by severity at baseline (IGA of 3 or 4). As the Agency is interested in investigating the center-to-center variability, randomization should be stratified by center and the analysis should account for stratifying by both baseline severity and center. It should be noted that as the average subject enrollment per treatment arm per center is small, you should reduce number of centers and enroll a reasonable number of subjects in each treatment arm per center (e.g. 12 subjects in each active arm and 4 subjects in vehicle arm per center) to enable a meaningful checking of the consistency of the trial findings across centers. The protocol should pre-specify an algorithm for pooling small centers if actual enrollment does not meet the minimum number of subjects per center.

Meeting Discussion:

The sponsor stated that it may be difficult to enroll a large number of “severe” subjects per center, and therefore it may be difficult to reduce the number of centers. The sponsor stated that they plan to investigate regional effects (5 countries). The Agency responded that we are interested in evaluation of center effects and treatment by center interactions, and we recommend enrollment of as large a number of subjects per center as feasible.

Question 3:

Trial objectives will be tested sequentially and conditionally on success of the previous objective:

1. Demonstrate Adapalene 0.2%/ BPO 2.5% is superior to Vehicle in the combined population of Moderate and Severe patients
2. Demonstrate Adapalene 0.3%/ BPO 2.5% is superior to Vehicle in Severe patients

3. Assess the relative efficacy of Adapalene 0.3%/ BPO 2.5% versus Adapalene 0.1%/ BPO 2.5% in Severe patients

The trial efficacy outcome will be considered positive if objectives (1) and (2) are met.

- Does the Agency agree with the clinical trial objectives and the definition of a positive efficacy outcome?

Response:

Provided that you adequately address the suggested revisions to trial design (see answer to question #2), the trial objectives and definition of a positive efficacy outcome appear reasonable. You propose to “assess” the relative efficacy of the new fixed-dose combination versus Epiduo[®] gel in the subgroup of subjects with severe acne using confidence intervals. If you plan to make a claim of superiority for this comparison, you should conduct formal hypothesis testing instead of using confidence intervals and you would need replication.

Question 4:

The sponsor intends to seek the Agency agreement on the primary efficacy analysis and sensitivity analyses for the 3 trial objectives.

- Does the FDA agree with this proposal as detailed in the attached Statistical Analysis Plan?

Response:

You have developed a Statistical Analysis Plan (SAP) as a separate document from the protocol. It should be noted that revision of the statistical methodology might impact control of the Type I error rate and consequently impact establishing efficacy claims; therefore, the SAP should be finalized along with the protocol. Details about table format and exploratory analyses can be delayed. The following are comments regarding your SAP:

- Secondary endpoints intended for labeling should be clinically meaningful, limited in number, and adjusted for multiplicity.
- You propose to use LOCF as the primary imputation method for missing data and use multiple imputation (MI) as a sensitivity analysis. As the scientific justification for LOCF is weak, you should provide your justification for using LOCF or propose an alternate method. For MI, you plan to assume monotone missingness and use a regression model. You should pre-specify the covariates to be used in the regression model for imputing the missing data.

Meeting Discussion:

The sponsor stated that they plan to have 3 secondary endpoints: percent change in inflammatory lesion counts, non-inflammatory lesion counts, and total lesion counts.

Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.
2. Please refer to the Guidance for Industry: Special Protocol Assessment and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT (SPA)**. Please clearly identify this submission as an SPA in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical or carcinogenicity) and refer to this Pre-Phase 3 meeting. Ten desk copies (or alternatively, an electronic copy) of this SPA should be submitted directly to the project manager.

Meeting Discussion:

The sponsor stated that they intend to submit a protocol for SPA.

3. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
4. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.
5. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.
6. In your application, you will need to address the potential for QT/QTc interval prolongation (see ICH E14).
7. You are encouraged to request a Pre-NDA Meeting at the appropriate time.

PREA PEDIATRIC STUDY PLAN

Please be advised that you must submit a Pediatric Study Plan within 60 days of your scheduled end-of-Phase 2 meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver,

if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

[http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/
ElectronicSubmissions/ucm248635.htm](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm)

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/s/

JILL A LINDSTROM
12/19/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 67,801

Galderma USA
Attention: Christine Shrank,
Sr. Director, Regulatory Submission
14501 N. Freeway
Fort Worth, TX 76177

Dear Ms. Shank:

Please refer to your Investigational New Drug Application (IND) file for Adapalene/benzoyl peroxide gel, for topical treatment of acne vulgaris.

We also refer to the meeting between representatives of your firm and the FDA on December 12, 2005. The purpose of the meeting was to your end of phase 2 plans.

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 Felecia Curtis, Regulatory Project Manager, at (301) 796-0877.

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Acting Division Director
Division of Dermatology & Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 12, 2005
TIME: 1:00 P.M.
LOCATION: 1313
APPLICATION: IND 67,801
DRUG NAME: Adapalene/benzoyl peroxide gel
TYPE OF MEETING: End of Phase 2 meeting
MEETING CHAIR: Jill Lindstrom, M.D./Acting Deputy Director, DDDP, HFD-540
MEETING RECORDER: Felecia Curtis/Regulatory Management Officer, DDDP, HFD-540

FDA ATTENDEES:

Division of Dermatology and Dental Products

Jill Lindstrom, M.D./Acting Deputy Director, DDDP, HFD-540
Markham Luke, M.D./Clinical Team Leader, Dermatology, DDDP, HFD-540
Jane Chang, Ph.D./Chemistry Reviewer, DNDCIII, HFD-830
Shulin Ding, Ph.D./Chemistry Reviewer, DNDCIII, HFD-830
John Hunt, Acting Director, DCPB III, HFD-850
Tapash Ghosh, Ph.D./Pharmacokinetic Reviewer, DCPB III, HFD-850
Paul Brown, Ph.D./Pharmacology Team Leader, DDDP, HFD-540
Daivender Mainigi, Ph.D. / Pharmacology Reviewer, DDDP, HFD-540
Mohamed Al-Osh, Ph.D./Team Leader, Biostatistics, DBIII, HFD-725
Clara Kim, Ph.D./Biostatistics Reviewer, DBIII, HFD-725
Felecia Curtis/Regulatory Management Officer, DDDP, HFD-540

EXTERNAL CONSTITUENT ATTENDEES:

Galderma Corporation

Pascale Tronche, Ph.D./CMC/Pharmaceutical Development Project Team Representative
Guy Bouvier, Ph.D./Preclinical Development Representative
Michael Graeber, M.D./Head of U.S. Clinical Development
Christian Loesche, M.D./Head of Global Clinical Development
Yin Liu, Ph.D./Head of U.S. Biometrics
Marjory Kadash, M.S./Global Project Team Leader
Stephane Mesaros, Pharm. D./Global Project Manager
Oliver Watts, Ph.D./Regulatory Affairs & Pharmacovigilance Manager
Denis Gross/Scientific Division Regulatory Affairs Representative
Paul Clark, B.S./V.P., Regulatory Affairs
Bill Carson, M.S./V.P., Medical and Regulatory Affairs

MEETING OBJECTIVES:

To provide general guidance on the content and format of the proposed new Investigational New Drug Application under 21CFR 312. The pre-meeting briefing document (submitted A) provides background and questions (page 6) for discussion.

Chemistry, Manufacturing and Controls:

Sponsor's Question:

1. Concurrence is sought that the specifications proposed for Adapalene/Benzoyl Peroxide Gel are acceptable to the Chemistry Reviewer.

Agency's Response:

Comments for Drug Substance Specifications:

1. Given the fact that both adapalene and benzoyl peroxide are formulated as a suspension, the polymorphisms of adapalene and benzoyl peroxide should be examined. A control of the (b)(4) form is required in the specifications if multiple (b)(4) forms exist.

The sponsor will submit information regarding the characterization of adapalene (b)(4) structure. The sponsor is aware of only one (b)(4) form for benzoyl peroxide. The information will also be submitted for NDA review.

Sponsor's Question:

2. The drug substance supplier, (b)(4), is not an approved supplier for benzoyl peroxide. A tighter limit for individual unspecified impurity may be requested if the impurity profile is not comparable to those of the approved supplier.

The sponsor agreed.

Comments for Finished Drug Product Release Specifications:

1. The acceptance criterion of NMT (b)(4)% for (b)(4) degradant is not acceptable. A lower limit should be established based on real time stability data.

The sponsor agreed.

2. Establish the inter-tubes content uniformity acceptance criteria using the concept described in USP <905> such that homogeneity of the bulk gel can be demonstrated.

Sponsor: The sponsor briefly described the sampling plan and sought concurrence.

Agency: The adequacy of the sampling plan will be a review issue. The sampling plan and testing should be submitted in the NDA for review

3. The microbial limit for total molds and yeasts count of NMT (b)(4) cfu/g has been acceptable traditionally. A tighter limit for total molds and yeasts count may be requested per Pharmacopeial Forum [Vol 29(5)].

The sponsor agreed.

4. Please see Item 2) from Comments for Drug Substance Specifications regarding individual unspecified impurity for benzoyl peroxide.

The sponsor agreed.

5. Please clarify how the particle size distribution for adapalene and benzoyl peroxide is determined.

Sponsor: The particle size distribution is determined by fluorescence microscopy. The information will be submitted in the NDA.

Sponsor's Question:

2. Concurrence is sought that the proposed primary stability study program for Adapalene/Benzoyl Peroxide Gel presented in the CMC section of the Meeting Briefing Package is suitable and adequate for the filing of a New Drug Application.

Agency's Response:

In addition to the acceptance criteria listed in the stability specifications for Adapalene/Benzoyl Peroxide Gel (page 36); the following acceptance criteria should be included in the stability specifications:

1. Establish the intra-tubes content uniformity acceptance criteria using the concept described in USP <905>.

Sponsor: Agreed. The sponsor informed the agency briefly about the sampling plan and sought concurrence of its proposal to address intra-tube content uniformity.

Agency: It will be a review issue, but the sponsor's plan appears to be satisfactory.

2. Please see Item 2) from Comments for the drug substance specifications regarding individual unspecified impurity for benzoyl peroxide.

The sponsor agreed.

3. Please see Item 3) from Comments for the finished drug product release specifications regarding the microbial limit for total molds and yeasts count.

The sponsor agreed.

Additional acceptance criteria and/or revision of the existing criteria may be required pending on the outcome of complete stability data. Validated analytical procedures should be used. The finished drug product should be stored in either the upright or inverted position to simulate a worst case scenario in case a settlement occurs.

Stability data from three batches of each container size from three commercial scale-up batches is required to support a NDA filing unless additional manufacturing and control information from both the pilot and commercial scale-up batches is submitted for evaluation.

Sponsor: The sponsor informed the agency that the same manufacturing process/control and the equipment of the same design are used in the manufacturing of the three pilot batches (b)(4) and the commercial batch (b)(4).

Agency: If the same manufacturing process/control and similar equipment are used in the manufacturing of the pilot batches and the commercial scale batch, the proposed plan is acceptable. The sponsor should submit manufacturing information for both scales in the NDA for review.

Sponsor's Question:

3. Concurrence is sought that the questions and issues raised by the Chemistry Reviewer (FDA Fax memo dated, February 3, 2004) have been adequately addressed in the CMC Response amendment (SN:0019) submitted to the IND on September 30, 2005.

Agency's Response:

Items 2 has been addressed in SN: 0019. The information about labels is acceptable.

The photostability data indicated that adapalene is very unstable in the presence of benzoyl peroxide when exposed to light (300-800 nm). The sponsor has responded that the dosing regimen for the combination drug product requires that the product be applied once daily in the evening after cleansing. The sponsor should address whether the seven major degradants, which were observed from irradiation of a THF-ACN-water solution containing adapalene and benzoyl peroxide, would form when the drug product is used under the proposed dosing regimen. If yes, please identify the extent of the degradants present and any potential for concern.

The sponsor will submit a stability protocol for review. The protocol will simulate the actual use.

Regarding Item 3, please see the comments from Question 1 above.

Additional Comments:

The following information is requested to support a future NDA during the phase III clinical trial:

- a. The drug product manufacturing, control and packaging procedures
- b. The stability data collected to-date for the finished drug product, two monads, and vehicle gel.
- c. Analytical procedures for both the drug substance and drug product and adequate method validation. (Note: The assay method for one active ingredient needs to be demonstrated to be free from the interferences from the second active ingredient and its degradants).
- d. Additional information, including stability data, regarding (b)(4)
- e. Additional information about the container/closure of 2-g, 60-g, and (b)(4) sizes. For example, are all of them (b)(4) tubes?

The sponsor agreed with items a-e except that there is no accelerated data for the two monads and vehicle gel.

Pharmacology/Toxicology:

Sponsor's Question:

1. Concurrence is sought that the Nonclinical database already presented for Adapalene/Benzoyl Peroxide topical Gel in the IND and in the end of Phase 2 briefing package, including information from the 13-week dermal toxicity study in minipig may be adequate to support the filing of a New Drug Application. Specifically, the Sponsor is seeking concurrence that no dermal carcinogenicity or reprotoxicology studies are requested.

Agency's Response:

The request for waiver from the carcinogenicity and teratogenicity studies shall be considered after review of the full report of the 13-week minipig study.

The sponsor agreed.

Clinical Pharmacology and Biopharmaceutics:

Sponsor's Question:

1. Concurrence is sought that the design of Study RD.06.SRE.18097 "A Pharmacokinetic Study to Determine the Systemic Exposure to Adapalene During Dermal Application of Either a Fixed-combination of Adapalene 0.1% and Benzoyl Peroxide 2.5% Topical Gel (Adapalene/Benzoyl Peroxide Gel) or Adapalene 0.1% Topical Gel (Adapalene Monad) for 30 days in Subjects with Acne Vulgaris" is adequate to address the biopharmaceutical requirements for the filing of an NDA for a fixed-dose combination treatment for Acne vulgaris.

The sponsor seeks concurrence on adequacy of the study # 18907 for fulfilling CPB requirements for NDA submission.

Agency Response:

Yes, the study was done under maximal usage condition as suggested by us and their result demonstrates low systemic exposure over 30 days. However, the results will be reviewed in detail during NDA review.

The sponsor agreed.

Clinical and Biostatistics:

Sponsor's Question: 1 (Clinical): Concurrence is sought that the completed Study RD.06.SPR.18094 meets the design criteria and has generated conclusive and robust results and therefore qualifies as one of two adequate and well-controlled efficacy and safety studies intended to support the filing of an NDA for Adapalene/Benzoyl Peroxide Topical Gel.

Biostatics Response: Whether the completed study RD.06.SPR.18094 can be used to establish the efficacy claim for Adapalene/Benzoyl Peroxide Topical Gel is a review issue which will depend on the study design, statistical method of analysis, and the efficacy findings. In general, the agency requires efficacy established based on two well-designed independent Phase 3 trials.

The Division stated that study (RD.06.SPR.18094) was a phase 2 trial and the study synopsis stated that “Study unblinded as prospectively defined in the protocol”. It is not clear when the unblinding was done. In addition, the study was powered at 80% to detect a 15% difference in success rate and percent change in lesion counts. It should be noted that the summary of efficacy results was 10% difference in the success rate with the IGA, 4 lesions for change in inflammatory lesions and 6 lesions for change of noninflammatory lesions, yet all the reported p-values were approximately 0.001. Further, the sponsor’s table gives results for ‘week 12’ which differ from the results the sponsor called “endpoint”. It is not clear what is meant by ‘endpoint’ and why results differ from week 12.

While the Division indicated that the utility of completed study RD.06.SPR.18094 for establishing efficacy is a review issue, it should be noted that the sponsor might be taking a risk by planning to conduct only one additional phase 3 trial (18087) to support their efficacy claim.

The sponsor stated the results for the ‘endpoint’ are those for the per-protocol population.

Sponsor's Question 2 (Clinical): The Sponsor proposes to conduct a second efficacy and safety study (RD.06.SPR.18087) with Adapalene/Benzoyl Peroxide Topical Gel to demonstrate that Adapalene/Benzoyl Peroxide Gel is safe and superior in efficacy compared with its monads and Gel Vehicle to support the filing of an NDA.

2a. The primary efficacy parameter is Success Rate (according to the Investigator's Global Assessment) at Week 12 (LOCF). The study will be claimed ‘positive’ for the indication acne vulgaris if Adapalene/Benzoyl Peroxide Topical Gel is superior to Adapalene Monad, Benzoyl Peroxide Monad and Gel Vehicle for Success Rate at the 0.05 level. Does the Agency agree?

2b. Change in Inflammatory Lesion Counts and Change in Noninflammatory Lesion Counts (from Baseline at Week 12 (LOCF)) are secondary efficacy variables. The Sponsor intends to include lesion count data in the CLINICAL STUDIES section of the final product label. Does the Agency agree?

Biostatic Response: See biostatistics response below.

Sponsor's Question 4 (Clinical): With respect to the requirement for independent substantiation the Sponsor would like the Agency to comment regarding the acceptability of using some or all investigators from the completed Study RD.06.SPR.18904 in the planned study RD.06.SPR.18087.

Biostatistics Response: For replication of study findings, the agency requests the Phase 3 trials to be independent, which in turn implies that the studies do not share common investigators.

Sponsor's Question 1: Concurrence is sought that the sample size justification for Study No. RD.06SPR.18087 is adequate.

Agency Response: The study should be powered for the two co-primary endpoints:

1. The success rate at week 12. Success is defined as 0 (clear) or 1 (almost clear) or alternatively success could defined as improvement of two grades from the baseline score on the IGA.
2. Change in inflammatory, noninflammatory and total lesion counts.

The sponsor's justification for the choices of the inflammatory and noninflammatory SDs is not clear. Adequacy of powering the study depends on the validity of the assumptions made.

Sponsor stated that the study will be powered for absolute change in inflammatory and noninflammatory lesion count, but not total lesion count. The Division agreed and noted that once the study is powered for change in inflammatory and noninflammatory lesions count, it is automatically powered for change in total lesions count. In addition to the analysis of absolute change in lesion count, the sponsor should carry out an analysis for percent change in lesion count as a supportive analysis.

Sponsor's Question 2: Concurrence is sought that the statistical analysis for Study No. RD.06. SPR.18087 is adequate.

Agency Response:

1. Use of the ITT population as the primary population and the PP as supportive is acceptable. The ITT population should be defined as all patients randomized and dispensed medication, whether or not they have any post-baseline assessments. Also, the sponsor should note that a list of criteria excluding subjects from PP analysis population should be defined in the protocol.
2. For imputation of missing data, the Sponsor's proposed approach of LOCF along with sensitivity analyses by imputing missing data as success in one analysis and failure in another analysis should be acceptable for the IGA. For imputation of missing data for the other co-primary endpoint, lesion counts, LOCF approach might be used along with a sensitivity analysis by imputing the missing data as the mean (median) lesion count in each arm.

The Agency clarified that imputing mean (median) lesion count should be consistent with the imputation of success/failure in the IGA. Specifically, when imputing missing data in the IGA as a failure, missing data in the change in lesion count should be imputed as mean (median) change in lesion count for those with failure in the IGA in the same treatment arm. Similarly when imputing missing data in the IGA as success, one should impute the mean (median) of change in lesion count for those in the success category in the same treatment arm.

3. It is not clear what the sponsor meant by "lesion counts (ranked)". Analysis of lesion counts should be done on the original scale if the underlying assumptions of the statistical methodology, such as normality, hold. The protocol should pre-specify an approach for testing such assumptions and propose an alternative approach for the analysis, (e.g. nonparametric analysis) if assumptions are not met.
4. In addition to testing normality of the data, ANCOVA model assumes a linear relationship between the covariate and the mean response, with equal slopes for each treatment. The protocol should test for equality of slopes of the different treatment regression lines (test for parallel slopes).
5. It is not clear what the sponsor meant by "the analysis of IGA (Full scale)". Analysis of the co-primary endpoint of the IGA should be carried out as a dichotomized IGA scale (i.e. success vs. failure). Success is usually defined as score 0 (clear) or 1 (almost clear) or alternatively could be defined as an improvement of two grades from the baseline score on a 5 point scale. Analysis for the second co-primary endpoint (change in lesion

counts) should be done without multiplicity adjustment as superiority should be established for each comparison of the combination against the monads.

6. Cochran-Mantel-Haenszel test compares two groups on a binary response. Percent change in lesion count is also not a binary response. Therefore, Cochran-Mantel-Haenszel test is not adequate.

Sponsor stated that analysis of percent change is secondary analysis and could place changes in categories and apply CMH test. The Division stated while one could categorize a continuous variable, however, there is already methodology already available and is expected to provide more power for testing.

Sponsor's Question 3: Concurrence is sought regarding multiplicity in Study No. RD.06.SPR.18087.

Agency Response: Agreeable. No multiplicity adjustment is required when efficacy need to be established on each of the co-primary endpoints

Sponsor's Question 4: Concurrence is sought regarding the handling of small centers and treatment-by-center effect for Study No. RD.06.SPR.18087.

Agency Response: The proposed protocol plans (b) (4)

The study should be planned with a smaller number of centers to reduce the chance of having small centers. With 4 treatment arms, the requirement of 10 subjects per arm per center could be relaxed somewhat (say 7 subjects per arm per center) to estimate the treatment effect by center and to investigate the variability in efficacy results across centers. Extensive pooling of centers will mask the variability across centers. Thus, the study should be planned to reduce the chance of extensive pooling of centers. However, the protocol should also pre-specify an approach for pooling small centers if actual enrollment does not meet the protocol plans.

The protocol should pre-specify an approach for handling significant center by treatment interaction to ensure that efficacy results are not driven by extreme counts, eg. carrying out a sensitivity analysis after deleting extreme centers.

Sponsor agreed with Agency comments regarding planning study with the above minimum number of subjects per treatment arm per center and to include an algorithm for pooling small centers if actual enrollment did not meet the above criterion.

Additional Comments:

1. The Division recommends co-primary endpoints that evaluate an IGA and acne lesion counts to evaluate efficacy in acne trials. Also, the Division recommends IGA with five severity grades; clear (0), almost clear (1), mild severity (2), moderate severity (3), and severe (4).

Sponsor noted Agency comment and stated for enrollment and stated they will enroll subjects with moderate severity (score 3).

2. Details of the randomization procedure are vague in the protocol. The protocol should provide details about randomization, including block size if any. Sponsor originally requested (b) (4) centers. Increasing the number of centers to (b) (4) implies that each center

will enroll [REDACTED] (b) (4) The randomization list, which shows treatment allocation, should be generated prior to subject enrollment. Subject demographic data should include time/date of enrollment for each individual.

3. The protocol does not describe subject's assessment of acne. Please provide details concerning the scale and method of evaluation.
4. The sponsor should plan subgroup efficacy analysis by age, race, and baseline characteristics.

Administrative Comments

1. For applications submitted after February 2, 1999, the applicant is required to either certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
2. Comments shared with you today 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 informational requests.
3. 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 to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.
4. The sponsor is reminded to please submit appropriate patent certification at the time of NDA submission.

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/s/

Jill Lindstrom
1/11/2006 04:09:56 PM