

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-320

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

1.3.5.3 EXCLUSIVITY REQUEST

Pursuant to 21 CFR 314.108 (b)(4), Adapalene 0.1% / Benzoyl Peroxide 2.5% Gel qualifies for three (3) years of exclusivity from the date of approval of NDA 22-320. Two clinical studies were conducted to demonstrate the safety and effectiveness of Adapalene 0.1% / Benzoyl Peroxide 2.5% Gel in once daily applications for the treatment of acne vulgaris. FDA deemed these studies essential for the review and approval of the NDA. Galderma Laboratories, L.P. sponsored all clinical investigations conducted under IND 67.801.

The applicant, Galderma Laboratories, L.P., requests listing of 3 year exclusivity in the "Orange Book" from the date of approval for Adapalene 0.1% / Benzoyl Peroxide 2.5% Gel.

EXCLUSIVITY SUMMARY

NDA # 22-320

SUPPL #

HFD # 540

Trade Name EPIDUO Gel

Generic Name adapalene and benzoyl peroxide gel 0.1%/2.5%

Applicant Name Galderma Laboratories, LP

Approval Date, If Known

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?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

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

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).

Appears This Way On Original

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# 20380	adapalene gel (0.1%)
NDA# 21753	adapalene gel (0.3%)
NDA# 20748	adapalene cream (0.1%)
NDA# 50819	benzoyl peroxide/clindamycin phosphate gel, 2.5%/1.2%
NDA# 50756	benzoyl peroxide/clindamycin phosphate gel, 5%/EQ 1%
NDA# 50741	benzoyl peroxide/clindamycin phosphate gel, 5%/EQ 1%
NDA# 50557	benzoyl peroxide/erythromycin gel, 5%/3%
NDA# 50769	benzoyl peroxide/erythromycin gel, 5%/3%
NDA# 65112	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:

Pivotal studies #18087 and 18094

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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"):

Pivotal studies #18087 and 18094

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 # 67,801 YES ! NO
! Explain:

Investigation #2

IND # 67,801

YES

!
!
! NO
! Explain:

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

Investigation #1

YES

Explain:

!
!
! NO
! Explain:

Investigation #2

YES

Explain:

!
!
! NO
! Explain:

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

YES NO

If yes, explain:

Name of person completing form: Dawn Williams

Title: Regulatory Project Manager
Date: November 12, 2008

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

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Susan Walker
12/8/2008 02:52:22 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-320

Supplement Number: _____

NDA Supplement Type (e.g. SE5): _____

Division Name: Division of
Dermatology and Dental Products

PDUFA Goal Date: 12-08-08

Stamp Date: 2/8/2008

Proprietary Name: TRADENAME

Established/Generic Name: adapalene 0.1%/benzoyl peroxide 2.5%

Dosage Form: Gel

Applicant/Sponsor: Galderma Laboratories, L.P.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

(1) n/a

(2) _____

(3) _____

(4) _____

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

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

Indication: acne vulgaris

Q1: Is this application in response to a PREA PMR? Yes Continue

No Please proceed to Question 2.

If Yes, NDA/BLA#: _____

Supplement #: _____

PMR #: _____

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

Yes. Please proceed to Section D.

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

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

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

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

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

Q3: Does this indication have orphan designation?

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

No. Please proceed to the next question.

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

Yes: (Complete Section A.)

No: Please check all that apply:

Partial Waiver for selected pediatric subpopulations (Complete Sections B)

Deferred for some or all pediatric subpopulations (Complete Sections C)

Completed for some or all pediatric subpopulations (Complete Sections D)

Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

Extrapolation in One or More Pediatric Age Groups (Complete Section F)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cdcrpmhs@fda.hhs.gov) OR AT 301-796-0700.

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

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

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

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

Justification attached.

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

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

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

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

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^A	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	0 yr. 0 mo.	8 yr. 11 mo.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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

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

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

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

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

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

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

Δ Formulation failed:

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

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

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

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

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Population	minimum	maximum	Ready for Approval in Adults
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	9 yr. 0 mo.	11 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

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

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

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cdcrpmhs@fda.hhs.gov) OR AT 301-796-0700.

* Other Reason: Ready for approval in 12 years of age and above.

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

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

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

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PerC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	<u>12</u> yr. <u>0</u> mo.	<u>17</u> yr. <u>11</u> mo.	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

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

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

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

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

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

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

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

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

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

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

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

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

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

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

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

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

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

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

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

/s/

Susan Walker
12/8/2008 02:50:47 PM

1.3.3 DEBARMENT CERTIFICATION

In accordance with the requirements of the Federal Food, Drug and Cosmetic Act section 306(k)(1), the Applicant, Galderma Laboratories, L.P., hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this New Drug Application 022320 for Adapalene / Benzoyl Peroxide Gel 0.1% / 2.5%.¹

21 Jan 2008

(Date)

Paul Clark

(Signature)

Paul M. Clark
Director, Regulatory Affairs
Galderma Laboratories, L.P.

¹ Guidance for Industry: Submitting Debarment Certification Statements *Drift Guidance* – September 1998

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22-320 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: EPIDUO Gel Established/Proper Name: adapalene/benzoyl peroxide gel (0.1%/2.5%) Dosage Form: gel		Applicant: Galderma Laboratories, LP Agent for Applicant (if applicable):
RPM: Dawn Williams		Division: DDDP
<p>NDA: 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)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input checked="" type="checkbox"/> If no listed drug, check here and explain: This is a new combination product.</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)		12/8/08
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<p>❖ Promotional Materials (<i>accelerated approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
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❖ Application ² Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): <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 NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: _____	11/19/08
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
❖ 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 checked="" type="checkbox"/> No
• Press Office notified of action (by OEP)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² All questions in all sections pertain 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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

<p>• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.</p> <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).</p> <p><i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i></p> <p>(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?</p> <p><i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.</i></p> <p><i>If "No," continue with question (3).</i></p> <p>(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).</p> <p><i>If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.</i></p> <p>(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?</p> <p><i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "No," continue with question (5).</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ³	yes
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) Approval; 12/8/08
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	FPL 12/8/08
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	9/10/08
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> None

³ Fill in blanks with dates of reviews, letters, etc.
Version: 9/5/08

<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (write submission/communication date at upper right of first page of each submission) 	Yes, submitted 9/10/08
<ul style="list-style-type: none"> • Most-recent division proposal for (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	FPL 12/8/08
<ul style="list-style-type: none"> ❖ Labeling reviews (indicate dates of reviews and meetings) 	<input type="checkbox"/> RPM <input type="checkbox"/> DMEDP <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC 10/24/08 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews DMEPA 11/26/08
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Review(s) (indicate date(s)) • Acceptability/non-acceptability letter(s) (indicate date(s)) 	11/26/08 Acceptable
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (e.g., RPM Filing Review⁴/Memo of Filing Meeting) (indicate date of each review) 	10/3/08
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (signed by Division Director) 	<input checked="" type="checkbox"/> Included 12/8/08
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/ajp_page.html 	
<ul style="list-style-type: none"> • Applicant in on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<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 (indicate date) ○ If yes, OC clearance for approval (indicate date of clearance communication) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatric Page (approvals only, must be reviewed by PERC before finalized) 	<input checked="" type="checkbox"/> Included PeRC 11/19/08
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (include certification) 	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Postmarketing Requirement (PMR) Studies 	Yes
<ul style="list-style-type: none"> • Outgoing communications (if located elsewhere in package, state where located) 	Action Letter
<ul style="list-style-type: none"> • Incoming submissions/communications 	
<ul style="list-style-type: none"> ❖ Postmarketing Commitment (PMC) Studies 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Outgoing Agency request for postmarketing commitments (if located elsewhere in package, state where located) 	

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.
Version: 9/5/08

• Incoming submission documenting commitment	
❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	Information Request 10/31/08; Information Request 7/15/08; Information Request 7/8/08
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• PeRC (<i>indicate date; approvals only</i>)	<input type="checkbox"/> Not applicable 11/19/08
• Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)	<input checked="" type="checkbox"/> Not applicable
• Regulatory Briefing (<i>indicate date</i>)	<input checked="" type="checkbox"/> No mtg
• Pre-NDA/BLA meeting (<i>indicate date</i>)	<input type="checkbox"/> No mtg 11/28/07
• EOP2 meeting (<i>indicate date</i>)	<input type="checkbox"/> No mtg 12/12/05
• Other (e.g., EOP 2a, CMC pilot programs)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/8/08
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/28/08
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	11/28/08
• Clinical review(s) (<i>indicate date for each review</i>)	10/22/08; 5/2/08
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	See 10/22/08 clinical review page 78
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	See 10/22/08 clinical review page 9
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Risk Management <ul style="list-style-type: none"> • Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) • REMS Memo (<i>indicate date</i>) • REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested

⁵ Filing reviews should be filed with the discipline reviews.
Version: 9/5/08

Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 10/21/08; 4/4/08
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 10/24/08; 3/19/08
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 12/5/08
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 9/16/08
❖ 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
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
CMC/Quality <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• CMC/product quality review(s) (indicate date for each review)	<input type="checkbox"/> None 11/7/08; 4/8/08
• BLAs only: Facility information review(s) (indicate dates)	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	See 11/7/08 review, page 107

<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>)	
❖ NDAs: Methods Validation	<input checked="" type="checkbox"/> Completed See 11/7/08 review, page 10 <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) 	Date completed: 11/12/08 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> • BLAs: <ul style="list-style-type: none"> ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (<i>date completed must be within 60 days prior to AP</i>) 	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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

/s/

Dawn Williams

12/18/2008 12:59:33 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-320

INFORMATION REQUEST LETTER

Galderma Laboratories, L.P.
Attention: Paul Clark
Director, Regulatory Affairs
14501 North Freeway
Fort Worth, TX 76177
USA

Dear Mr. Clark:

Please refer to your February 8, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Epiduo Gel (adapalene/benzoyl peroxide) 0.1%/2.5%.

We are reviewing the Clinical section of your submission and have the following information request. We request your response by close of business Tuesday, November 4, 2008.

Provide a pediatric plan with attention to studies for subjects ages 9 to 12 years. You have not provided any substantiation to support a waiver for pediatric patients below the age of 12.

If you have any questions, call Dawn Williams, at 301-796-0155.

Sincerely,

{See appended electronic signature page}

LT Dawn Williams, RN, BSN, US PHS
Regulatory Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Dawn Williams
10/31/2008 07:07:51 AM

505(b)(2) ASSESSMENT FORM

GENERAL INFORMATION

1. Is this application for a drug that is an "old" antibiotic as described in the Guidance to Industry, Repeal of Section 507 of the Federal Food, Drug and Cosmetic Act? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES NO

If "YES," proceed to question #3.

2. Is this application for a recombinant or biologically-derived product and/or protein or peptide product?

YES NO

If "YES "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

3. List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Published Literature	Nonclinical Data

4. Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The applicant submitted the appropriate nonclinical bridging studies that were requested by the Agency (repeat-dose dermal toxicity studies with proposed drug in rats and dogs).

RELIANCE ON LISTED DRUG(S)

5. Does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #12.

6. Name of listed drug(s) referenced by the applicant and NDA/ANDA #(s):

Name of Drug	NDA/ANDA #

7. If this is a supplement, does the supplement reference the same listed drug(s) as the original (b)(2) application?

YES NO

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

8. Were any of the listed drug(s) referenced by the applicant:

a. Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

b. Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

c. Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d. Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d.1.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

1. Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9. Describe the change from the listed drug(s) referenced by this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

10. (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO," to (a) proceed to question #12.

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

- (c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If "YES" and there are no additional pharmaceutical equivalents listed, proceed to question #17.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in

NDA 22-320

the Orange Book. Please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11. (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #13.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #17.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

RELIANCE ON PUBLISHED LITERATURE

12. (a) Does the application rely on published literature to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If "NO," proceed to question #13.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) drug product?

YES NO

*If "NO", proceed to question #13
If "YES", list the listed drug(s) identified by name.*

- (c) Are the drug product(s) listed in (b) referenced as the listed drug(s)?

YES NO

If "NO", list what drug product(s) are cited in the literature necessary to support the approval.

PATENT CERTIFICATION/STATEMENTS

13. List the patent numbers of all patents listed in the Orange Book for the listed drug(s) referenced by the applicant.

Patent number(s): n/a

14. Did the applicant address (with an appropriate certification or statement) all of the patents listed in the Orange Book for the referenced listed drug(s)?

YES NO

If "NO", list which patents were not addressed by the applicant.

Patent number(s): n/a

15. Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application solely based on published literature that does not cite a specific innovator product or for an "old antibiotic" (see question 1.))
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

YES NO

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES NO

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

YES NO

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES NO

- Written statement from patent owner that it consents to an immediate effective date of approval (applicant must also submit paragraph IV certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

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

/s/

Dawn Williams
10/3/2008 10:49:19 AM
CSO

Maria Walsh
10/3/2008 10:55:43 AM
CSO

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # 22-320 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: TRADENAME Established/Proper Name: adapalene 0.1%/benzoyl peroxide 2.5% Dosage Form: Gel Strength: 45g		
Applicant: Galderma Laboratories, L.P. Agent for Applicant (if applicable):		
Date of Application: 2/8/08 Date of Receipt: 2/8/08 Date clock started after UN:		
PDUFA Goal Date: 12/8/08		Action Goal Date (if different):
Filing Date: 4/8/08 Date of Filing Meeting: 3/24/08		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 4		
Proposed Indication(s): Acne Vulgaris		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>Refer to Appendix A for further information.</i>		
Review Classification:		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical disease Priority review voucher submitted
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		
Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

b(4)

Collaborative Review Division (if OTC product):	
List referenced IND Number(s): 67801	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? Check the AIP list at: http://www.fda.gov/ora/compliance_ref/aip.html If yes, explain: If yes, has OC/DMPQ been notified of the submission? Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status Comments:	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
Exclusivity	
Does another product have orphan exclusivity for the same indication? Check the <i>Electronic Orange Book</i> at: http://www.fda.gov/cder/ob/default.htm If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments:</p>	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES # years requested: 3 <input type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	<p><input type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>

<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i></p>		<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO												
<p>If yes, please list below:</p> <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>			Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration								
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration											
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>														
<p>Format and Content</p>														
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p>Comments:</p>		<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)												
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>														
<p>If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments:</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO												
<p>If electronic submission, does it follow the eCTD guidance? (http://www.fda.gov/cder/guidance/7087rev.pdf)</p> <p>If not, explain (e.g., waiver granted):</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO												

<p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Patent Information (NDAs/NDA efficacy supplements only)	
<p>Patent information submitted on form FDA 3542a?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Debarment Certification	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

sign the certification.	
<i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	
Comments:	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)	<input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>) <input type="checkbox"/> YES <input type="checkbox"/> NO
<i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	
Financial Disclosure	
Financial Disclosure forms included with authorized signature?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i>	
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	
Comments:	
Pediatrics	
PREA	
<i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	
Are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
If no , is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <i>If no, request in 74-day letter.</i> If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	

BCPA (NDAs/NDA efficacy supplements only):	
Is this submission a complete response to a pediatric Written Request? <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Comments:	
Prescription Labeling	
Check all types of labeling submitted. Comments:	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments: SPL submitted 9/10/08	
Package insert (PI) submitted in PLR format? <i>If no, was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request? If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments: sent 8/26/08	
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
REMS consulted to OSE/DRISK?	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments: sent 8/26/08	

OTC Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments: End-of Phase 2 meeting minutes 12/12/05.</p>	<input checked="" type="checkbox"/> YES Date(s): <input type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments: Date of Pre-NDA meeting 11/28/07.</p>	<input checked="" type="checkbox"/> YES Date(s): <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

**Appears This Way
On Original**

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this page is the manifestation of the electronic signature.**

/s/

Dawn Williams
10/3/2008 10:13:42 AM
CSO

Maria Walsh
10/3/2008 10:20:39 AM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-320

INFORMATION REQUEST LETTER

Galderma Laboratories, L.P.
Attention: Paul Clark
Director, Regulatory Affairs
14501 N Freeway
Fort Worth, TX 76177

Dear Mr. Clark:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (adapalene 0.1%/benzoyl peroxide 2.5%) Gel

We are reviewing the Clinical section of your submission and have the following information request. We request a written response within seven days of receipt in order to continue our evaluation of your NDA.

Please provide the number of patients seen by each site, or the number of patients seen by each principal investigator for the two pivotal studies, 1809, and 18087.

If you have any questions, call me at 301-796-0155.

Sincerely,

Dawn Williams, RN, BSN
Regulatory Project Manager
Division of Dermatology and Dental Products, HFD-540
Office of New Drugs III
Center for Drug Evaluation and Research

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

/s/

Dawn Williams
9/15/2008 06:45:06 AM
CSO

Dear Mr. Clark

We are reviewing the Clinical Pharmacology section of your new drug application for Adapalene 0.1%/Benzoyl Peroxide 2.5% Gel and have the following information request:

Please submit the SAS Datasets for Study Report No. RD.06.SRE.18097. The datasets that were previously submitted as SRE 18097 contained only information for Study SRE 18094.

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this page is the manifestation of the electronic signature.**

/s/

Maria Walsh
7/8/2008 02:30:41 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-320

Galderma Laboratories, L.P.
Paul Clark
Director, Regulatory Affairs
14501 North Freeway
Fort Worth, Texas 76177

Dear Mr. Clark:

Please refer to your new drug application (NDA) dated February 8, 2008, received February 8, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for EPIDUO™ (adapalene 0.1% and benzoyl peroxide 2.5%) gel.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is December 8, 2008.

During our filing review of your application, we identified the following potential review issues:

- 1.) The effect of the product on cardiac repolarization has not been adequately addressed. Data from a thorough QT/QTc study or a rationale for why such a study is not needed is not included in your application.

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

We also request that you submit the following information:

- A. Information to assess the effect of the product on cardiac repolarization
- B. A rationale for assuming the applicability of foreign data in the submission to the U.S. population

- C. A rationale with supportive information to justify your request for a pediatric waiver for patients ages 12 and under
- F. A statement of Good Clinical Practice for all of the clinical studies
- G. Representative samples (3 units for each size) with rheograms (viscosity versus shear rate and shear stress versus shear rate)
- H. A mock-up for each container/carton label

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

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

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable. We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied. We note that you have submitted pediatric studies with this application for pediatric patients 12 to 17 years of age. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for those age groups.

If you have any questions, call Kalyani Bhatt, Regulatory Project Manager, at (301) 796-2110.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Susan Walker
4/21/2008 06:05:55 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 67,801

Galderma Laboratories, L.P.
Attention: Paul Clark, Director Regulatory Affairs
14501 N. Freeway
Fort Worth, Texas 76177

Dear Mr. Clark:

Please refer to your Investigational New Drug Application (IND) file for Adapalene 0.1%/Benzoyl Peroxide 2.5% Gel for the indication of the topical treatment of acne vulgaris.

We also refer to the pre-NDA meeting between representatives of your firm and the FDA on November 28, 2007. The purpose of the meeting was to discuss CMC and clinical data, and to obtain advice regarding the format and organization of the data in the NDA.

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 Catherine Carr, Regulatory Project Manager, at (301) 301-796-2311.

Sincerely,

{See appended electronic signature page}

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

Enclosure:

MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 28, 2007
TIME: 9:30 am
LOCATION: White Oak, Room 1313
APPLICATION: IND 67,801
DRUG NAME: Adapalene 0.1%/Benzoyl Peroxide 2.5% Gel
TYPE OF MEETING: Pre-NDA (Type B)

MEETING CHAIR: Susan J. Walker, M.D., F.A.A.D./Director, Division of Dermatology and Dental Products (DDDP)

MEETING RECORDER: Catherine Carr/Regulatory Health Project Manager, DDDP

FDA ATTENDEES: (Title and Office/Division)

Susan Walker, M.D., F.A.A.D./Director, DDDP
Markham Luke, M.D., Ph.D./Team Leader, Clinical, DDDP
David Kettl, M.D./Medical Officer, DDDP
Jane Liedtka, M.D./Medical Officer, DDDP
Paul Brown, Ph.D./Pharmacology Toxicology Team Leader, DDDP
Kumar Mainigi, Ph.D./Toxicology Reviewer, DDDP
Catherine Carr, M.S./Regulatory Health Project Manger, DDDP
Shulin Ding, Ph.D./Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment, Division of Pharmaceutical Assessment II (DPA-II)
Jane Chang, Ph.D./CMC Reviewer, Office of New Drug Quality Assessment, Division of Pharmaceutical Assessment II (DPA-II)
Abimbola Adebowale, Ph.D./Pharmacokinetics Reviewer, Office of Clinical Pharmacology, Division of Pharmaceutical Evaluation III (DPE-III)
Mohamed Alesh, Ph.D./Biostatistics Team Leader, Division of Biometrics III (DB-III)
Clara Kim, Ph.D./Biostatistcian, Office of Biostatistics, Division of Biometrics III (DB-III)

EXTERNAL CONSTITUENT ATTENDEES (Galderma Laboratories):

Michael Graeber, M.D./Head of U.S. Development
Oliver Watts, Ph.D., Director of Regulatory Affairs
Paul Clarck/Director, U.S. Regulatory Affairs
Marie-Line Abou Chacra-Vernet, Ph.D., Pharm.D./Corporate Regulatory Affairs
Judi Gidner/Clinical Project Manager
Yin Liu, Ph.D./Head of Biometrics
Djemila Kohil, MSc/Pharmaceutics
Gay Bouvier/Pharmacology Toxicology Representative

BACKGROUND:

The sponsor submitted a briefing document, dated October 24, 2007, which included background information and questions for discussion. Preliminary responses were sent to the sponsor on November 26, 2007.

The sponsor submitted a request for guidance, dated June 12, 2007 (SN:056), regarding the need for data to establish bioequivalence between clinical materials used during clinical trials. The sponsor's question presented in SN:056 was also presented in the pre-NDA briefing document as CMC Question #2. The Agency's response is provided in the minutes below.

MEETING OBJECTIVES:

The purpose of the meeting was to discuss the CMC and clinical studies to be submitted to the NDA. In addition, the sponsor sought to obtain advice regarding the format and organization of the data for submission to the NDA.

DISCUSSION POINTS:

Regulatory:

It appears that you will be referring to information to support your application from studies that were not conducted by or for you. Consequently, this NDA may be filed under section 505(b)(2) of the FD&C Act. See comments about 505(b)(2) applications below:

1. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/cder/guidance/index.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdln0001-vol1.pdf>)).
2. You may rely upon studies not conducted by or for you and to which you have not obtained a right of reference or use (i.e., published literature or the Agency's finding of safety and/or effectiveness for a listed drug) to support your nonclinical development program.
3. If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for

approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

4. If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.
5. You may cross-reference relevant studies in your NDAs for adapalene that were conducted by or for you or to which you have obtained a right of reference or use. If you own all the data or have a right of reference to data that you are relying upon for approval, then your application may not be a 505(b)(2) application.
6. Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a duplicate of that drug and eligible for approval under section 505(j) of the act, we may refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

Meeting Discussion:

The sponsor indicated that they will rely on published literature for benzoyl peroxide and submit NDA as a 505(b)(2) application.

The company was reminded to indicate the reference listed drug (RLD) in the NDA if it is cited in the published literature.

Chemistry, Manufacturing and Controls:

Question 1:

Concurrence is sought that the Agency considers these specifications appropriate for benzoyl peroxide drug substance.

Response:

Justification, e.g. batch analysis for lots used in toxicology and clinical studies, should be provided in the NDA for the proposed limits for benzoic acid, Γ

b(4)

Meeting Discussion:

The sponsor agreed to include specifications in the NDA.

Question 2:

Concurrence is sought that the Agency agrees that no additional tests, such as In Vitro Release Testing, should be necessary to establish equivalence of the materials used in the clinical studies.

Response:

If the clinical trials used to demonstrate safety and efficacy used the to-be-marketed formulation, then additional data, e.g. IVRT, will not be necessary, given the fact that clinical supply for Study 18087 was manufactured at the designated commercial manufacturing site (Canada site).

Question 3:

The Sponsor intends to propose tightened limits for benzoic acid content (benzoyl peroxide main degradation product): NMT — instead of NMT — this limit being considered unacceptable by the Agency. **b(4)**

Concurrence is sought that the proposed limit of NMT — based on stability data, is acceptable. **b(4)**

Response:

The adequacy of the proposed limit (NMT — for benzoic acid content in the drug product is a review issue. We would consider data/information from various aspects such as batch analysis, primary and supporting stability batches, levels tested in non-clinical/clinical studies, pharmacopeias, etc. Please provide justification for the proposed limit in the NDA. **b(4)**

Meeting Discussion:

The sponsor agreed to submit justification in the NDA.

Question 4:

Regarding stability, as requested at End of Phase 2 meeting, results of a photostability study performed under "in-use" light conditions will be submitted in the NDA. The application of the protocol agreed by the FDA show no degradation of the product under house light.

Concurrence is sought that this issue is closed.

Response:

The "in use" photostability protocol submitted in the July 26, 2007 amendment (SN: 060) is acceptable. Whether this issue is satisfactorily resolved is a review issue. Please provide the study report in the NDA.

Meeting Discussion:

The sponsor agreed to submit the study report in the NDA.

Question 5:

Concurrence is sought that this set of stability data will adequately support the 24-month shelf-life proposed for the commercial batches of Adapalene/Benzoyl Peroxide Gel manufactured by GPCI with benzoyl peroxide from both sources. b(4)

Response:

The actual expiration date to be granted is a review issue. If acceptable stability data for critical product quality attributes, e.g. degradation products and homogeneity, etc. for the GDI batches are submitted in the NDA, these batches, along with the proposed 4 GPCI batches, could be used in establishing the shelf-life of the drug product. Otherwise, stability data from the GDI batches will only be supportive information. In such case, the proposed stability data, i.e. 1 batch of 18 months and 3 batches of 3 months, for the four GPCI batches will be insufficient to support the proposed 24-month shelf life. A minimum of 12-month stability data from three primary stability batches is recommended at the time of submission per ICH Q1A.

You are reminded that an agreement was reached in the December 12, 2005 End of Phase 2 meeting to incorporate the homogeneity test in the stability protocol.

We acknowledge your committed CMC information to support as an alternative supplier for benzoyl peroxide. It is our understanding that the information would include impurity profile, particle size distribution, characterization of benzoyl peroxide crystal structure, and drug product stability, etc. At this time, we do not have other information request items on this matter. We will review the data pertinent to this issue upon NDA submission to decide on the acceptance of as the second supplier. b(4)

Meeting Discussion:

The sponsor will provide data in the NDA.

Additional CMC Comments:

The drug product specification should include a test and acceptance criterion for intra-tube content uniformity. You are reminded that an agreement was reached during the December 12, 2005 End of Phase 2 meeting for inclusion of this test.

Pharmacology/Toxicology:

There were no Pharmacology/Toxicology questions identified in this briefing document.

Clinical Pharmacology:

There were no specific clinical pharmacology questions identified in this briefing document. However, we have the following comments:

1. We acknowledge the summary of your evaluation of the systemic exposure of the adapalene component of your product under maximized conditions in study 2685 (10-day pharmacokinetic study in the EU) and, study 18097 (a 30-day pharmacokinetic study in

the US) in patients with acne vulgaris. We also note that you intend to submit two well controlled studies (18094 and 18087) that were conducted with clinical supplies that were manufactured at 2 different manufacturing sites in France (industrial development site) and, Canada (proposed commercial manufacturing site). These two studies are intended to support the determination of the effectiveness and safety of the drug product.

Meeting Discussion:

The sponsor indicated that the above comment reflects their current situation.

2. We acknowledge that the PK study 18097 was conducted with the same clinical trial material (manufactured in France) as that used in one of the clinical studies (18094). We also note that there is no PK information using the clinical trial material manufactured in Canada. In general, PK information from the to-be-marketed formulation is required. Please provide justification for lack of information to this regard.
3. Please provide adequate information on how the effect of adapalene on the percutaneous penetration of benzoyl peroxide was evaluated in your NDA submission.

Clinical:

Question 1:

Concurrence is sought that the Agency considers the completed clinical program is adequate to file a New Drug Application.

Response:

Please refer to the comments conveyed at the End of Phase (EOP) 2 meeting, dated December 12, 2005. The utility of RD.06.SPE.18094 (Phase 2) for establishing safety and efficacy is a review issue. Also, the status of the sponsor's second Phase 3 study, RD.06.SPR.18088, which was submitted for Agency's review as SN033 (stamp date, August 24, 2006), is not clear. Please clarify. We recommend the completion of this study prior to submitting the NDA.

Please clarify whether Study RD.06.SPR.18094 which was discussed at the EOP 2 meeting as a phase 2 study with concerns regarding adequacy due to blinding among other issues is the same the study as RD.06.SPR.18094, which you propose to be submitted as one of the two adequate and well-controlled trials in this submission.

The adequacy of the dermal safety evaluation will also be a review issue. The numbers of subjects in the phototoxicity study (25 instead of 30), photosensitization study (33 instead of 45), and cumulative irritation study (25 instead of 35) are less than those typically recommended by the Division.

Meeting Discussion:

The sponsor clarified that no unblinding of data was performed in Study RD.06.SPR.18094 prior to database lock.

Additional Clinical Comments:

1. With regard to format and content, it is acceptable to provide a combined safety database; however, safety information for each study should also be presented separately.
2. All Case Report Forms (CRFs) should be submitted from the two safety and efficacy studies and electronic links for:
 - a) all Serious AEs
 - b) all Severe AEs
 - c) all patients who discontinued for whatever the reason (not just because of adverse events)
3. Please also submit annotated tabulations for clinical adverse events. Please refer to the Final Guidance for Industry: Providing Regulatory Submissions in Electronic Format-- Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications.
4. A request for a waiver for pediatric studies with a suitable justification for each age group should be submitted with the NDA.
5. Please submit study photographs for review with the NDA submission.

Biostatistics:

Question 1:

Concurrence is sought that the statistical analyses plan and format of the statistical tables to be presented in the ISE and ISS of the NDA are appropriate to support submission of an NDA.

Response:

Seeking concurrence of the statistical analysis plan is meaningful at the protocol development stage. As the study has already been completed, any additional or modified analyses conducted would be post-hoc. We provided comments on the protocol of Study SPR.18087. Efficacy will be evaluated using the protocol that incorporated our comments.

Regarding Study SRE.18094, the statistical analysis plan needs to be pre-specified. Therefore, it is not appropriate to use the statistical methodology specified in SPR.18087 to SRE.18094 in a post-hoc manner.

The statistical tables to be presented in the ISE and ISS appear to be appropriate.

Meeting Discussion:

The sponsor was reminded to confirm readability of electronic datasets prior to NDA submission and to schedule a meeting with the FDA electronic submission group to discuss the electronic submission.

Additional Statistical Comments

The sponsor should provide the Agency with SAS transport files in electronic form. The data sets should include demographic and baseline data as well as efficacy and safety data. Data Sets should include:

- a. The database for each of the Phase 3 studies should include both raw variables (from the CRF) and derived variables suitable for conducting primary and secondary efficacy analyses.
- b. Each data set should include the treatment assignments. For each of the primary and secondary endpoints, an indicator variable that denotes whether measurements are actual or imputed should be included.
- c. The submission should include adequate documentation for the data sets including definitions of each variable in the data set, formulas for derived variables and decodes for any factor variables so that all categories are well-defined in the documentation.
- d. In addition to the electronic data sets, the NDA submission should include the following items:
 - o Study protocols including the statistical analysis plan, protocol amendments and their dates.
 - o The generated treatment assignment lists and the actual treatment allocations (along with date of enrollment) from the trials.

Project Management:

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 the information submitted to the IND or NDA might identify additional comments or information requests.
2. Per 21 CFR 54.3 and 21 CFR 54.4, an NDA applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests.
3. We remind you of the Pediatric Research Equity Act of 2007 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. 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.

5. You are reminded that effective June 30, 2006, all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for additional details).

Linked Applications	Sponsor Name	Drug Name
IND 67801	GALDERMA LABORATORIES INC	ADAPALENE/BENZOYL PEROXIDE GEL

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

/s/

CATHERINE A CARR
12/11/2007

SUSAN J WALKER
12/13/2007



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 67,801

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

C. E. SHANK

JAN 20 2006

Regulatory Affairs

Dear Ms. Shrank:

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 Felicia 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 crystalline form is required in the specifications if multiple crystalline forms exist.

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

Sponsor's Question:

2. The drug substance supplier, 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.

b(4)

The sponsor agreed.

Comments for Finished Drug Product Release Specifications:

1. The acceptance criterion of NMT — for benzoic acid degradant is not acceptable. A lower limit should be established based on real time stability data.

b(4)

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: — has been acceptable traditionally. A tighter limit for total molds and yeasts count may be requested per Pharmacopeial Forum [Vol 29(5)].

b(4)

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 information will be submitted in the NDA.

The

b(4)

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 _____ 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 _____. The sponsor has responded that the dosing regimen for the combination drug product requires that the product be applied once daily in the _____ after cleansing. The sponsor should address whether the _____ major degradants, which were observed from irradiation of a _____ 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.

b(4)

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 Simulgel @ 600PHA
- e. Additional information about the container/closure of _____ tubes? _____ For example, are all of them _____ tubes?

b(4)

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.

Biostatistics 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.18094 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.06.SPR.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 be 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.13087 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 to enroll 80 centers which implies about 20 subjects per center (i.e. 5 subjects per arm) which is clearly much smaller than 10 subjects per treatment arm per center. 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 30-40 centers. Increasing the number of centers to 80 implies that each center

will enroll approximately 5 subjects per treatment arm per center. 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
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