CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-320

CHEMISTRY REVIEW(S)

NDA 22-320

Epiduo™(adapalene/benzoyl peroxide)Gel 0.1%/2.5%

Galderma Laboratories

Maria Ysern, MSc.
Review Chemist

Office of New Drug Quality Assessment
Division II, Branch III

CMC REVIEW OF NDA 22-320
For the Division of Dermatologic and Dental Products (HFD-540)

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B. Description of How the Drug Product is Intended to be Used: 8

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1. NDA 22-320

2. REVIEW #: 3

3. REVIEW DATE: Dec 05, 2008

4. REVIEWER: Maria Ysern, MSc.

5. PREVIOUS DOCUMENTS:
IND 67,801

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA Submission	8-FEB-2008
BZ Amendment	25-APR-2008
BZ Amendment	06-JUN-2008
SU Amendment	06-JUN-2008
BC Amendment	19-AUG-2008
BL Amendment	10-SEP-2008
Labeling Amendment	08-Dec-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Galderma Laboratories, LP
Address:	14501 North Freeway Fort Worth, TX 76177
Representative:	Paul Clark, Director regulatory Affairs
Telephone:	817-961-5356

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Epiduo™ Gel
b) Non-Proprietary Name: Adapalene/Benzoyl Peroxide
c) Code Name/# (ONDQA only): n/a
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: Type 4
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: The drug product is a fixed dose combination for the topical treatment of *acne vulgaris.*

Adapalene is a naphtoic acid derivative with retinoid-like activity and anti-inflammatory properties.
Benzoyl peroxide is a powerful oxidizing agent with a bactericidal effect.

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: Tubes for marketing are 45 g. [redacted] b(4)

13. ROUTE OF ADMINISTRATION: Topical

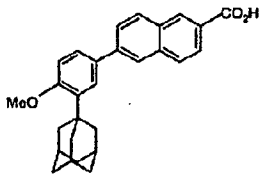
14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__√__Not a SPOTS product

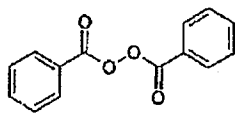
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

1. Adapalene:



Molecular Formula: $C_{28}H_{28}O_3$
Molecular Weight: 412.5

2. Benzoyl Peroxide:



Molecular Formula: $C_{14}H_{10}O_4$ (anhydrous)
Molecular Weight: 242.23 (anhydrous)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
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—	II	—	Benzoyl Peroxide	3	Adequate	July 31, 2008 Maria Ysern	
—	II	—	Benzoyl peroxide	3	Adequate	Dr. Benjamin Lim 03/04/2008	

b(4)

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7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	67,801	

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	Nov 12, 2008	Adams, Shawante
Pharm/Tox	N/A		
Biopharm	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMETS			
EA	Categorical exclusion is granted	Nov 17, 2008	Maria Ysern
Microbiology	N/A		

Executive Summary Section

The CMC Review for NDA 22-320

The Executive Summary
I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. The labels have adequate information as required. An "Acceptable" site recommendation from the Office of Compliance has been made. Therefore, from the CMC perspective, this NDA is now recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable : None.

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance:
See Review #1

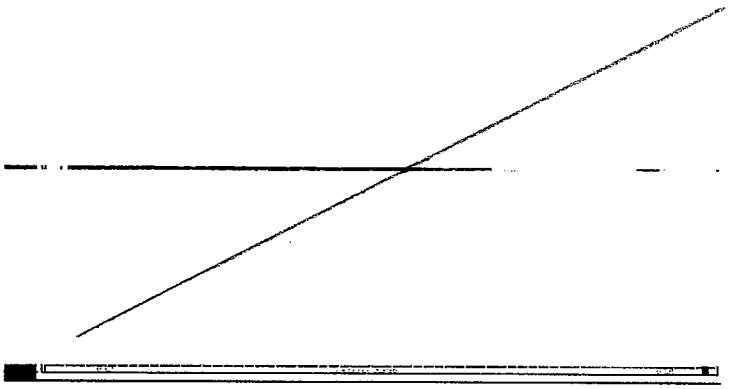
(2) Drug Product:
See Review # 1

Labeling and package insert:

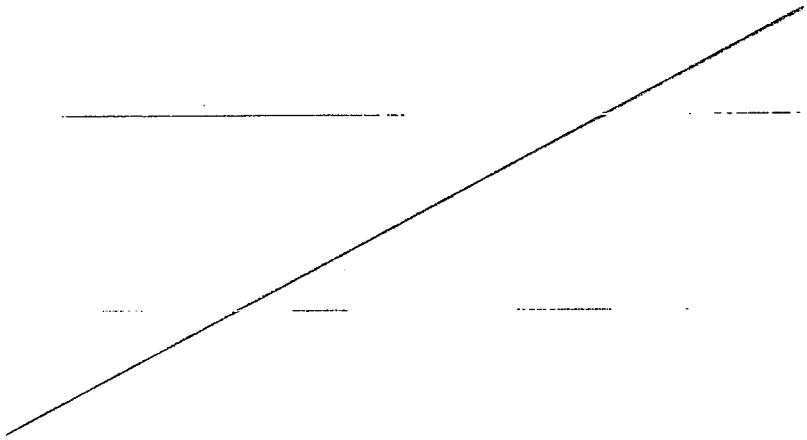
The following corrections were done by the sponsor:
1. The strength was placed outside the established name, which is the correct location.
2. The size of the established name was not adequate and has been corrected to be ½ of the proprietary name
3. In the non-proprietary name there is the word "and" instead of a "/" between the two components, and this is acceptable.
4. The term "nightly" was deleted to make the dosage and administration section identical to that in the package insert

***Evaluation**: The corrections done to the label are satisfactory. The label is now adequate.*

A copy of the correct tube and carton label is provided below:



b(4)



b(4)

B. Description of How the Drug Product is Intended to be Used:

See Review # 1

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent

product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

All facilities have acceptable site recommendations.

All labels have the required information

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)
Maria Ysern, MSc., Review Chemist, Branch III, Division II, ONDQA

B. Endorsement Block:

(See appended electronic signature page)
Moo-Jhong Rhee, PhD, Branch Chief, Branch III, Division II, ONDQA

C. CC Block: entered electronically in DFS

Attachment:

4-DEC-2008 FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application: NDA 22320/000
Org Code : 540
Priority : 4S
Brand Name: ADAPALENE 0.1% BENZOYL PEROXIDE 2.5% GEL
Stamp Date : 08-FEB-2008
PDUFA Date : 08-DEC-2008
Action Goal:
District Goal: 09-OCT-2008

Sponsor: GALDERMA LAB
NO CITY, XX
Estab. Name:
Generic Name:
Dosage Form: (GEL)
Strength : 0.1% AND 2.5%

FDA Contacts:	S. GOLDIE	Project Manager	301-796-2055
	M. YSERN	Review Chemist	301-796-1487
	S. DING	Team Leader	301-796-1349

Overall Recommendation: ACCEPTABLE on 12-NOV-2008by S. ADAMS (HFD-325)

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

/s/

Maria Ysern
12/8/2008 01:38:37 PM
CHEMIST

Moo-Jhong Rhee
12/8/2008 01:40:53 PM
CHEMIST
Chief, Branch III

CMC REVIEW

NDA 22-320

Epiduo™(adapalene/benzoyl peroxide)Gel
0.1%/2.5%

Galderma Laboratories

Maria Ysern, MSc.
Review Chemist

Office of New Drug Quality Assessment
Division II, Branch III

CMC REVIEW OF NDA 22-320
For the Division of Dermatologic and Dental Products (HFD-540)

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B. Description of How the Drug Product is Intended to be Used: 7

C. Basis for Approvability or Not-Approval Recommendation 7

III. Administrative 8

CMC Review Data Sheet

1. NDA 22-320

2. REVIEW #: 2

3. REVIEW DATE: Nov 17, 2008

4. REVIEWER: Maria Ysern, MSc.

5. PREVIOUS DOCUMENTS:
IND 67,801

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA Submission	8-FEB-2008
BZ Amendment	25-APR-2008
BZ Amendment	06-JUN-2008
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BC Amendment	19-AUG-2008
BL Amendment	10-SEP-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Galderma Laboratories, LP
Address:	14501 North Freeway Fort Worth, TX 76177
Representative:	Paul Clark, Director regulatory Affairs
Telephone:	817-961-5356

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Epiduo™ Gel
b) Non-Proprietary Name: Adapalene/Benzoyl Peroxide
c) Code Name/# (ONDQA only): n/a
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: Type 4
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: The drug product is a fixed dose combination for the topical treatment of *acne vulgaris*.
Adapalene is a naphtoic acid derivative with retinoid-like activity and anti-inflammatory properties.

CMC Review Data Sheet

Benzoyl peroxide is a powerful oxidizing agent with a bactericidal effect.

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: Tubes for marketing are — 45 g, ⌐ ⌊ b(4)

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
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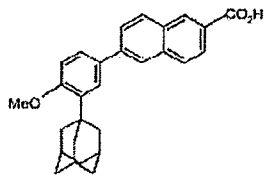
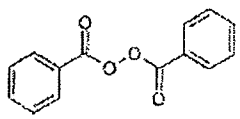


Molecular Formula: $C_{28}H_{28}O_3$
Molecular Weight: 412.5

2. Benzoyl Peroxide:



Molecular Formula: $C_{14}H_{10}O_4$ (anhydrous)
Molecular Weight: 242.23 (anhydrous)

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
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—	II	—	Benzoyl Peroxide	3	Adequate	July 31, 2008 Maria Ysern	
—	II	—	Benzoyl peroxide	3	Adequate	Dr. Benjamin Lim 03/04/2008	

b(4)

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7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	67,801	

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	Nov 12, 2008	Adams, Shawante
Pharm/Tox	N/A		
Biopharm	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMETS			
EA	Categorical exclusion is granted	Nov 17, 2008	Maria Ysern
Microbiology	N/A		

Executive Summary Section

The CMC Review for NDA 22-320

The Executive Summary
I. Recommendations

A. Recommendation and Conclusion on Approvability
This NDA has provided sufficient information to assure the identity, strength, purity and quality of the drug product. An "Acceptable" overall recommendation from the Office of Compliance has been received for all the sites inspected. However, labeling issues are still pending. Therefore, from the CMC perspective, this NDA is not recommended for approval until labeling issues are resolved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable : None.

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance:
See Review #1

(2) Drug Product:
See Review # 1

B. Description of How the Drug Product is Intended to be Used:
See Review # 1

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

All facilities have acceptable site recommendations.

The pending labeling issue is the following:

The established name should be revised in all labels as follows:

Epiduo
(adapalene/benzoyl peroxide) gel
0.1%/2.5 %

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)
Maria Ysern, MSc., Review Chemist, Branch III, Division II, ONDQA

B. Endorsement Block:

(See appended electronic signature page)
Moo-Jhong Rhee, PhD, Branch Chief, Branch III, Division II, ONDQA

C. CC Block: entered electronically in DFS

Attachment:

4-DEC-2008 FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application: NDA 22320/000 Sponsor: GALDERMA LAB
Org Code : 540 NO CITY, XX
Priority : 4S
Brand Name: ADAPALENE 0.1% BENZOYL
Stamp Date : 08-FEB-2008 PEROXIDE 2.5% GEL
PDUFA Date : 08-DEC-2008 Estab. Name:
Action Goal: Generic Name:
District Goal: 09-OCT-2008 Dosage Form: (GEL)
Strength : 0.1% AND 2.5%

FDA Contacts:	S. GOLDIE	Project Manager	301-796-2055
	M. YSERN	Review Chemist	301-796-1487
	S. DING	Team Leader	301-796-1349

Overall Recommendation: ACCEPTABLE on 12-NOV-2008by S. ADAMS (HFD-325)

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

/s/

Maria Ysern
12/4/2008 03:44:46 PM
CHEMIST

Moo-Jhong Rhee
12/4/2008 03:50:27 PM
CHEMIST
Chief, Branch III

CMC REVIEW

NDA 22-320

Epiduo™(adapalene/benzoyl peroxide)Gel 0.1%/2.5%

Galderma Laboratories

Maria Ysern, MSc.
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Office of New Drug Quality Assessment
Division II, Branch III

CMC REVIEW OF NDA 22-320
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B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 8

II. Summary of CMC Assessments 8

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P.6 Reference Standards or Materials 86
P.7 Container Closure System 86
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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 22-320

2. REVIEW #: 1

3. REVIEW DATE: Nov 17, 2008

4. REVIEWER: Maria Ysern, MSc.

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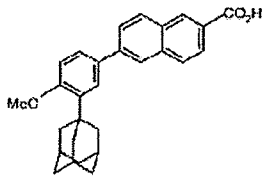

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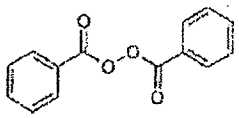
2. Benzoyl Peroxide:



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DMETS			
EA	Categorical exclusion is granted	Nov 17, 2008	Maria Ysern
Microbiology	N/A		

Executive Summary Section

The CMC Review for NDA 22-320

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
This NDA has provided sufficient information to assure the identity, strength, purity and quality of the drug product. Therefore, from the view point of CMC, this NDA can be approved pending satisfactory results from the site inspections and final labeling corrections.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable : None.

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance:

Two drug substances are used in this drug product:

Adapalene, a naphtoic acid derivative and retinoid analogue with actions similar to those of retinoids. It is commonly used in the topical treatment for the mild to moderate acne.
Three different formulations are currently marketed in the USA: Differin® gel (NDA 020-380), Differin® cream 0.1% (NDA 020-748) and Differin® gel 0.3% (NDA 021-753). For detailed information on adapalene refer to —— DMF —— b(4)

Benzoyl peroxide is commonly used as antimicrobial and keratolytic agent in the commercial production of topical drug products, with more than 20 different prescriptions and over the counter drug products marketed worldwide.
It is marketed in different topical dosage forms including cream, gel and solution formulations, each containing either 2.5, 5, or 10% w/w (respectively 25, 50 and 100 mg/g) of the drug substance.

Refer to ⌜ ⌟ for additional information. b(4)

(2) Drug Product:

Adapalene/Benzoyl Peroxide Gel is a white to very pale yellow opaque aqueous gel, containing 0.1% w/w (1 mg/g) of adapalene and 2.5% w/w (25 mg/g) of benzoyl peroxide, as the drug substances, dispersed in an aqueous gel dosage form, for the topical treatment of *acne vulgaris*.
The active ingredients in adapalene/benzoyl peroxide gel were selected to minimize the potential chemical interactions that could produce unexpected degradation products.
The absence of reactivity of adapalene in the presence of the oxidizing agent, benzoyl peroxide, was confirmed by the data when both drug substances are in suspension at concentrations corresponding to those of the drug products. The absence of reactivity of adapalene in the presence of the oxidizing agent, benzoyl peroxide, is supported by the whole set of stability data generated for the drug product. It is concluded that adapalene is chemically compatible with benzoyl peroxide under normal conditions of storage.

The excipients present in the combination formulation are: Edetate disodium ⌜ ⌟propylene glycol ⌜ ⌟ and ⌜ ⌟ and Poloxamer 124 ⌜ ⌟ Glycerin is ⌜ ⌟ and sodium docusate as ⌇ —— Purified water is used —— All the excipients with exception of the gelling agent (Simulgel 600 PHA) are controlled in accordance with USP monograph, the identity and weight of the raw materials are checked.
The main difference between adapalene/benzoyl peroxide gel and the previously approved adapalane 0.1% gel and benzoyl peroxide 2.5% gel pertains to the gelling agent. ⌜ b(4)

⌟ This excipient is used at a —— concentration in adapalene/benzoyl peroxide gel formulation.

⌜

b(4)

⌟

A preservative system is not necessary in the combination formulation, given the bactericidal properties of benzoyl peroxide.
All excipients selected for the commercial formulation are described in USP/NF with exception of Simulgel 600 PHA (Full details of its manufacture, characterization and controls are provided).

The adapalene/benzoyl peroxide Gel must comply with established specification that include: description (macroscopic appearance, presence of agglomerates); identification of each active ingredient by TLC and HPLC; tests that include pH, viscosity, particle size of the two active ingredients; assay for both active ingredients as well as intratube content uniformity; degradation products limits for both adapalene and benzoyl peroxide;
and microbiology (includes total aerobic microbial count, total yeast and mold count, Pseudomonas aeroginosa and Staphylococcus aureus.

The drug product is packaged in plastic tubes ——— with a ———
[ ] head and [ ] screw closure cap from two suppliers [ ] b(4)
Tube sizes proposed for marketing are — 45 g, [ ]

The individual comparator products used as the control in the adapalene/benzoyl peroxide gel clinical studies were Adapalene Gel, 0.1% and Benzoyl Peroxide Gel 2.5%.
These comparators were also formulated with the Simulgel 600 PHA gelling system to match the combination formulation (instead of using the commercially available individual products).
The transdermal penetration of each of the individual active ingredient, both from the monads (the individual products) and from the fixed combination product, is not different to the delivery achieved with the individual commercially available products, Differin gel, 0.1% and Benzac gel, 2.5%, as confirmed by the evidence from studies conducted during the product development.
Studies were done using excised human skin (epidermis, including stratum corneum, and dermis) in a diffusion cell system to compare the liberation and penetration of the individual components of the fixed combination formulation with that of their commercial counterparts, Differin gel 0.1% and Benzac gel , 2.5% and with the comparators used in the clinical trials, Adapalene Gel, 0.1% and Benzoyl peroxide gel, 2.5%.

Based on the stability data obtained from pilot scale batches as well as the to-be marketed product, the proposed 24 month of expiration dating period is granted.

B. Description of How the Drug Product is Intended to be Used:

Epiduo Gel is indicated for the topical treatment of acne vulgaris in patients 12 years or older.
It should be applied to acne affected areas of the skin once daily, [redacted] after washing gently with non medicated cleanser
A pea-sized amount of drug product should be applied to each affected area, e.g. forehead, chin, each cheek, with the finger tips, avoiding the eyes, lips and mucous membranes. If the patient is treating acne of the trunk, a thin film should be applied to the affected area.
Exposure to sunlight and sunlights should be avoided. Sunscreen should be used when sun exposure cannot be avoided.

b(4)

Epiduo Gel is not for oral, ophthalmic, or intra vaginal use.

C. Basis for Approvability or Not-Approval Recommendation

This NDA provided adequate information on the raw material controls, manufacturing process specifications, and container /closure. Sufficient stability data was also provided to assure identity, strength, purity and quality of the drug product during its expiration dating period.
The Overall Recommendation from the Office of Compliance for all facilities involved in the manufacturing is still pending as well as the final labeling corrections.

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)
Maria Ysern, MSc., Review Chemist, Branch III, Division II, ONDQA

B. Endorsement Block:

(See appended electronic signature page)
Moo-Jhong Rhee, PhD, Branch Chief, Branch III, Division II, ONDQA

C. CC Block: entered electronically in DFS

98 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

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/s/

Maria Ysern
11/7/2008 01:13:56 PM
CHEMIST

Moo-Jhong Rhee
11/7/2008 01:52:28 PM
CHEMIST
Chief, Branch III

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division:	Division of Dermatology and Dental Products
NDA:	22-320
Applicant:	Galderma Laboratories, L.P.
Stamp Date:	Feb. 8, 2008
PDUFA Date	Dec. 8, 2008
Trademark:	Epiduo™
Established Name:	Adapalene and Benzoyl Peroxide
Dosage Form:	Gel
Route of Administration:	Topical
Indication:	Acne Vulgaris
PAL:	Shulin Ding

	YES	NO
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☒	☐

Summary and Critical Issues:

A. Summary

Galderma Laboratories is submitting a 505(b) (2) New Drug Application (NDA) for the prescription use of Epiduo™ (Adapalene 0.1%/benzoyl peroxide 2.5%) gel in the treatment of acne vulgaris. The applicant references to public literature to support this NDA.

The proposed drug substance, adapalene, is referenced to DMF — held by —— The DMF has been reviewed multiple times for multiple submissions (most recently for the approved NDA 21-753 Differin gel), and deemed adequate to support referenced submissions. b(4)

The proposed drug substance, hydrous benzoyl peroxide, is referenced to DMF — held by ——— and DMF — held by ——— DMF — was most recently reviewed on March 4, 2008 for ANDA 65-112 Erythromycin/Benzoyl Peroxide Gel, and deemed adequate to support the ANDA. DMF — has never been reviewed. b(4)

The drug product, Epiduo™ (adaplene 0.1% and benzoyl peroxide 2.5%), is a white to very pale yellow opaque aqueous gel with suspended particles of adaplene and benzoyl peroxide. The product is packaged in —— aluminum tubes with ——— closures at fill sizes of —— 45, ——— grams. b(4)

The to-be-marketed formulation is the same formulation used in Phase 3 clinical trials and registration stability batches. The formulation contains the following excipients: Simulgel 600 PHA, docusate sodium, USP; edetate disodium, USP; glycerin, USP; poloxamer 124, USP; propylene glycol, USP; and purified water, USP. All excipients are compendial except Simulgel

600 PHA, which is a mixture of polysorbate 80, sorbitan oleate, and two novel excipients (isohexadecane and a copolymer of acrylamide and sodium acryloyldimethyltaurate).

The proposed commercial manufacturing scale is The designated commercial site, Galderma Production Canada Inc., is also the manufacturing site of one Phase 3 batch. The commercial manufacturing process consists of the following steps: b(4)

Stability data provided in the initial submission to support an expiry period of 24 months at controlled room temperature with excursions permimtted between 59-86°F (15-30°C) include long term (25°C/60% RH), intermediate (30°C/65% RH), and accelerated temperature (40°C/75% RH) data from four commercial — and five pilot scale — batches. The long term data from the commercial batches are 3-18 months. Those from the pilot batches are 18-36 months. Special stability data provided in the NDA to support storage/handling/shipping of the product include data from the following studies: photostability, in-use photostability, temperature cycling, and free/thaw b(4)

B. Critical issues for review

Dosage Form Nomenclature

- The applicant proposes gel as the dosage form. To assist the assessment of dosage form, the applicant should officially submit a representative sample to the NDA with rheograms (viscosity versus shear rate and shear stress versus shear rate).

Labels

- The trade dressing for labels is not provided.

Drug Substance Hydrous Benzoyl Peroxide

- There are major manufacturing changes between the lots evaluated in clinical/ non-clinical studies and the proposed commercial lots. The lots evaluated in clinical/non-clinical studies were manufactured by — using a large scale — process. The proposed commercial lots are to be manufactured by — using a smaller scale — process or by a second vendor, — Since — scale material and — material have never been evaluated in clinical and non-clinical studies, their impurity profiles and physical properties need to be carefully reviewed and compared with the clinical lots. b(4)

Drug Substance Adapalene

- The applicant proposes no post-approval stability commitment for adapalene drug substance.

- The applicant proposes no polymorph test in the drug substance specification despite the finding of multiple polymorphs in the polymorphism investigation study. There is no monitoring of polymorph in the registration stability studies either.

Drug Product

Formulation Composition

- There is a —overage of benzoyl peroxide incorporated in the formulation to compensate the loss of drug due to degradation. Overage is not normally allowed unless it is due to manufacturing loss. b(4)

Specification

- The proposed limit for benzoic acid, the major degradant of benzoyl peroside, is quite high (NMT —). b(4)

- The proposed viscosity acceptance criterion is considered to be tentative by the applicant.

- The proposed drug product specification includes a test on agglomerates without a proposed acceptance criterion. This is unacceptable. It is unclear what the aggregates are, and how they are related to drug substances' particles. Sizing of drug substances' particles are a routine test proposed for this product.

Novel Excipient

- The formulation contains Simulgel 600 PHA, which is a mixture of polysorbate 80, sorbitan oleate, and two novel excipients (isohexadecane, and a copolymer of acrylamide and sodium acryloyldimethyltaurate). The CMC information of Simulgel 600 PHA is provided in the NDA without referencing to a DMF. The adequacy of the CMC information needs to be carefully reviewed. b(4)

Stability

- [redacted] The applicant employed a bracketing strategy to support the proposed fill sizes. The provided justification for bracketing is inadequate since no comparative information is provided regarding head space, ratio of formulation to surface area, etc. b(4)

C. Comments for 74-Day Letter:

- Provide representative samples (3 units for each size) to the NDA with rheograms (viscosity versus shear rate and shear stress versus shear rate) to assist the assessment of dosage form.

- Provide a mock-up for each container/carton label to assist label/labeling review.

D. Comments/Recommendation:

The application is fileable from the CMC and quality perspective.

The major review issues of this NDA include overage, drug product specification, drug product stability, and drug substance comparison between different scales and different

vendors. Drug substance manufacturing sites are located in Mexico, France, and Italy. Drug product manufacturing site is located in Canada. GMP inspection requests have been submitted.

Shulin Ding
Pharmaceutical Assessment Lead

Moo Jhong Rhee
Chief, Branch III

Filing Checklists

A. Administrative Checklists

YES	NO		Comments
x		On its face, is the section organized adequately?	
x		Is the section indexed and paginated adequately?	
x		On its face, is the section legible?	
x		Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	
x		Has an environmental assessment report or categorical exclusion been provided?	

B. Technical Checklists

1. Drug Substance: Hydrous Benzoyl Peroxide and Adapalene

	x	Does the section contain synthetic scheme with in-process parameters?	Reference to DMF
	x	Does the section contain structural elucidation data?	Reference to DMF
x		Does the section contain specifications?	
x		Does the section contain information on impurities?	
	x	Does the section contain validation data for analytical methods?	Reference to DMF
x		Does the section contain container and closure information?	Also Reference to DMF
	x	Does the section contain stability data?	Reference to DMF

2. Drug Product

x		Does the section contain manufacturing process with in-process controls?	
x		Does the section contain quality controls of excipients?	
x		Does the section contain information on composition?	
x		Does the section contain specifications?	
x		Does the section contain information on degradation products?	
x		Does the section contain validation data for analytical methods?	
x		Does the section contain information on container and closure systems?	
x		Does the section contain stability data with a proposed expiration date?	
x		Does the section contain information on labels of container and cartons?	Art works are not submitted.
x		Does the section contain tradename and established name?	

C. Review Issues

x		Has all information requested during the IND phases, and at the pre-NDA meetings been included?	
	x	Is a team review recommended?	
x		Are DMFs adequately referenced?	

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/s/

Shulin Ding
4/8/2008 10:52:12 AM
CHEMIST

Moo-Jhong Rhee
4/8/2008 11:01:41 AM
CHEMIST
Chief, Branch III