

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207917Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: June 29, 2015

From: Gene W. Holbert, Ph.D.

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II
ONDP

To: CMC Review #1 of NDA207917

Subject: Final Recommendation

Gene W.
Holbert -A

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DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300122836,
cn=Gene W. Holbert -A
Date: 2015.06.30 13:08:56 -04'00'

Moojhong
Rhee -S

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ou=FDA, ou=People, cn=Moojhong Rhee -
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Date: 2015.06.30 13:13:08 -04'00'

The CMC review #1 noted the following pending issue:

Final “Acceptable” recommendation from the Office of Compliance had not been issued.

Because of this deficiency, this NDA was not recommended for approval from the ONDP perspective in CMC Review #1.

On June 29, 2015, the Office of Compliance issued an overall “Acceptable” recommendation for the facilities involved in the NDA (see **Attachment I**).

The label and labeling revised as of June 2 and June 16, 2015 are deemed satisfactory from ONDP perspective (see **Attachment II**).

Recommendation:

This NDA is **now** recommended for APPROVAL from the ONDP perspective.

Attachment II: Final Labels/labeling

The following PI update is based on the Amendment June 16, 2015.

A. PI

a. Highlights section

EPIDUO FORTE (adapalene and benzoyl peroxide) gel, 0.3%/2.5% is for topical use
Initial U.S. Approval: XXXX

----- **INDICATIONS AND USAGE** -----

EPIDUO FORTE gel, is a combination of adapalene, a retinoid, and benzoyl peroxide, and, is indicated for the topical treatment of acne vulgaris (b) (4)

----- **DOSAGE AND ADMINISTRATION** -----

EPIDUO FORTE gel is not for oral, ophthalmic, or intravaginal use. (2)
Apply a thin layer of EPIDUO FORTE gel to affected areas of the face and/or trunk once daily after washing. Use a pea-sized amount for each area of the face (e.g., forehead, chin, each cheek). Avoid the eyes, lips, and mucous membranes. (2)

----- **DOSAGE FORMS AND STRENGTHS** -----

Gel, 0.3%/2.5% in 15-g, 30-g, 45-g, 60-g and 70-g pumps

b. Dosage Forms and Strengths

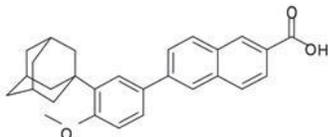
Each gram of EPIDUO FORTE gel contains 3 mg (0.3%) adapalene and 25 mg (2.5%) benzoyl peroxide in a white to very pale yellow, opaque gel. EPIDUO FORTE is available in pumps containing 15 g, 30 g, 45 g, 60 g or 70 g.

c. Description

EPIDUO FORTE (adapalene and benzoyl peroxide) gel, 0.3%/2.5% is a white to very pale yellow, opaque gel for topical use containing adapalene 0.3% and benzoyl peroxide 2.5%.

Adapalene, a synthetic retinoid, is a naphthoic acid derivative with retinoid-like properties. The chemical name for adapalene is (6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid). It has the following structural formula:

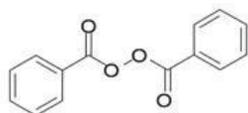
Adapalene:



Molecular formula: C₂₈H₂₈O₃ Molecular weight: 412.5

Benzoyl Peroxide is a highly lipophilic oxidizing agent that localizes in both bacterial and keratinocyte cell membranes. The chemical name for benzoyl peroxide is dibenzoyl peroxide. It has the following structural formula:

Benzoyl Peroxide:



Molecular formula: C₁₄H₁₀O₄ Molecular weight: 242.23

EPIDUO FORTE gel contains the following inactive ingredients: acrylamide/sodium acryloyldimethyltaurate copolymer, docusate sodium, edetate disodium, glycerin, isohexadecane, poloxamer 124, polysorbate 80, propylene glycol, purified water, and sorbitan oleate.

b. How supplied

EPIDUO FORTE (adapalene and benzoyl peroxide) gel 0.3% / 2.5% is white to very pale yellow in color and opaque in appearance, and is supplied as follows:

15 gram pump	NDC 0299-5906-15
30 gram pump	NDC 0299-5906-30
45 gram pump	NDC 0299-5906-45
60 gram pump	NDC 0299-5906-60
70 gram pump	NDC 0299-5906-70

Storage and handling

- Store at controlled room temperature 20 – 25°C (68 – 77°F) with excursions permitted to 15° – 30°C (59° – 86°F) [see USP controlled room temperature].
- Protect from light.
- Keep out of reach of children.
- Keep away from heat.

B. Labels

a. Container

On **June 2, 2015**, Galderma submitted revised container labels. A copy of the 15-g container label is shown below and is representative of the other product sizes. The labels are adequate.



b. Cartons

On **June 16, 2015**, Galderma submitted revised carton labels. A copy of the 15-g carton is shown below and is representative of the other product sizes. The labels are adequate.



NDA 207917

**Epiduo Forte
(adapalene and benzoyl peroxide)
Topical Gel, 0.3%/2.5%**

Galderma Research and Development, LLC

Gene W. Holbert, Ph.D.

**Branch V
Division of New Drug Products II
Office of New Drug Products**

**Chemistry Review for the
Division of Dermatological and Dental Products**

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Chemistry Review Data Sheet

1. NDA 207917
2. REVIEW #: 1
3. REVIEW DATE: May 7, 2015
4. REVIEWER: Gene W. Holbert, PhD
5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Amendment

Amendment

Amendment

Amendment

Amendment

Amendment

Document Date

September 18, 2014

October 23, 2014

November 14, 2014

January 9, 2015

April 10, 2015

April 17, 2015

May 4, 2015

7. NAME & ADDRESS OF APPLICANT:

Name: Galderma Research and Development, LLC
Address: 5 Cedar Brook Drive, Suite 1
Cranbury, NJ 08512
Representative: Elaine Clark
Sr. Director, US Regulatory Submissions
14501 North Freeway
Fort Worth, TX 76177
Telephone: (817) 961-5492
Fax: (817) 720-1040

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Epiduo Forte
b) Non-Proprietary Name (USAN): Adapalene and Benzoyl Peroxide
c) Code Name/# (ONDP only): CD0271+CD1579 Gel
d) Chem. Type/Submission Priority:
 - Chem. Type: 5
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Anti-acne

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 0.3%/2.5%

13. ROUTE OF ADMINISTRATION: Topical

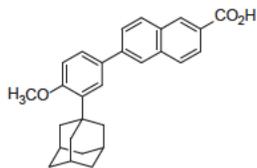
14. Rx/OTC DISPENSED: Rx OTC

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

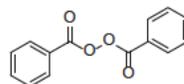
SPOTS product – Form Completed

Not a SPOTS product

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



Adapalene
Chemical Formula: C₂₈H₂₈O₃
Molecular Weight: 412.52



Benzoyl Peroxide
Chemical Formula: C₁₄H₁₀O₄
Molecular Weight: 242.23

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF # (b) (4)	TYPE	HOLDER	ITEM REFERENCED (b) (4)	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	11/05/2014 GHolbert	LOA: 07/05/2014
	II			1	Adequate	11/05/2014 GHolbert	LOA: 09/07/2014
	II			1	Adequate	01/07/2015 GHolbert	LOA: 06/26/2014
	II			1	Adequate	12/12/2014 GHolbert	LOA: 07/21/2014
	III			3	Adequate	06/06/2014 RFrankewich	LOA: 10/08/2013
	III			3	Adequate	06/06/2014 RFrankewich	LOA: 06/15/2012
	III			1, 4	Adequate	12/11/2014 GHolbert	LOA: 07/09/2014

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

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
NDA	022320	Epiduo (adapalene 0.1% and benzoyl peroxide 2.5%) Gel
NDA	021753	Differin (Adapalene 0.3%) Gel

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending	10/12/2014	
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
OPDRA	N/A		
EA	Categorical exclusion is claimed and granted.	04/30/2015	G.W. Holbert, PhD
Microbiology	Approval	10/27/2014	E. Pfeiler, PhD

The Chemistry Review for NDA 207917

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has provided sufficient information to assure identity, strength, purity, and quality of the drug product.

All label/labeling have adequate information as required.

However, an “Acceptable” site recommendation from the Office of Compliance has *not* been made as of the date of this review.

Therefore, from the ONDP perspective, this NDA is *not* ready for approval in its present form per 21 CFR 314.125(6) until above issues are satisfactorily resolved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

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

Epiduo Forte (adapalene and benzoyl peroxide) gel, 0.3%/2.5% is a white to very pale yellow gel for topical application. For commercial distribution, the gel is supplied in 15 and 45-g (b)(4) pumps although additional size containers (30, 60 and 70-g) were included in the application. Physician’s samples are available in 2 and 5-g tubes.

Adapalene, a synthetic retinoid, is a naphthoic acid derivative with retinoid-like properties. The chemical name for adapalene is (6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid).

Benzoyl Peroxide is a highly lipophilic oxidizing agent that localizes in both bacterial and keratinocyte cell membranes. The chemical name for benzoyl peroxide is dibenzoyl peroxide.

Epiduo Forte® contains the following inactive ingredients: acrylamide/sodium acryloyldimethyltaurate copolymer, docusate sodium, edetate disodium, glycerin,

Executive Summary Section

isohexadecane, poloxamer 124, polysorbate 80, propylene glycol, purified water, and sorbitan oleate.

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

Epiduo Forte (adapalene and benzoyl peroxide) gel, 0.3%/2.5% is indicated for the topical treatment of acne vulgaris [REDACTED] ^{(b) (4)}. A thin layer of the gel is applied to affected areas of the face and/or trunk once daily after washing using a pea-sized amount for each area of the face (e.g., forehead, chin, each cheek) while avoiding the eyes, lips and mucous membranes.

The product is intended to be stored at controlled room temperature 20-25 °C (68-77 °F) with excursions permitted to 15-30 °C (59-86 °F), protected from light.

C. Basis for Approvability or Not-Approval Recommendation

Approval of this application is *not* recommended at this time for the following reasons:

- 21 CFR 314.125 (b) (13) - The Office of Compliance has not issued an "Acceptable" recommendation.

III. Administrative**A. Reviewer's Signature**

Gene W.
Holbert -A

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Holbert -A
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
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122836, cn=Gene W. Holbert -A
Date: 2015.05.11 13:00:01 -04'00'

B. Endorsement Block

Gene W. Holbert, PhD/05/07/2015
Moo-Jhong Rhee, PhD/05/08/2015

Moojhong
Rhee -S

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ou=FDA, ou=People, cn=Moojhong Rhee
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C. CC Block

ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **NDA 207917**

2. DATES AND GOALS:

Letter Date: Sep. 17, 2014	Submission Received Date : Sep. 17, 2014
PDUFA Goal Date: July 17, 2015	

3. PRODUCT PROPERTIES:

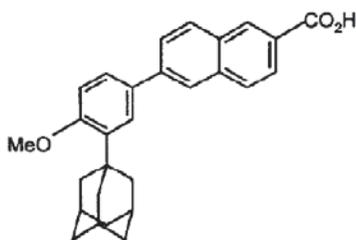
Trade or Proprietary Name:	Epiduo Forte
Established or Non-Proprietary Name (USAN):	Adapalene and Benzoyl Peroxide
Dosage Form:	Gel
Route of Administration	Topical
Strength/Potency	0.3%/2.5%
Rx/OTC Dispensed:	Rx

4. INDICATION:

Acne vulgaris (b) (4)

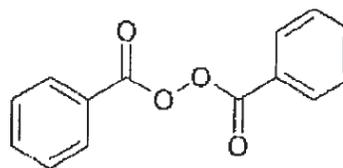
5. DRUG SUBSTANCE STRUCTURAL FORMULA:

Adapalene:



Molecular formula: C₂₈H₂₈O₃
Molecularweight: 412.5 g/mol

Benzoyl Peroxide



Molecular formula: C₁₄H₁₀O₄ (anhydrous)
Molecularweight: 242.23 g/mol (anhydrous)

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

6. NAME OF APPLICANT (as indicated on Form 356h):

Galderma Research and Development LLC

7. SUBMISSION PROPERTIES:

Review Priority:	Standard
Submission Classification (Chemical Classification Code):	Type 5
Application Type:	505(b)(2)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	Division of Dermatology and Dental Products
Other Information	

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		x	
Clinical Pharmacology		x	
Establishment Evaluation Request (EER)	x		Submitted.
Pharmacology/Toxicology		x	
Methods Validation		x	Not a new molecular entity. Furthermore, the proposed product is a higher strength of an approved product, Epiduo gel (NDA 22320). Its formulation is identical to that of Epiduo gel except for a higher strength of adapalene.
Environmental Assessment		x	Categorical exclusion claimed.
CDRH		x	
Other	x		Quality Microbiology. The assignment has been made to Erika Pfeiler.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective?	
Yes	<input checked="" type="checkbox"/>
No	<input type="checkbox"/>
<p>Three potential issues were identified. One was inadequate establishment information in the initial submission. The firm did not provide the statement of readiness for inspection for testing facilities in the initial submission, and did not include the testing facilities in the attachment to Form 356h.</p> <p>The second issue was regarding drug product Master Batch Records, which was not found in the initial submission. The drug product Master Batch Records is required information for NDA filing.</p> <p>The third issue was regarding the analytical samples. The information which clearly indicated that the analytical samples for the pump configurations were taken from the pumped out formulation (as advised in the pre-NDA meeting dated June 25, 2014) was not found in Module 3 of the initial submission.</p> <p>The following three IR items were sent to the applicant on Oct. 16, 2014:</p> <ol style="list-style-type: none">1. Update the establishment attachment to Form 356h by (1) adding all <u>testing/stability storage facilities</u> that are involved in this NDA for the release/stability of <u>drug substance and/or drug product</u>, and (2) providing all information (including function and Readiness for inspection or not) as instructed by Form 356h for <u>each facility</u>.2. Provide Master Batch Record (with English translation) for the drug product. If it has been included in the initial submission, provide its location.3. Provide information that clearly indicates that analytical samples for the pump configurations were taken from the pumped out formulation as agreed to in the pre-NDA meeting in June 2014. <p>The applicant's response was received on Oct. 23, 2014. The requested information has been provided and deemed adequate. The issues have, therefore, been resolved.</p> <p>1. None</p>	

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?	
Yes	<input checked="" type="checkbox"/>
No	<input type="checkbox"/>
<p>CMC Comments for 74-Day Letter:</p> <ol style="list-style-type: none">1. Provide representative samples (3 units for each fill size) to the NDA to assist the verification of dosage form.2. Provide stability update for all registration stability batches.3. It is noted that [REDACTED] ^{(b) (4)} is assigned as the function for glycerin and propylene glycol. [REDACTED] ^{(b) (4)}. Assign a function for glycerin and propylene glycol according to their physicochemical properties.	

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?	
Yes	No
Not applicable.	

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter?	
Yes	No <input checked="" type="checkbox"/>
Biopharmaceutics Comments for 74-Day Letter: Not applicable.	

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?	
Yes <input checked="" type="checkbox"/>	No
Microbiology Filing Issues:	
None. Microbiology Review was filed in DARRTS on Oct. 27, 2014, recommending Approval . The assigned Quality Micro reviewer is Erika Pfeiler.	

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
No	No	No	No

Is a team review recommended?	Yes	No <input checked="" type="checkbox"/>
Suggested expertise for team: Not applicable.		

Summary of Critical Issues and Complexities

1. Bracketing Design for In-Use Stability Studies

The proposed (b) (4) pump configuration (b) (4)
The rationale for bracketing was requested by the Agency in the pre-NDA meeting. The rationale will need a critical review.

2. (b) (4) Pump ((b) (4) Fill Size)

(b) (4) Pump is not currently approved for Epiduo gel. Therefore, the Agency has not had experience with the (b) (4) pump for this product line.

3. Limited Stability Data for 5 g tubes, and 15 g, 30 g, 60 g, and 70 g Pumps

Although a total of seven registration stability batches are included in the initial submission, the actual data for the following packaging configuration are only 3 months (2 time points): 5 g tube, and 15 g, 30 g, 60 g, and 70 g pumps. A stability update to six months is thus highly desirable so that data from 3 time points would become available for shelf-life projection and specification setting.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Initial Quality Assessment

This 505(b) (2) New Drug Application (NDA) provides for a new adapalene strength, 0.3%, as a **line extension for the approved Epiduo™** (adapalene and benzoyl peroxide) gel. 0.1%/2.5%. A new trade name, **Epiduo Forte**, is proposed for this new strength. The applicant could have submitted a supplement for this strength change, but has chosen to submit a NDA instead.

The proposed drug substance suppliers for this NDA are the **same** suppliers that have been approved for the Epiduo gel. The suppliers are (b) (4) (DMF (b) (4)), located in (b) (4) and (b) (4) (DMF (b) (4)), located in (b) (4) for adapalene, and (b) (4) (DMF (b) (4)), located in (b) (4) and (b) (4) (DMF (b) (4)), located in (b) (4) for benzoyl peroxide. All four DMFs have been deemed adequate to support the approval of similar topical products according to their most recent CMC reviews.

The formulation of Epiduo Forte gel is identical to that of Epiduo gel except for the increased concentration of adapalene to 0.3%. The to-be-marketed formulation is the same formulation used in the clinical trials and registration stability batches. The proposed drug product specification for Epiduo Forte gel is, however, only similar (not identical) to Epiduo gel.

Formulation Comparison

Ingredient	Grade	% w/w	
		Epiduo Forte Gel NDA 207917	Epiduo Gel NDA 22320
Adapalene	In-House	0.30	0.10
Benzoyl Peroxide (b) (4)	USP ^(b)	2.50	2.50
(b) (4)	In-House	(b) (4)	
Docusate Sodium	USP		
Edetate Disodium	USP		
Glycerin	USP		
Poloxamer 124	NF		
Propylene Glycol	USP		
Purified Water	USP		

The packaging systems proposed for Epiduo Forte gel are described below. They are different from those for Epiduo gel.

Epiduo Forte Trade sizes: (b) (4) pump (15 g), and (b) (4) pump (30 g, 45 g, 60 g and 70 g)
Epiduo Forte Physician sample: (b) (4) tubes (2 g and 5 g).

The proposed drug product manufacturer, GPI, Canada is the approved manufacturer for Epiduo gel. The proposed commercial batch size (b) (4) and manufacturing process for Epiduo Forte are the same as that of Epiduo gel. The process consists of the following steps: (b) (4)

Stability data provided in the initial submission to support an expiry period of 24 months (for both tube and pump configurations) at controlled room temperature with excursions permitted 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 seven commercial (b) (4) batches made by the designated commercial manufacturing site (GPI). The long term data from the commercial batches are 3-18 months. Special stability data provided in the NDA to support storage/handling/shipping of the product include data from the following studies: cold storage (5°C), photostability, in-use stability, temperature cycling, and free/thaw.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Initial Risk Assessment

Initial Risk Assessment on Drug Product Based on OGD's Product Risk Ranking System

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay, stability (Benzoly peroxide)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	4	2	Release (1) Stability (3)	Release (8) stability (24)	Poorly stable drug but not high risk.
Assay, stability (Adapalene)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	1	2	Release (1) Stability (3)	Release (2) stability (6)	Highly stable drug and not high risk.
Physical stability (API)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	1	3	Release (1) Stability (3)	Release (3) stability (9)	Experience with Epiduo gel suggests that change in polymorph is not likely.
Physical stability (phase separation) (particle size and/or droplet size)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	2	3	Release (1) Stability (3)	Release (6) stability (18)	Physical appearance and particle sizing are included in the drug product specification
Content uniformity	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	3	2	2	12	Included in the assay test.
Viscosity	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	3	3	With spec (2)	18	
In-vitro release (cream, ointment, gel)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • 	2	2	4	16	Not proposed as a spec.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

	Scale/equipment • Site • Site					
Microbiological properties (MLT and AME)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	With preervative or bacteriostatic/bacteriocidal (1)	1	With spec (3)	3	MLT and AET are included in the DP spec.
Leachables	<ul style="list-style-type: none"> • Formulation • Raw materials • Container closure • Process parameters • Scale/equipment • Site 	3	2	5	30	Overestimated by the ranking system. It should be low risk.
Minimal fill	<ul style="list-style-type: none"> • Process parameters • Scale/equipment • Site 	1	1	1	1	Controlled by in-process test on fill weight.
Package integrity (interior, exterior, leakage, etc.)	<ul style="list-style-type: none"> • Process parameters • Scale/equipment • Site 	1	1	With spec (3)	3	Weight loss is included in registration stability protocols not in DP spec. It was demonstrated to be very low in supporting stability studies.
Pump Functionality	<ul style="list-style-type: none"> • Formulation • Container closure • Process parameters • Scale/equipment • Site 	4	1 (Non-metered design)	With spec (1) Without spec (3)	With spec (4) Without spec (12)	Significant change in the amount dispensed per actuation was observed at 12 month time point for two g batches (Batches 102186 and 102187). (b) (4)

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		Sampling from pumped out formulation was confirmed in the 10/23/14 amendment.

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		Not in the initial submission. The single comprehensive list of all involved facilities was provided in the amendment dated Oct. 23, 2014.
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			n/a

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

	Parameter	Yes	No	Comment
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		Not in the initial submission. The single comprehensive list of all involved facilities is provided in the amendment dated Oct. 23, 2014.
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		Not in the initial submission. It is provided in the amendment dated Oct. 23, 2014.

C. ENVIRONMENTAL ASSESMENT

	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	x		Categorical exclusion claimed based on EIC below 1 ppb.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?		x	Referenced to a Type II DMF for each supplier.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		x	Referenced to a Type II DMF for each supplier.
14.	Does the section contain information regarding the characterization of the DS?		x	Referenced to a Type II DMF for each supplier.
15.	Does the section contain controls for the DS?	x		
16.	Has stability data and analysis been provided for the drug substance?		x	Referenced to a Type II DMF for each supplier.
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			n/a
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			n/a

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		Master Batch Record is provided in the amendment dated Oct. 23, 2014.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?		x	Not applicable.
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?			n/a
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			n/a

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	x		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product		x	This is not a sterile product.

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

DMF # (b) (4)	TYPE	HOLDER	ITEM REFERENCED (b) (4)	LOA DATE	COMMENTS
	II			7/5/14	
	II			9/7/14	
	II			6/26/14	
	II			7/21/14	
	III			10/8/13	
	III			7/9/14	

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

See appended electronic signature page

Shulin Ding
CMC-Lead
Division II
Office of New Drug Quality Assessment

Shulin Ding
-S



Digitally signed by Shulin Ding -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Shulin Ding -S,
0.9.2342.19200300.100.1.1=1300215977
Date: 2014.11.03 09:18:17 -05'00'

{See appended electronic signature page}

Moo-Jhong Rhee
Branch Chief
Division II
Office of New Drug Quality Assessment

Moojhong
Rhee -S



Digitally signed by Moojhong Rhee -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Moojhong Rhee
-S,
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Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre- Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

I. Review Cover Sheet

- 1. OMPQ Reviewer: Christina Capacci-Daniel, PhD
- 2. NDA/BLA Number: NDA 207917
Submission Date: September 17, 2014
21st C. Review Goal Date: May 17, 2015
PDUFA Goal Date: July 17, 2015

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Epiduo Forte
Established or Non-Proprietary Name (USAN) and strength:	0.3% Adapalene and 2.5% Benzoyl Peroxide
Dosage Form:	Topical Gel

4. SUBMISSION PROPERTIES:

Review Priority :	Standard
Applicant Name:	Galderma Research and Development Inc.
Responsible Organization (OND Division):	DDDP

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

II. Application Detail

1. INDICATION: Topical treatment of acne vulgaris
2. ROUTE OF ADMINISTRATION: Topical gel
3. STRENGTH/POTENCY: 0.3%/2.5%
4. Rx/OTC DISPENSED: Rx OTC
5. ELECTRONIC SUBMISSION (yes/no)? YES
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V		<input checked="" type="checkbox"/>		
2.	Breakthrough Therapy Designation		<input checked="" type="checkbox"/>		
3.	Orphan Drug Designation		<input checked="" type="checkbox"/>		
4.	Unapproved New Drug		<input checked="" type="checkbox"/>		
5.	Medically Necessary Determination		<input checked="" type="checkbox"/>		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		<input checked="" type="checkbox"/>		
7.	Rolling Submission		<input checked="" type="checkbox"/>		
8.	Drug/device combination product with consult		<input checked="" type="checkbox"/>		
9.	Complex manufacturing		<input checked="" type="checkbox"/>		
10.	Other (e.g., expedited for an unlisted reason)		<input checked="" type="checkbox"/>		

III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	Yes	No	Comment
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	<input checked="" type="checkbox"/>		Updated 356h attachment
12.	Do all sites indicate they are ready to be inspected (on 356h)?	<input checked="" type="checkbox"/>		
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	<input checked="" type="checkbox"/>		Updated 356h attachment
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	<input checked="" type="checkbox"/>		Residual catalyst testing (adapalene) and particle size testing (benzoyl peroxide), all other testing performed at manufacturing facilities
15.	Additional notes (non-filing issue)	<input checked="" type="checkbox"/>		
	1. Are all sites registered or have FEI #?			
	2. Do comments in EES indicate a request to participate on inspection(s)?		<input checked="" type="checkbox"/>	IMS will be updated when available
	3. Is this first application by the applicant?		<input checked="" type="checkbox"/>	Galderma currently markets two similar products

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
16.	Have any Comparability Protocols been requested?		<input checked="" type="checkbox"/>	

IMA CONCLUSION				
	Parameter	Yes	No	Comment
17.	Does this application fit one of the EES Product Specific Categories?		<input checked="" type="checkbox"/>	
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?		<input checked="" type="checkbox"/>	IMS pending
19.	From a CGMP/facilities perspective, is the application fileable? If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	<input checked="" type="checkbox"/>		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology <input type="checkbox"/>	RTRT Proposal <input type="checkbox"/>	PAT <input type="checkbox"/>	Drug/Device Combo <input type="checkbox"/>
PET <input type="checkbox"/>	Design Space <input type="checkbox"/>	Continuous Mfg <input type="checkbox"/>	Naturally derived API <input type="checkbox"/>
Other (explain):		<input checked="" type="checkbox"/> Not Applicable	

Manufacturing Highlights

1. Drug Substance

Parameter	Yes	No	Comment
Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<ul style="list-style-type: none"> Adapalene sourced from two manufacturers per DMF (b)(4) & (b)(4) Benzyl Peroxide sourced from two manufacturers per DMF (b)(4) & (b)(4); different synthetic methods are used at the two source facilities Final particle size is critical quality attribute

Adapalene Synthesis



OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

Benzoyl peroxide Synthesis –

(b) (4)

(b) (4)

Benzoyl peroxide Synthesis –

(b) (4)

(b) (4)

2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		<input checked="" type="checkbox"/>	<ul style="list-style-type: none"> • Adapalene and benzoyl peroxide are (b) (4) • There is a (b) (4) % overage for benzoyl peroxide in the formulation because this API typically (b) (4) FDA has already determined this to be acceptable. • BP specification is thus (b) (4) %, (b) (4) is NMT (b) (4) % • (b) (4) • Only 2 IPC: Visual inspection used to determine homogeneity of Adapalene phase and excipient dissolution • Two Validation campaigns (20 batches total) have been completed

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

(b) (4)

3. Facility-Related Risks (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc.). Describe any potential 21CFR 211 compliance issues.

- There are no outstanding facility issues at this time.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

4. Drug Product Facility Inspectional History that could impact the manufacturing of this product

- There are no outstanding compliance issues.

Additional information not covered above

- This NDA makes reference to two similar products:
 - **NDA 22320** Epiduo (Adapalene 0.1% and Benzoyl Peroxide 2.5%) – A lower Adapalene strength gel, Approved 12/2008
 - **NDA 21753** Differin (Adapalene 0.3%) – Adapalene gel alone at the proposed strength, Approved 6/2007
- The proposed API and drug product facilities for NDA 207917 are the same as for NDA 22320 and NDA 21753, except for (b) (4) (Adapalene API source) which is new to this NDA.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

Manufacturing Facilities Chart (created 10/15/2014):

Establishment Name	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Inspection History, Dates, Classifications	Most Recent Milestone	Comment
(b) (4)								
G Production Inc. (GPI)	3003671557	AME	CAN	FDF manufacture	OIN	5/17/2013 OIN NAI	<i>Pending addition to IMS</i>	PAI & GMP inspection needed This facility currently makes two similar products (NDA 22320 & NDA 21753) which have been covered in previous inspections

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

(b) (4)



V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no, Yes to questions 11-12) YES
Based on Section IV, is a KTM warranted for any PAI? (yes/no). If yes, please identify the sites in the above chart. <ul style="list-style-type: none">• There will be a brief pre-inspection briefing for G Production Inc. due to the similarity of this product to NDA 22320 which is currently made there.
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no) NO
Comments for 74 Day Letter
1.
2.
3.

REVIEW AND APPROVAL (DARRTS)

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

/s/

CHRISTINA A CAPACCI-DANIEL
10/24/2014

MAHESH R RAMANADHAM
10/29/2014