

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-502**

**CHEMISTRY REVIEW(S)**

# Memorandum

**Date:** 3-MAR-2010  
**From:** Rajiv Agarwal, Ph.D., Review Chemist  
**Through:** Moo-Jhong Rhee, Ph.D., Chief, Branch III/DPA II/ONDQA  
**To:** CMC Memorandum (23-DEC-09) of NDA 22-502  
**Subject:** Final Recommendation

The previous memorandum indicated two pending cGMP and labeling issues.

The Office of Compliance has now issued an overall “Acceptable” recommendation (**Attached-1**) on 14-JAN-2010.

The labeling issues are also resolved as follows:

- Since the Phase III Study was conducted with the product containing pump, (b) (4) (via amendment dated 25-NOV-2009) and labeling was revised to reflect (b) (4) (via amendment dated 28-JAN-2010).
- Based on the DMEPA’s recommendation, the applicant amended the container/closure labels for 2 and 4 oz bottles (b) (4) with the following information and provided the labels on 22-FEB-2010 and they deemed adequate from a CMC stand point.
  - Ensure the presentation of the established name is at least half as large and with a prominence commensurate to the proprietary name.
  - Revise the carton and container labels to include the route of administration “For external use only” on the principal display panel.
  - Increase the prominence of the statement “SAMPLE- NOT FOR SALE” on the 15 mL sample container label.

Therefore, from the CMC perspective, this NDA is now recommended for approval.

**Attached: 1**

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

<b>Application:</b>	NDA 22502/000	<b>Action Goal:</b>	
<b>Stamp Date:</b>	02-MAR-2009	<b>District Goal:</b>	03-NOV-2009
<b>Regulatory:</b>	02-JAN-2010		
<b>Applicant:</b>	GALDERMA R AND D 5 CEDAR BROOK DR STE 1 CRANBURY, NJ 08512	<b>Brand Name:</b>	DIFFERIN LOTION
		<b>Estab. Name:</b>	
		<b>Generic Name:</b>	ADAPALENE
<b>Priority:</b>	3S	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	
<b>Org. Code:</b>	540		001; LOTION; ADAPALENE; .1%
<b>Application Comment:</b>			
<b>FDA Contacts:</b>	J. DAVID	Project Manager	301-796-4247
	R. AGARWAL	Review Chemist	301-796-1322
	S. DING	Team Leader	301-796-1349

<b>Overall Recommendation:</b>	ACCEPTABLE	on 14-JAN-2010	by M. STOCK	(HFD-320)	301-796-4753
	WITHHOLD	on 18-DEC-2009	by C. CRUZ	(HFD-323)	301-796-3254

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Establishment:** (b) (4)

**DMF No:** (b) (4)

**Responsibilities:** (b) (4)

**Estab. Comment:** (b) (4)

**Profile:** (b) (4)      **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	24-APR-2009				DINGS
SUBMITTED TO DO	27-APR-2009	GMP Inspection			FERGUSONS
ASSIGNED INSPECTION TO IB	15-JUN-2009	Product Specific			RYOUNG
INSPECTION SCHEDULED	03-DEC-2009		11-DEC-2009		RYOUNG
INSPECTION PERFORMED	10-DEC-2009		10-DEC-2009		RYOUNG
DO RECOMMENDATION	14-DEC-2009			ACCEPTABLE INSPECTION	RYOUNG
OC RECOMMENDATION	14-DEC-2009			ACCEPTABLE DISTRICT RECOMMENDATION	INYARDA

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

Establishment: (b) (4)

DMF No:

Responsibilities:

Estab. Comment:

Profile:

OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	24-APR-2009				DINGS
OC RECOMMENDATION	27-APR-2009			ACCEPTABLE	STOCKM
INSPECTION CONDUCTED 4/30-5/3/07 COVERED THE CSN PROFILE AND WAS CLASSIFIED NAI. BASED ON PROFILE					

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

Establishment: CFN: FEI: 3003671557

GALDERMA PRODUCTION CANADA, INC.  
19400 ROUTE TRANSCANADIENNE  
BAIE-D'URFE, QUEBEC, CANADA

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER  
FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE RELEASE TESTER.

Estab. Comment: THIS SITE MANUFACTURE THE DRUG PRODUCT. IT ALSO RELEASES THE DRUG SUBSTANCE AND THE DRUG  
PRODUCT. (on 14-APR-2009 by S. DING () 301-796-1349)

Profile: LIQUIDS (INCLUDES SOLUTIONS, SUSPENSIONS, ELIXIRS. OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	24-APR-2009				DINGS
SUBMITTED TO DO	27-APR-2009	GMP Inspection			STOCKM
ASSIGNED INSPECTION TO IB	04-MAY-2009	GMP Inspection			JOHNSONE
INSPECTION SCHEDULED	12-AUG-2009		04-SEP-2009		IRIVERA
INSPECTION PERFORMED see endorsement text	04-SEP-2009		04-SEP-2009		KATHLEEN.CULVER
DO RECOMMENDATION	10-SEP-2009			ACCEPTABLE INSPECTION	JOHNSONE
OC RECOMMENDATION	11-SEP-2009			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

Establishment:

(b) (4)

DMF No:

Responsibilities:

Estab. Comment:

Profile:

Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	27-APR-2009				DINGS
SUBMITTED TO DO	27-APR-2009	GMP Inspection			STOCKM
DO RECOMMENDATION	04-MAY-2009			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	06-MAY-2009			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

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

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/s/

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RAJIV AGARWAL

03/03/2010

This is the FINAL Recommendation for the NDA.

MOO JHONG RHEE

03/03/2010

Chief, Branch III

# Memorandum

**Date:** 1-MAR-2010  
**From:** Rajiv Agarwal, Ph.D., Review Chemist  
**Through:** Moo-Jhong Rhee, Ph.D., Chief, Branch III/DPA II/ONDQA  
**To:** CMC Memorandum (23-DEC-09) of NDA 22-502  
**Subject:** Final Recommendation

The previous memorandum indicated two pending cGMP and labeling issues.

The Office of Compliance has now issued an overall “Acceptable” recommendation (**Attached-1**) on 14-JAN-2010.

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  - Ensure the presentation of the established name is at least half as large and with a prominence commensurate to the proprietary name.
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Therefore, from the CMC perspective, this NDA is now recommended for approval.

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<b>Regulatory:</b>	02-JAN-2010		
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		<b>Estab. Name:</b>	
		<b>Generic Name:</b>	ADAPALENE
<b>Priority:</b>	3S	<b>Product Number; Dosage Form; Ingredient; Strengths</b>	001; LOTION; ADAPALENE; .1%
<b>Org. Code:</b>	540		
<b>Application Comment:</b>			
<b>FDA Contacts:</b>	J. DAVID	Project Manager	301-796-4247
	R. AGARWAL	Review Chemist	301-796-1322
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<b>Overall Recommendation:</b>	ACCEPTABLE	on 14-JAN-2010	by M. STOCK	(HFD-320)	301-796-4753
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ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Establishment:** (b) (4)

**DMF No:**

**Responsibilities:**

**Estab. Comment:**

**Profile:**

**OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
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DO RECOMMENDATION	14-DEC-2009			ACCEPTABLE INSPECTION	RYOUNG
OC RECOMMENDATION	14-DEC-2009			ACCEPTABLE DISTRICT RECOMMENDATION	INYARDA

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

Establishment: (b) (4)

DMF No:

Responsibilities:

Estab. Comment:

Profile:

OAI Status: NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	24-APR-2009				DINGS
OC RECOMMENDATION	27-APR-2009			ACCEPTABLE	STOCKM
INSPECTION CONDUCTED 4/30-5/3/07 COVERED THE CSN PROFILE AND WAS CLASSIFIED NAI. BASED ON PROFILE					

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DETAIL REPORT**

Establishment: CFN: FEI: 3003671557  
GALDERMA PRODUCTION CANADA, INC.  
19400 ROUTE TRANSCANADIENNE  
BAIE-D'URFE, QUEBEC, CANADA

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER  
FINISHED DOSAGE MANUFACTURER  
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PRODUCT. (on 14-APR-2009 by S. DING () 301-796-1349)

Profile: LIQUIDS (INCLUDES SOLUTIONS, SUSPENSIONS, ELIXIRS. OAI Status: NONE

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<u>Comment</u>				<u>Reason</u>	
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SUBMITTED TO DO	27-APR-2009	GMP Inspection			STOCKM
ASSIGNED INSPECTION TO IB	04-MAY-2009	GMP Inspection			JOHNSONE
INSPECTION SCHEDULED	12-AUG-2009		04-SEP-2009		IRIVERA
INSPECTION PERFORMED see endorsement text	04-SEP-2009		04-SEP-2009		KATHLEEN.CULVER
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**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Establishment:**

(b) (4)

**DMF No:**

**Responsibilities:**

**Estab. Comment:**

**Profile:**

**Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	27-APR-2009				DINGS
SUBMITTED TO DO	27-APR-2009	GMP Inspection			STOCKM
DO RECOMMENDATION	04-MAY-2009			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	06-MAY-2009			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

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

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/s/

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RAJIV AGARWAL  
03/01/2010

MOO JHONG RHEE  
03/02/2010  
Chief, Branch III

# Memorandum

**Date:** 23-DEC-2009  
**From:** Rajiv Agarwal, Ph.D., Review Chemist  
**Through:** Moo-Jhong Rhee, Ph.D., Chief, Branch III/DPA II/ONDQA  
**To:** **CMC Review #1 of NDA 22-502**  
**Subject:** Final Recommendation

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

However, the Office of Compliance has issued an overall recommendation of “Withhold” Also there are some unresolved issues on labeling including labels in terms of packaging configurations, but this will be resolved in the next review cycle.

Therefore, from the CMC perspective, this NDA is *not* recommended for Approval in its present form.



(b) (4)

Establishment:

DMF No:

Responsibilities:

Estab. Comment:

Profile:

OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
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Establishment:

CFN:

FEI: 3003671557

GALDERMA PRODUCTION CANADA, INC.

19400 ROUTE TRANSCANADIENNE

BAIE-D'URFE, QUEBEC, CANADA

DMF No:

AADA:

Responsibilities:

DRUG SUBSTANCE RELEASE TESTER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE RELEASE TESTER

Estab. Comment:

THIS SITE MANUFACTURE THE DRUG PRODUCT. IT ALSO RELEASES THE DRUG SUBSTANCE AND THE DRUG PRODUCT. (on 14-APR-2009 by S. DING () 301-795-1349)

Profile:

LIQUIDS (INCLUDES SOLUTIONS, SUSPENSIONS, ELIXIRS,

OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
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SUBMITTED TO DO	27-APR-2009	GMP Inspection			STOCKM
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DO RECOMMENDATION	10-SEP-2009			ACCEPTABLE INSPECTION	JOHNSONE
OC RECOMMENDATION	11-SEP-2009			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

Establishment:



(b) (4)

DMF No:

Responsibilities:

Estab. Comment:

Profile:

Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
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DO RECOMMENDATION	04-MAY-2009			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	06-MAY-2009			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM

Establishment:

CFN:

FEI:

(b) (4)



DMF No:

Responsibilities:

Estab. Comment:

ORIGINAL ADDRESS WAS (b) (4) SITE OF TESTING HAS MOVED TO (b) (4) CONFIRMED BY NDA APPLICANT. (on 30-JUL-2009 by (b) (4))

Profile:



<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	03-AUG-2009				DAVIDJE
SUBMITTED TO DO	07-AUG-2009	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	13-AUG-2009	Product Specific			JOHNSONE
OC RECOMMENDATION	18-DEC-2009			WITHHOLD DISTRICT RECOMMENDATION FIRM NOT READY	CRUZZ
			AS PER DISCUSSION WITH (b) (4) FIRM WAS NOT READY AS THERE IS NO METHOD TRANSFER AND NO ANALYTICAL WORK DONE YET.		

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-22502

-----  
ORIG-1

-----  
GALDERMA  
RESEARCH AND  
DEVELOPMENT  
INC

-----  
DIFFERIN LOTION

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RAJIV AGARWAL  
12/23/2009

MOO JHONG RHEE  
12/23/2009  
Chief, Branch III

**NDA 22-502**

**Differin**  
**(Adapalene) Lotion**  
**0.1%**

**Galderma Research and Development Inc.**

**Rajiv Agarwal, Ph.D.**

**Review Chemist**

**Office of New Drug Quality Assessment**  
**Division of Pre-Marketing Assessment II**  
**Branch III**

**CMC REVIEW OF NDA 22-502**  
**For the Division of Dermal and Dental products (HFD-540)**

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## CMC Review Data Sheet

# CMC Review Data Sheet

1. NDA 22-502
2. REVIEW #: 1
3. REVIEW DATE: 21-OCT-2009
4. REVIEWER: Rajiv Agarwal, Ph.D; Ph.D
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	27-FEB-2009
Amendment	14-JUN-2009
Amendment	02-JUL-2009
Amendment	28-JUL-2009
Amendment	06-AUG-2009
Amendment	10-AUG-2009
Amendment	24-SEP-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Galderma Laboratories, LP  
Address: 14501 N. Freeway, Fort Worth, TX 76177  
Representative: Allen E. Fields, Director of Regulatory Submissions  
Telephone: 817-961-5227

8. DRUG PRODUCT NAME/CODE/TYPE:

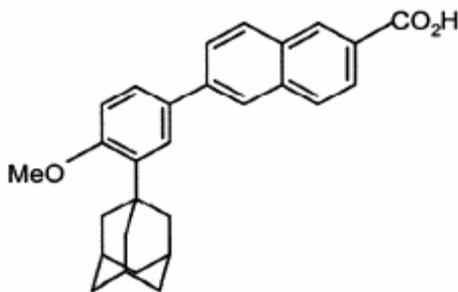
a) Proprietary Name: Differin  
b) Non-Proprietary Name: Adapalene  
c) Code Name/# (ONDQA only):  
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

## CMC Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOL. CATEGORY: Acne vulgaris
11. DOSAGE FORM: Lotion
12. STRENGTH/POTENCY: 0.1%
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:



Chemical name: 6-(4-methoxy-3-tricyclo[3.3.1.1<sup>3,7</sup>]dec-1-ylphenyl) naphthalene-2-carboxylic acid

2,6- [3-(1-adamantyl)- 4-methoxyphenyl]-2-naphthoic acid

Molecular formula: C<sub>28</sub>H<sub>28</sub>O<sub>3</sub>

Molecular weight: 412.5

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	31-JAN-2007	Adequate for NDA 20-773
	III			3	Adequate	12-JAN-2005	Adequate for NDA 50-795
	III			4	Adequate	Refer to the subject NDA review	Adequate for NDA 22-502
	III			1	Adequate	21-OCT-2009	Adequate for NDA 22-502
	III			3	Adequate	24-JUN-1996	Adequate for ANDA 74-347
	IV			4	Adequate	Refer to the subject NDA review	Adequate for NDA 22-502
	IV			4	Adequate	Refer to the subject NDA review	Adequate for NDA 22-502

<sup>1</sup> 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")

<sup>2</sup> 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	76,057	Differin Lotion
NDA	20-380, 20-338, 21-753, 20-748, and 22-320	Gel and cream

## CMC Review Data Sheet

## 18. STATUS:

## ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Pharm/Tox	Adequate	17-SEP-2009	Dr. Daivender K Mainigi
Methods Validation	N/A, according to the current ONDQA policy		
EA	Categorical exclusion is granted (see review)		

## Executive Summary Section

# The CMC Review for NDA 22-502

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. However, there are two pending issues:

- The final recommendation from the Office of Compliance involving all facilities pertaining to the cGMP inspections of drug substance and drug product manufacturing and testing operations is pending.
- Required information on the carton and container closure labels is not in the recommended format and must be presented as recommended (see the List of Deficiencies on page 53 of this review).

Therefore, from the CMC standpoint, this NDA is not recommended for approval in its present form until the Office of Compliance issues an ACCEPTABLE recommendation, and 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

The drug substance is Adapalene, which is available as a white to off white powder and melts at 317<sup>0</sup> to 328<sup>0</sup>C, is very slightly soluble in most common organic solvents and is practically insoluble in water. Adapalene contains no asymmetric carbon center and the theoretical possibility of positional isomers can be rejected on the basis of the structural analysis performed on the molecule. There is no evidence of polymorphism observed by (b) (4)

For details regarding physical and chemical properties of adapalene, refer to

## Executive Summary Section

DMF No. (b) (4). A letter authorizing Galderma Research and Development to refer to this DMF is provided. Please refer to the CMC review of DMF (b) (4) for NDA 20-748 dated 25-JUL-2005 for more information. The sponsor of this NDA also owns the rights of the NDA 20-748.

The recommendation from the Office of Compliance pertaining to the manufacturing and testing sites for drug substance is pending.

**(2) Drug Product**

Four different adapalene formulations are currently marketed by Galderma in the USA: Differin Gel 0.1% (NDA 20-380), Differin Cream 0.1% (NDA 20-748), Differin Gel 0.3% (NDA 21-753), and Epiduo Gel (Adapalene 0.1%/Benzoyl Peroxide 2.5%, NDA 22-320).

The proposed drug product, Differin Lotion, 0.1% is a new dosage form of adapalene 0.1% (w/w) dispersed in a fluid emulsion containing a low percentage of oil phase (< 10%). The proposed lotion formulation is intended for the topical treatment of *acne vulgaris*.

All but two excipients in Differin Lotion, 0.1% are compendial. These two excipients, Polyoxyl-6 & Polyoxyl-32 Palmitostearate and PPG-12/SMDI Copolymer, are described in the FDA's Inactive Ingredient Guide (IIG) for topical products. The concentrations of all ingredients in Differin Lotion, 0.1% are within acceptable ranges per the IIG.

The drug product is an oil-in-water emulsion, where drug substance particles are uniformly dispersed in the vehicle matrix. This was accomplished by controlling the drug substance particle size distribution and by selection of vehicle matrix in which drug substance is essentially insoluble but that possesses the appropriate rheological properties to maintain a uniform dispersion of drug particles and meets the criteria for a lotion. The acceptance criterion of the particle size is established at release and is also evaluated during stability testing.

(b) (4)

Differin Lotion, 0.1% is provided in 0.5-oz (~15g), 2-oz (~60g) and 4-oz (~120g) bottles equipped with a dispensing cap. The 0.5-oz bottles will be used as physician samples (without pump) and the 2-oz and 4-oz bottles provided with a

## Executive Summary Section

pump will be the commercial packaging. (b) (4)  
for the 2-oz and the 4-oz bottles from (b) (4). Extractable testing on  
these (b) (4). The results of such testing demonstrate  
and establish these materials as food grade quality, therefore, meeting the test  
criteria 21CFR175.300 and 21CFR 177.1520. The primary container closure  
(pump) manufacturer, (b) (4), has performed extractables testing on the pump.  
The results of such testing demonstrate and establish these materials as food grade  
quality, therefore, meeting the test criteria in 21CFR 175. 300 and 21CFR  
177.1520. In addition, the data obtained for the bottle (2-oz size) and the closure  
systems (cap (b) (4) used for 2-oz and 4-oz bottles, and cap (b) (4)  
used for 0.5-oz bottles from (b) (4) indicate that the container closure system components  
comply with USP 30 <661> requirements for Containers – Plastics.

A 24-month of expiration dating period is requested and, based on the available  
stability, it is granted.

The recommendation from the Office of Compliance pertaining to the  
manufacturing and testing sites for drug product is pending.

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

Apply a thin film of DIFFERIN Lotion to the entire face and other affected areas of the  
skin once daily, after washing gently with a mild soapless cleanser. Avoid application  
to the areas of skin around eyes, lips and mucous membranes.

**C. Basis for Approvability or Not-Approval Recommendation**

- Through the satisfactory responses to the CMC requests from 74 day  
letter/Information Request letter dated 2-MAR-2009, which were received on 14-  
JUN-2009, 02-JUL-2009, 28-JUL-2009, 06-AUG-2009, 10-AUG-2009, and 24-SEP-  
2009, this NDA is now deemed to provide adequate information on the raw material  
controls, manufacturing process, specification, and container/closure. It also provided  
sufficient stability data to assure identity, strength, purity and quality of the drug  
product during the expiration dating period,

However, the final recommendation from the Office of Compliance on the  
compliance to the cGMP involving all facilities pertaining to the drug substance and  
drug product manufacturing and testing operations is PENDING, and the required  
information on the labels is not in the recommended format and must be presented as  
recommended (see the List of Deficiencies on page 53).

## Executive Summary Section

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

*(See appended electronic signature page)*

Rajiv Agarwal, Ph.D; Ph.D

**B. Endorsement Block:**

*(See appended electronic signature page)*

Moo-Jhong Rhee, Ph.D, Branch Chief, Branch III, ONDQA

**C. CC Block:** entered electronically in DARRTS

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(CCI/TS)

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22502

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ORIG-1

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GALDERMA  
RESEARCH AND  
DEVELOPMENT  
INC

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DIFFERIN LOTION

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/s/  
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RAJIV AGARWAL  
10/21/2009

MOO JHONG RHEE  
10/22/2009  
Chief, Branch III

Initial Quality Assessment  
Branch III  
Pre-Marketing Assessment Division II

**OND Division:** Division of Dermatology and Dental Products  
**NDA:** 22-502  
**Applicant:** Galderma Laboratories, L.P.  
**Stamp Date:** March 2, 2009  
**PDUFA Date:** Jan. 2, 2010  
**Trademark:** Differin™  
**Established Name:** Adapalene  
**Dosage Form:** Lotion  
**Route of Administration:** Topical  
**Indication:** Acne Vulgaris

**PAL:** Shulin Ding

	YES	NO
<b>ONDQA Fileability:</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<b>Comments for 74-Day Letter</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

**Summary and Critical Issues:**

A. Summary

Galderma Laboratories is submitting a 505(b) (1) New Drug Application (NDA) for the prescription use of Differin™ (Adapalene) Lotion 0.1% in the treatment of acne vulgaris. This is a line extension of established Differin™ products: Differin (adapalene) Solution, 0.1%; Differin (adapalene) Gel, 0.1% and 0.3%; and Differin (adapalene) Cream 0.1%.

The proposed drug substance, adapalene, is referenced to DMF <sup>(b) (4)</sup> held by <sup>(b) (4)</sup>. The DMF has been reviewed multiple times for multiple submissions (most recently for the approved NDA 21-753 Differin gel and NDA 22-320 Epiduo gel), and deemed adequate to support referenced submissions.

The drug product, Differin™ (adapalene) Lotion 0.1% is a white to off-white, oil-in-water emulsion with suspended particles of adapalene. The product is packaged in 0.5-oz (15 g), 2-oz (60 g), and 4-oz (120 g) white, high-density-polyethylene bottles equipped with a white, <sup>(b) (4)</sup> dispensing cap. The 0.5 ounce size is the sample size. The 2-oz and 4-oz sizes are also co-packaged (on the side of the bottle) with a lotion pump (0.14 mL nominal delivery volume).

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: disodium edetate, USP; propylparaben, NF; carbomer 9<sup>(b) (4)</sup>1, NF; methylparaben, NF; poloxamer 124, NF; phenoxyethanol, NF; stearyl alcohol, NF; PPG-12/SMDI copolymer; propylene glycol, USP; polyoxyl-6 & polyoxyl-32 palmitostearate; medium chain triglycerides, NF; sodium hydroxide, NF; and purified water, USP. All excipients are compendial except PPG-12/SMDI copolymer

and polyoxyl-6 & polyoxyl-32 palmitostearate. These two non-compendial ingredients, either themselves or their components, have been used in approved products; therefore, they are not novel excipients.

The proposed commercial manufacturing scale is (b) (4). The designated commercial site, Galderma Production Canada Inc., is also the manufacturing site of Phase 3 clinical and registration stability batches. The commercial manufacturing process consists of the following

(b) (4)

Stability data provided in the initial submission to support an expiry period of 24 months for both cap and pump configurations at controlled room temperature (20-25°C) with excursions permitted between 15-30°C include long term (25°C/60% RH), intermediate (30°C/65% RH), and accelerated temperature (40°C/75% RH) data from three commercial (b) (4) batches. There are 6 months of long term data from the commercial batches for the pump configurations and 12 months for the cap configurations. Special stability data provided in the NDA to support storage/handling/shipping of the product include data from the following studies: 5°C, warm/cold temperature cycling, and free/thaw cycling. The applicant also proposes additional storage statements such as “Do not freeze or refrigerate.” and “Protect from light.” in SPL.

## B. Critical issues for review

### Establishment

- The Establishment Registration number for one testing laboratory, (b) (4) (b) (4) is missing. This issue is not considered to be a filing issue because this laboratory is only a backup to the primary testing laboratory (GPCI) and it is only for microbiology testing.

(b) (4)

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**D. Comments/Recommendation:**

The application is fileable from the CMC and quality perspective.

The major review issues of this NDA include dosage form, drug product specification, and drug product stability. Drug substance manufacturing site is located in (b) (4). Drug product manufacturing site is located in (b) (4). GMP inspection requests have been submitted.

Shulin Ding, Ph.D.  
Pharmaceutical Assessment Lead

Moo Jhong Rhee, Ph.D.  
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?	CFN# missing for one back-up testing lab.
x		Has an environmental assessment report or categorical exclusion been provided?	

### B. Technical Checklists

#### 1. Drug Substance Adapalene: Reference to DMF 8784

	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?	Also reference to DMF
	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?	Also 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?	Each noncompdial excipient is referenced to a DMF
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?	
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?	Some are not addressed*. But they are review issues not filing issues.
	x	Is a team review recommended?	
x		Are DMFs adequately referenced?	The LOA on the excipient, PPG-12/SMDI copolymer, has no DMF#

\*Outstanding ones are the following (1) nature of tin in PPG-12/SMDI copolymer, (2) homogeneity as in-process control, (3) polymorph in registration stability program, and (4) container extractables in registration stability program. Although not in the registration stability studies, special studies were conducted on Items (3) and described in the section on Pharmaceutical Development. Container extractables test is not typical in the registration stability program unless the special extractables study per USP<661> has unusual results. The applicant states in the NDA that all product contacting packaging components have tested for extractables and defers to DMFs for results.

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/s/

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Shulin Ding  
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CHEMIST

Moo-Jhong Rhee  
4/27/2009 03:23:56 PM  
CHEMIST  
Chief, Branch III