CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 091314Orig1s000

Name: Adapalene Gel, 0.1%

Sponsor: Glenmark Generics Inc., USA

Approval Date: July 1, 2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091314Orig1s000

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
Labeling Review(s)	**X**
Medical Review(s)	
Chemistry Review(s)	**X**
Pharm/Tox Review(s)	
Statistical Review(s)	**X**
Microbiology Review(s)	
Bioequivalence Review(s)	**X**
Other Review(s)	
Administrative & Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091314Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 091314

Glenmark Generics Inc., USA
Attention: William R. McIntyre, Ph.D.
EVP, Regulatory Affairs
750 Corporate Drive
Mahwah, NJ 07430

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated February 6, 2009, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Adapalene Gel, 0.1%.

Reference is also made to your amendments dated August 27, 2009, and January 25, 2010.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Adapalene Gel, 0.1%, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Differin Gel, 0.1%, of Galderma Laboratories LP.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

We note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS, See 505-1(i).

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/U_CM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91314	ORIG-1	GLENMARK GENERICS INC USA	ADAPALENE

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

/s/

ROBERT L WEST

07/01/2010

Deputy Director, Office of Generic Drugs
for Keith Webber, Ph.D.

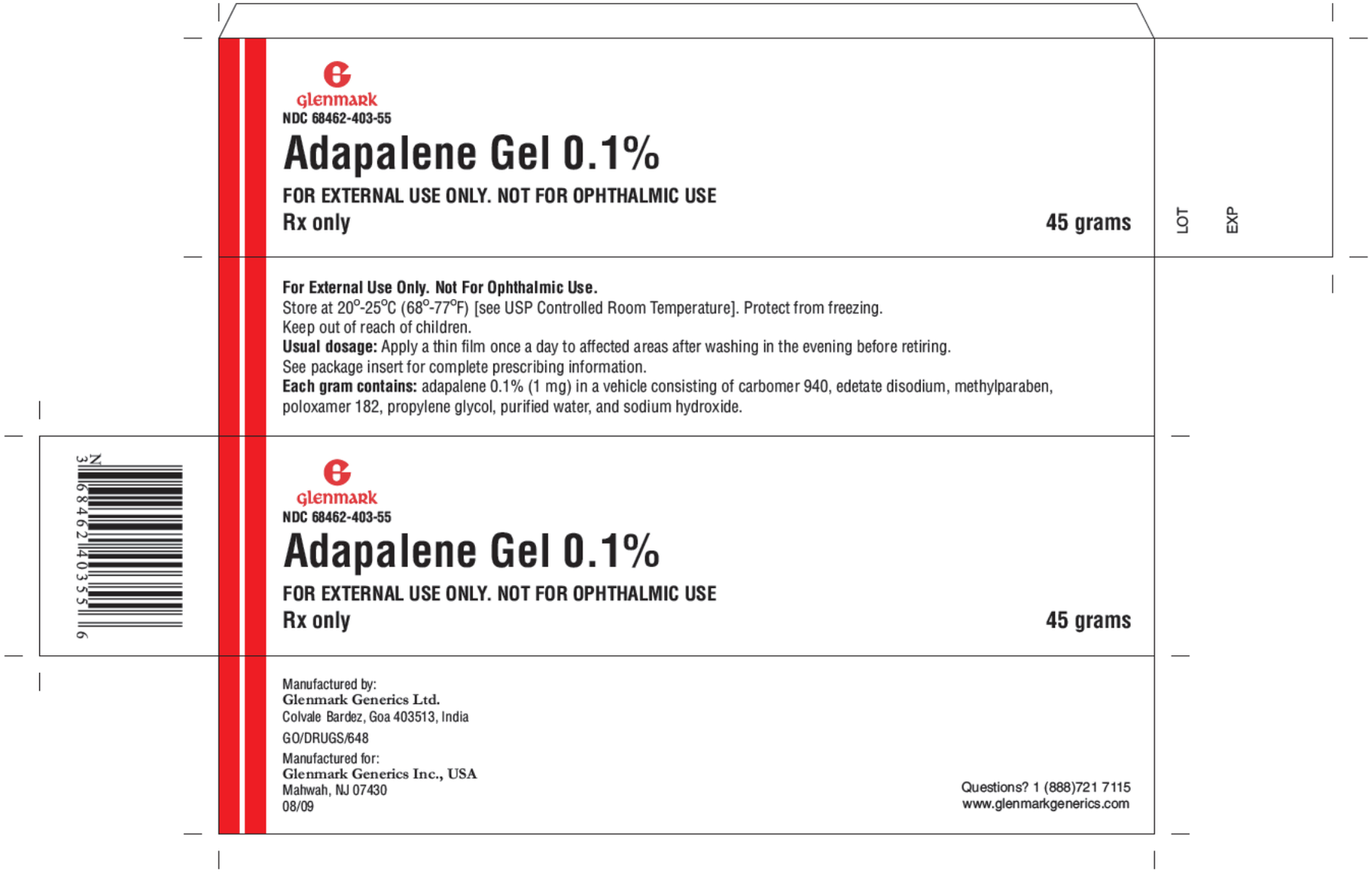
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091314Orig1s000

LABELING

SAME SIZE ARTWORK
CARTON SIZE: 162 mm x 38 mm x 31 mm



(b) (4) ADAPALENE GEL 0.1%, 45 G
SIZE: DIA 28 mm x 132 mm Length

Glenmark

NDC 68462-403-55

Adapalene Gel 0.1%

Rx only **45 grams**

For External Use Only. Not For Ophthalmic Use.
Store at 20° 25°C (68° 77°F) [see USP Controlled Room Temperature]. Protect from freezing.
Usual dosage: Apply a thin film once a day to affected areas after washing in the evening before retiring.
See package insert for complete prescribing information.
Each gram contains: adapalene 0.1% (1 mg) in a vehicle consisting of carbomer 940, edetate disodium, methylparaben, poloxamer 182, propylene glycol, purified water, and sodium hydroxide.
Lot no. and exp. date on crimp.

Manufactured by:
Glenmark Generics Ltd.
Colvale Bardez,
Goa 403513, India

Manufactured for:
Glenmark Generics Inc., USA
Mahwah, NJ 07430
08/09

GO/DRUGS/648

N 3 68462 40355 6

Questions? 1 (888)721-7115
www.glenmarkgenerics.com

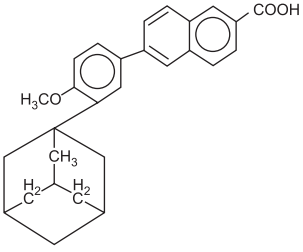
132 mm

Adapalene Gel, 0.1%

Rx Only

DESCRIPTION: Adapalene gel 0.1%, containing adapalene, is used for the topical treatment of acne vulgaris. Each gram of adapalene gel 0.1% contains adapalene 0.1% (1 mg) in a vehicle consisting of carbomer 940, edetate disodium, me hylparaben, poloxamer 182, p opylene glycol, purified water and sodium hyd oxide.

The chemical name of adapalene is 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid. Adapalene is a white to off-white powder which is soluble in tetrahyd ofuran, sparingly soluble in e hanol, and practically insoluble in water. The molecular formula is $C_{28}H_{28}O_3$ and molecular weight is 412.53. Adapalene is represented by the following structural formula:



CLINICAL PHARMACOLOGY: Adapalene is a chemically stable, retinoid-like compound. Biochemical and pharmacological p ofile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization, and inflammatory p ocesses all of which represent important features in he pa hology of acne vulgaris.

Mechanistically, adapalene binds to specific retinoic acid nuclear receptors but does not bind to he cytosolic receptor p otein. Al hough he exact mode of action of adapalene is unknown, it is suggested hat topical adapalene may normalize the differentiation of follicular epi helial cells resulting in decreased mic ocomedone formation.

Pharmacokinetics: Absorption of adapalene h ough human skin is low. Only trace amounts (<0.25 mg/mL) of parent substance have been found in he plasma of acne patients following ch onic topical application of adapalene in cont olled clinical trials. Excretion appears to be primarily by he biliary oute.

INDICATIONS AND USAGE: Adapalene is indicated for the topical treatment of acne vulgaris.

CONTRAINDICATIONS: Adapalene should not be administered to individuals who are hypersensitive to adapalene or any of he components in he vehicle gel.

WARNINGS: Use of adapalene should be discontinued if hypersensitivity to any of he ingredients is noted. Patients with sunbu n should be advised not to use the p oduct until fully recovered.

PRECAUTIONS: ***General:*** If a reaction suggesting sensitivity or chemical irritation occurs, use of he medication should be discontinued. Exposure to sunlight, including sunlamps, should be minimized during the use of adapalene. Patients who normally experience high levels of sun exposure, and hose wi h inherent sensitivity to sun, should be wa ned to exercise caution. Use of sunscreen p oducts and p otective clo hing over treated areas is recommended when exposure cannot be avoided. Wea her extremes, such as wind or cold, also may be irritating to patients under treatment with adapalene. Avoid contact wi h the eyes, lips, angles of he nose, and mucous membranes. The p oduct should not be applied to cuts, abrasions, eczematous skin, or sunbu ned skin.

Certain cutaneous signs and symptoms such as ery hema, dryness, scaling, bu ning, or pruritus may be experienced during treatment. These are most likely to occur during he first two to four weeks and will usually lessen wi h continued use of he medication. Depending upon he severity of adverse events, patients should be instructed to reduce the frequency of application or discontinue use.

Drug Interactions: As adapalene has he potential to p oduce local irritation in some patients, concomitant use of other potentially irritating topical products (medicated or abrasive soaps and cleansers, soaps and cosmetics hat have a st ong drying effect, and p oducts wi h high concentrations of alcohol, astringents, spices, or lime) should be app oached with caution. Particular caution should be exercised in using preparations containing sulfur, resorcinol, or salicylic acid in combination with adapalene. If hese preparations have been used, it is advisable not to start herapy with adapalene until he effects of such preparations in the skin have subsided.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies wi h adapalene have been conducted in mice at topical doses of 0.3, 0.9, and 2.6 mg/kg/day and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day, app oximately 4-75 times the maximal daily human topical dose. In he oral study, positive linear trends were observed in he incidence of follicular cell adenomas and carcinomas in he hy oid glands of female rats, and in he incidence of benign and malignant pheoch omocytomas in the adrenal medullas of male rats.

No photocarcinogenicity studies were conducted. Animal studies have shown an increased tumorigenic risk wi h he use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in he laboratory or to sunlight. Although he significance of hese studies to human use is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial UV irradiation sources.

In a series of *in vivo* and *in vitro* studies, adapalene did not exhibit mutagenic or genotoxic activities.

Pregnancy: Teratogenic effects. Pregnancy Category C. No teratogenic effects were seen in rats at oral doses of adapalene 0.15 to 5.0 mg/kg/day, up to 120 times he maximal daily human topical dose. Cutaneous oute teratology studies conducted in rats and rabbits at doses of 0.6, 2.0, and 6.0 mg/kg/day, up to 150 times the maximal daily human topical dose exhibited no fetotoxicity and only minimal increases in supe numerary ribs in rats. There are no adequate and well-cont olled studies in pregnant women. Adapalene should be used during pregnancy only if he potential benefit justifies he potential risk to he fetus.

Nursing Mothers: It is not known whether his drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when adapalene is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 12 have not been established.

ADVERSE REACTIONS: Some adverse effects such as ery hema, scaling, dryness, pruritus, and bu ning will occur in 10-40% of patients. Pruritus or bu ning immediately after application also occurs in app oximately 20% of patients. The following additional adverse experiences were reported in app oximately 1% or less of patients: skin irritation, bu ning/stinging, ery hema, sunbu n, and acne flares. These are most commonly seen during he first mon h of therapy and decrease in frequency and severity thereafter. All adverse effects with use of adapalene during clinical trials were reversible upon discontinuation of herapy.

OVERDOSAGE: Adapalene is intended for cutaneous use only. If the medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, or discomfort may occur. The acute oral toxicity of adapalene in mice and rats is greater than 10 mL/kg. Ch onic ingestion of he drug may lead to he same side effects as hose associated with excessive oral intake of Vitamin A.

DOSAGE AND ADMINISTRATION: Adapalene gel 0.1% should be applied once a day to affected areas after washing in he evening before retiring. A thin film of he gel should be applied, avoiding eyes, lips, and mucous membranes.

During he early weeks of herapy, an apparent exacerbation of acne may occur. This is due to he action of the medication on previously unseen lesions and should not be considered a reason to discontinue herapy. Therapeutic results should be noticed after eight to twelve weeks of treatment.

HOW SUPPLIED: Adapalene gel, 0.1% is supplied in the following size:

45g laminate tube NDC 68462-403-55

Storage: Store at cont olled room temperature 68° - 77°F (20° - 25°C), excursions permitted between 59° and 86°F (15° - 30°C). P otect f om freezing.

Manufactured by:
Glenmark Generics Ltd.
Colvale-Bardez, Goa 403 513, India

Manufactured for:

Glenmark Generics Inc., USA
Mahwah, NJ 07430

Questions? 1 (888)721-7115
www.glenmarkgenerics.com

August 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091314Orig1s000

LABELING REVIEWS

APPROVAL SUMMARY #1

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 91-314

Date of Submission: **August 27, 2009**

Applicant's Name: Glenmark Generics Inc., USA

Established Name: Adapalene Gel, 0.1%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): Do you have Final Printed Labels and Labeling? **YES**

Container Labels: (45 g) – Satisfactory in final print as of **August 27, 2009** electronic submission.

Carton Labeling: (45 g) – Satisfactory in final print as of **August 27, 2009** electronic submission.

Insert Labeling: Satisfactory in final print as of **August 27, 2009** electronic submission.

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Differin Gel, 0.1%
- NDA Number: 20-380
- NDA Drug Name: Adapalene Gel, 0.1%
- NDA Firm: Galderma
- Date of Approval of NDA Insert: **NDA 20-380/S-004: Approved September 5, 2007**
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side-by-side comparison
- Basis of Approval for the Carton Labeling: Side-by-side comparision
- Revisions needed post-approval: NO
- Patents/Exclusivities: Refer to chart below.

Patent Data – NDA 20-380

No	Expiration	Use Code	Use	File
4717720	May 31, 2010			III
RE34440	May 31, 2008	U-275	METHOD OF USE OF THE DRUG SUBSTANCE	III

Exclusivity Data - NDA 20-380

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There is no unexpired exclusivity for this product		NONE

FOR THE RECORD:

1. MODEL LABELING:

This review was based on the labeling for the reference listed drug, Differin Gel, 0.1% [NDA 20-380/S-004: Approved September 5, 2007] by Galderma Laboratories.

2. PATIENTS/EXCLUSIVTIES:

Patent Data – NDA 20-380

No	Expiration	Use Code	Use	File
4717720	**May 31, 2010**			III
RE34440	May 31, 2008	U-275	METHOD OF USE OF THE DRUG SUBSTANCE	III

Exclusivity Data - NDA 20-380

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There is no unexpired exclusivity for this product		NONE

3. INACTIVE INGREDIENTS

There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.

Proposed Generic Adapalene Gel 0.1% Mfg by Glenmark Generics Ltd., India	**Reference listed drug Differin® (Adapalene) Gel 0.1% Mfg by Galderma Laboratories, L.P.**	**Function**
Edetate Disodium	Edetate Disodium	(b) (4)
Carbomer 940	Carbomer 940	
Methylparaben	Methylparaben	
Propylene Glycol	Propylene Glycol	
Poloxamer 182	Poloxamer 182	
Sodium Hydroxide	Sodium Hydroxide	
Purified Water	Purified Water	
--	Hydrochloric Acid	pH adjustment

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- USP: Preserve in collapsible tubes, at controlled room temperature.
- RLD: Store between 15° - 30°C (59 - 86°F)
- ANDA: Store at controlled room temperature 20° - 25°C (68 - 77°F)
-

5. PACKAGE CONFIGURATION

- RLD: Packaged in 45g and 75 g laminate tubes.
- ANDA: 45 g Laminated tube (b) (4)

6. CONTAINER/CLOSURE: 45 g Laminated Tube (b) (4)

7. FNISHED DOSAGE FORM

- RLD: Gel
- ANDA: (b) (4) gel.

8. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Glenmark Generics Limited
(b) (4)
Goa 403 513, India

Date of Submission: August 27, 2009

Primary Reviewer: Beverly Weitzman **Date:**

Team Leader: John Grace **Date:**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91314	ORIG-1	GLENMARK GENERICS INC USA	ADAPALENE
ANDA-91314	ORIG-1	GLENMARK GENERICS INC USA	ADAPALENE

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

/s/

BEVERLY WEITZMAN
09/08/2009

JOHN F GRACE
09/09/2009

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 91-314

Date of Submission: February 6, 2009

Applicant's Name: Glenmark Generics Inc., USA

Established Name: Adapalene Gel, 0.1%

Labeling Deficiencies:

1. **CONTAINER** (45 *g):*
   a. Revise your storage statement to read as "Stored at 20° - 25°C (68° - 77°F) [See USP Controlled Room Temperature]" Protect from freezing.
   b. *P*lease assure that your container label is of actual size, color and clarity when submitting in final printed labeling.
2. **CARTON** (45 g):
   a. **Principal panels**: Repeat the statement of route of administration and "NOT FOR OPHTHALMIC USE" appearing on the side panel, such that is appears with prominence on each of the principal display panels.
   b. Recommend adding the statement "Keep out of reach of children".
   c. See CONTAINER comment (a).
3. **INSERT:** Satisfactory in DRAFT

Revise your labeling, as instructed above, and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with that of your last submission with all differences annotated and explained.

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): Do you have Final Printed Labels and Labeling?

Container Labels: (45 g) – Satisfactory in final print as of electronic submission.

Carton Labeling: (45 g) – Satisfactory in final print as of electronic submission.

Insert Labeling: Satisfactory in final print as of electronic submission.

BASIS OF APPROVAL:

- Was this approval based upon a petition? No
- What is the RLD on the 356(h) form: Differin Gel, 0.1%
- NDA Number: 20-380
- NDA Drug Name: Adapalene Gel, 0.1%
- NDA Firm: Galderma
- Date of Approval of NDA Insert: **NDA 20-380/S-004: Approved September 5, 2007**
- Has this been verified by the MIS system for the NDA? Yes
- Was this approval based upon an OGD labeling guidance? No
- Basis of Approval for the Container Labels: Side-by-side comparison
- Basis of Approval for the Carton Labeling: Side-by-side comparision
- Revisions needed post-approval: NO
- Patents/Exclusivities: Refer to chart below.

Patent Data – NDA 20-380

No	Expiration	Use Code	Use	File
4717720	May 31, 2010			III
RE34440	May 31, 2008	U-275	METHOD OF USE OF THE DRUG SUBSTANCE	III

Exclusivity Data - NDA 20-380

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There is no unexpired exclusivity for this product		NONE

FOR THE RECORD:

1. MODEL LABELING:

This review was based on the labeling for the reference listed drug, Differin Gel, 0.1% [NDA 20-380/S-004: Approved September 5, 2007] by Galderma Laboratories.

2. PATIENTS/EXCLUSIVTIES:

Patent Data – NDA 20-380

No	Expiration	Use Code	Use	File
4717720	**May 31, 2010**			III
RE34440	May 31, 2008	U-275	METHOD OF USE OF THE DRUG SUBSTANCE	III

Exclusivity Data - NDA 20-380

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There is no unexpired exclusivity for this product		NONE

3. INACTIVE INGREDIENTS

There does not appear to be a discrepancy in inactives between the DESCRIPTION and the composition statement.

Proposed Generic Adapalene Gel 0.1% Mfg by Glenmark Generics Ltd., India	Reference listed drug Differin® (Adapalene) Gel 0.1% Mfg by Galderma Laboratories, L.P.	Function
Edetate Disodium	Edetate Disodium	(b) (4)
Carbomer 940	Carbomer 940	
Methylparaben	Methylparaben	
Propylene Glycol	Propylene Glycol	
Poloxamer 182	Poloxamer 182	
Sodium Hydroxide	Sodium Hydroxide	
Purified Water	Purified Water	
--	Hydrochloric Acid	pH adjustment

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

- USP: Preserve in collapsible tubes, at controlled room temperature.
- RLD: Store between 15° - 30°C (59 - 86°F)
- ANDA: Store at controlled room temperature 20° - 25°C (68 - 77°F)
-

5. PACKAGE CONFIGURATION

- RLD: Packaged in 45g and 75 g laminate tubes.
- ANDA: 45 g Laminated tube (b) (4)

6. CONTAINER/CLOSURE: 45 g Laminated Tube (b) (4)

7. FNISHED DOSAGE FORM

- RLD: Gel
- ANDA: (b) (4) gel.

8. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Glenmark Generics Limited
(b) (4)
Goa 403 513, India

Date of Submission: October 24, 2008

Primary Reviewer: Beverly Weitzman **Date:**

Team Leader: John Grace **Date:**

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
ANDA 91314	ORIG 1	GLENMARK GENERICS INC USA	ADAPALENE

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

/s/

BEVERLY WEITZMAN
08/18/2009

JOHN F GRACE
08/20/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091314Orig1s000

CHEMISTRY REVIEWS

ANDA 91-314

Adapalene Gel 0.1%

Glenmark Generics Ltd.

Liang-Lii Huang, Ph.D.

OGD/DC1

Table of Contents

Table of Contents 2

Chemistry Review Data Sheet 3

The Executive Summary 8

I. Recommendations 8

A. Recommendation and Conclusion on Approvability 8

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 8

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s) 8

B. Description of How the Drug Product is Intended to be Used 9

C. Basis for Approvability or Not-Approval Recommendation 9

Chemistry Assessment 10

Chemistry Review Data Sheet

1. ANDA 91-314

2. REVIEW #: 2

3. REVIEW DATE: 3/15/10

4. REVIEWER: Liang-Lii Huang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	February 6, 2009
Acceptable for filing	February 9, 2009
Minor amendment	January 25, 2010

7. NAME & ADDRESS OF APPLICANT:

Glenmark Generics Inc. USA
Attention: William R. McIntyre
750 Corporate Drive
Mahwah, NJ 07430

Tel: 201-684-8017 Fax: 201-831-0080

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN):

Adapalene Gel 0.1%

9. LEGAL BASIS FOR SUBMISSION:

RLD: Differin® (Adapalene) Gel 0.1%
NDA 20-380, NDA holder: Galderma Laboratory L.P.
Comparison between Generic Drug and Reference Listed Drug [505(j)(2)(A)]
Conditions of use, active ingredient, and inactive ingredients, route of administration, dosage form, and strength of the proposed drug product are the same as that of the RLD.

The US Patent N o. 4,717,720 held by Galderma Laboratory L.P. which includes a claim related to the reference listed drug Differin® (Adapalene) Gel 0.1% (NDA 20-380), will expire on May 31, 2010.

US Patent No. RE34,440 will expire May 31, 2010.

Appl No	Prod No	Patent No	Patent expiration	Drug substance	Drug Product	Patent use code	Delist requested
020380	001	4717720	5/31/10	claim	claim	U-275	

Exclusivity data

There is no unexpired exclusivity for this product.

PARAGRAPH III PATENT CERTIFICATION
Pursuant to 505 (j)(2)(A)(vii)(III) of the FD&C act, Glenmark hereby certifies that US patent No. 4,717,720, expiring May 31, 2010, will not be infringed because Glenmark will not seek to commercially manufacture, use, sell or offer for sale within the united states, or import into the united states, Glenmark's Adapalene Gel 0.1% product until after the expiration of US patent No. 4,717,720.

Pursuant to 505 (j)(2)(A)(vii)(III) of the FD&C act, Glenmark hereby certifies that US patent No.RE34,440, expiring May 31, 2010, will not be infringed because Glenmark will not seek to commercially manufacture, use, sell or offer for sale within the united states, or import into the united states, Glenmark's Adapalene Gel 0.1% product until after the expiration of US patent No. RE34,440.

Exclusivity statement
Pursuant to 2I CFR Part 314.94(a)(3)(ii), information published in the Approved Drug Products with Therapeutic Equivalence Evaluations, currently updated electronic version, published by the Food and Drug Administration as of the date of this filing, there is no unexpired exclusivity covering Adapalene Gel 0.1%.

10. PHARMACOL. CATEGORY:

The drug product is intended to be used for topical treatment of acne vulgaris.

11. DOSAGE FORM:

Gel

12. STRENGTH/POTENCY:
    0.1%

13. ROUTE OF ADMINISTRATION:
    topical

14. Rx/OTC DISPENSED: _X_Rx ___OTC

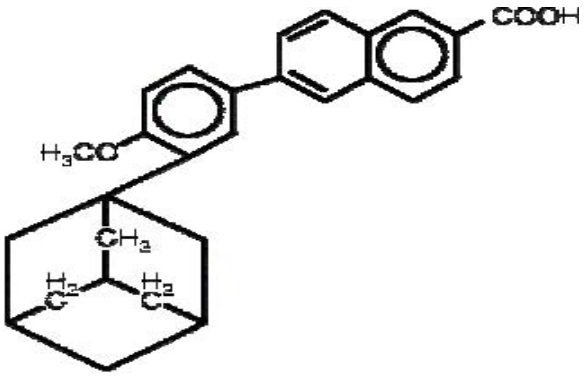
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

    _____SPOTS product – Form Completed

    ___X___Not a SPOTS product

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

    Chemical name: 6-(4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)phenyl)-2-naphthalenecarboxylic acid CAS# 106685-40-9 Adapalene



Molecular formula: $C_{28}H_{28}O_3$ MW 412.53

17. RELATED/SUPPORTING DOCUMENTS:

A. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
18756	II	Glenmark Generics Ltd, India	Adapalene	1	adequate	9/4/2009	Reviewer: LL Huang, Ph.D.
(b) (4)	III	(b) (4)		4			

[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
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	4/16/09	
Methods Validation	Not required		
Labeling	Acceptable	9/9/09	B. Weitzman
Bioequivalence	pending		
EA	EA is not required.		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___X_ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 91-314

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC is approvable.

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

N/A

II. Summary of Chemistry Assessments

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

Drug product

Adapalene Gel 0.1% containing adapalene, is used for the topical treatment of acne vulgaris. Each gram of adapalene gel 0.1% contains adapalene 0.1% (1 mg) in a vehicle consisting of carbomer 940, edentate disodium, methylparaben, poloxamer 182, propylene glycol, purified water and sodium hydroxide.

Drug substance

The Adapalene is a white to off white powder. (b) (4)

(b) (4)

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

The drug product is intended to be used for topical treatment of acne vulgaris.

C. Basis for Approvability or Not-Approval Recommendation

CMC is approvable.

Question Base Review
Table of content

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

2.3. Quality Overall Summary
2.3.S DRUG SUBSTANCE

2.3.S.1 General Information
2.3.S.2 Manufacture
2.3.S.3 Characterization
2.3.S.4 Control of Drug Substance
2.3.S.5 Reference Standards
2.3.S.6 Container Closure System
2.3.S.7 Stability

2.3.P DRUG PRODUCT

2.3.P.1 Description and Composition of Drug Product
2.3.P.2 Pharmaceutical Development
- 2.3.P.2.1 Components of the Product
  - 2.3.P.2.1.1 Drug Substance
  - 2.3.P.2.1.2 Excipients
- 2.3.P.2.2 Drug Product
- 2.3.P.2.3 Manufacturing Process Development
- 2.3.P.2.4 Container Closure System

2.3.P.3 Manufacture
2.3.P.4 Control of Excipients
2.3.P.5 Control of Drug Product
2.3.P.5.1 Specifications
2.3.P.6 Reference Standards and Materials
2.3.P.7 Container Closure System
2.3.P.8 Stability

A APPENDICES

A.1 Facilities and Equipment (biotech only)
A.2 Adventitious Agents Safety Evaluation
A.3 Novel Excipients

R REGIONAL INFORMATION

R1 Executed Batch Records
R2 Comparability Protocols
R3 Methods Validation Package

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert
B. Environmental Assessment Or Claim Of Categorical Exclusion

III. List Of Deficiencies To Be Communicated

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

2.3 Quality Overall Summary (QOS)

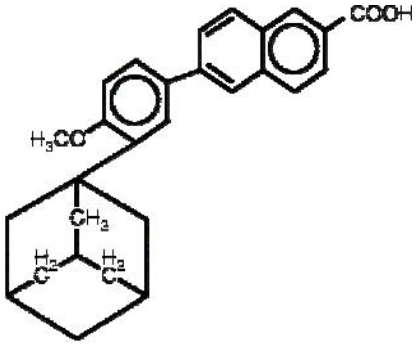
2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product:	--
Non-Proprietary Name of Drug Product:	Adapalene Gel 0.1%
Non-Proprietary Name of Drug Substance:	Adapalene
Company Name:	Glenmark Generics Inc.,USA
Dosage Form:	Gel
Strength(s):	0.1%
Route of Administration:	Topical
Proposed Indication(s):	Topical treatment of acne vulgaris

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

What are the nomenclature, molecular structure, molecular formula and molecular weight?

Chemical Name:	6-(4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)phenyl)-2-naphthalenecarboxylic acid
CAS #:	106685-40-9
USAN:	Adapalene
Molecular Structure:	
Molecular Formula:	$C_{28}H_{28}O_3$
Molecular Weight:	412.53

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

Acceptable 9/9/09 B. Weitzman

B. Environmental Assessment Or Claim Of Categorical Exclusion

Satisfactory

Adapalene Gel 0.1% to be manufactured by Glenmark Generics Limited, Bardez, Goa, India and marketed by Glenmark Generics Inc., USA will be administered at the same dosage levels, the same duration and for the same indications as NDA 020380 Differin® (Adapalene Gel 0.1%) manufactured by Galderma Laboratories L.P. Therefore, Glenmark Generics Limited, India hereby requests exclusion as specified in 21 CFR 25.31 (a) from the preparation of an environmental assessment.
Glenmark Generics Limited, Bardez, Goa is also in full compliance with applicable local, state, and federal environmental rules and regulations.

III. List Of Deficiencies To Be Communicated

cc: ANDA 91-314
ANDA DUP 91-314
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627 /Liang-Lii Huang, Ph.D. /3/16/10

HFD-627/ James Fan, Team Leader/3/30/10

HFD-617/T. Tran, PM/3/31/10

V:\Chemistry Division I\Team 3\FIRMSAM\GLENMARK\LTRS&RVS\91-314 rev2.doc

March 16, 2010

TYPE OF LETTER: APPROVABLE

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91314	ORIG-1	GLENMARK GENERICS INC USA	ADAPALENE

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

/s/

LIANG LII HUANG
04/01/2010

TRANG Q TRAN
04/01/2010

JAMES M FAN
04/12/2010

ANDA 91-314

Adapalene Gel 0.1%

Glenmark Generics Ltd.

Liang-Lii Huang, Ph.D.

OGD/DC1

Table of Contents

Table of Contents 2

Chemistry Review Data Sheet 3

The Executive Summary 8

I. Recommendations 8

A. Recommendation and Conclusion on Approvability 8

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 8

II. Summary of Chemistry Assessments 8

A. Description of the Drug Product(s) and Drug Substance(s) 8

B. Description of How the Drug Product is Intended to be Used 9

C. Basis for Approvability or Not-Approval Recommendation 9

Chemistry Assessment 10

Chemistry Review Data Sheet

1. ANDA 91-314

2. REVIEW #: 1

3. REVIEW DATE: 11-Jul-2009;8/6/09

4. REVIEWER: Liang-Lii Huang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	February 6, 2009
Acceptable for filing	February 9, 2009

7. NAME & ADDRESS OF APPLICANT:

Glenmark Generics Inc. USA
Attention: William R. McIntyre
750 Corporate Drive
Mahwah, NJ 07430

Tel: 201-684-8017 Fax: 201-831-0080

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN):
Adapalene Gel 0.1%

9. LEGAL BASIS FOR SUBMISSION:

RLD: Differin® (Adapalene) Gel 0.1%
NDA 20-380, NDA holder: Galderma Laboratory L.P.
Comparison between Generic Drug and Reference Listed Drug [505(j)(2)(A)]
Conditions of use, active ingredient, and inactive ingredients, route of administration, dosage form, and strength of the proposed drug product are the same as that of the RLD.

The US Patent N o. 4,717,720 held by Galderma Laboratory L.P. which includes a claim related to the reference listed drug Differin® (Adapalene) Gel 0.1% (NDA 20-380), will expire on May 31, 2010.

US Patent No. RE34,440 will expire May 31, 2010.

Appl No	Prod No	Patent No	Patent expiration	Drug substance claim	Drug Product claim	Patent use code	Delist requested
020380	001	4717720	5/31/10			U-275	

Exclusivity data

There is no unexpired exclusivity for this product.

PARAGRAPH III PATENT CERTIFICATION

Pursuant to 505 (j)(2)(A)(vii)(III) of the FD&C act, Glenmark hereby certifies that US patent No. 4,717,720, expiring May 31, 2010, will not be infringed because Glenmark will not seek to commercially manufacture, use, sell or offer for sale within the united states, or import into the united states, Glenmark's Adapalene Gel 0.1% product until after the expiration of US patent No. 4,717,720.

Pursuant to 505 (j)(2)(A)(vii)(III) of the FD&C act, Glenmark hereby certifies that US patent No.RE34,440, expiring May 31, 2010, will not be infringed because Glenmark will not seek to commercially manufacture, use, sell or offer for sale within the united states, or import into the united states, Glenmark's Adapalene Gel 0.1% product until after the expiration of US patent No. RE34,440.

Exclusivity statement
Pursuant to 2I CFR Part 314.94(a)(3)(ii), information published in the Approved Drug Products with Therapeutic Equivalence Evaluations, currently updated electronic version, published by the Food and Drug Administration as of the date of this filing, there is no unexpired exclusivity covering Adapalene Gel 0.1%.

10. PHARMACOL. CATEGORY:

The drug product is intended to be used for topical treatment of acne vulgaris.

11. DOSAGE FORM:

Gel

12. STRENGTH/POTENCY:
    0.1%

13. ROUTE OF ADMINISTRATION:
    topical

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

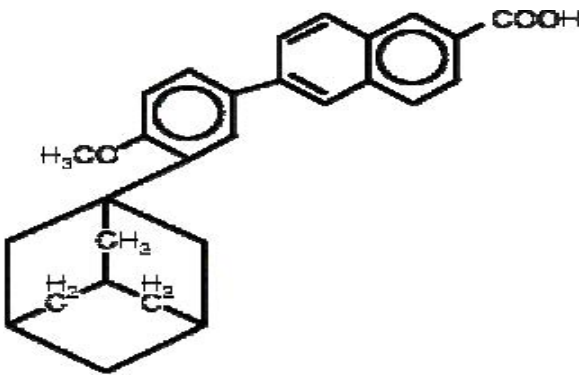
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

    _____SPOTS product – Form Completed

    ___X___Not a SPOTS product

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

Chemical name: 6-(4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)phenyl)-2-naphthalenecarboxylic acid CAS# 106685-40-9 Adapalene



Molecular formula: $C_{28}H_{28}O_3$ MW 412.53

17. RELATED/SUPPORTING DOCUMENTS:

A. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
18756	II	Glenmark Generics Ltd, India	Adapalene	1	adequate	9/4/2009	Reviewer: LL Huang, Ph.D.
(b) (4)	III	(b) (4)		4			

[1] Action codes for DMF Table:
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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
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	4/16/09	
Methods Validation	Not required		
Labeling	Acceptable	9/9/09	B. Weitzman
Bioequivalence	pending		
EA	EA is not required.		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___X_ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 91-314

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application ANDA 91-314 is not approvable.

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

N/A

II. Summary of Chemistry Assessments

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

Drug product

Adapalene Gel 0.1% containing adapalene, is used for the topical treatment of acne vulgaris. Each gram of adapalene gel 0.1% contains adapalene 0.1% (1 mg) in a vehicle consisting of carbomer 940, edentate disodium, methylparaben, poloxamer 182, propylene glycol, purified water and sodium hydroxide.

Drug substance

The Adapalene is a white to off white powder. (b) (4)

(b) (4)

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

The drug product is intended to be used for topical treatment of acne vulgaris.

C. Basis for Approvability or Not-Approval Recommendation

This application is not approvable due to deficiencies found in the drug substance and drug product areas.

Table of content

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

2.3. Quality Overall Summary
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2.3.S.3 Characterization
2.3.S.4 Control of Drug Substance
2.3.S.5 Reference Standards
2.3.S.6 Container Closure System
2.3.S.7 Stability

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2.3.P.2 Pharmaceutical Development
- 2.3.P.2.1 Components of the Product
  - 2.3.P.2.1.1 Drug Substance
  - 2.3.P.2.1.2 Excipients
- 2.3.P.2.2 Drug Product
- 2.3.P.2.3 Manufacturing Process Development
- 2.3.P.2.4 Container Closure System

2.3.P.3 Manufacture
2.3.P.4 Control of Excipients
2.3.P.5 Control of Drug Product
2.3.P.5.1 Specifications
2.3.P.6 Reference Standards and Materials
2.3.P.7 Container Closure System
2.3.P.8 Stability

A APPENDICES
A.1 Facilities and Equipment (biotech only)
A.2 Adventitious Agents Safety Evaluation
A.3 Novel Excipients

R REGIONAL INFORMATION
R1 Executed Batch Records
R2 Comparability Protocols
R3 Methods Validation Package

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert
B. Environmental Assessment Or Claim Of Categorical Exclusion

III. List Of Deficiencies To Be Communicated

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

2.3 Quality Overall Summary (QOS)

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product:	--
Non-Proprietary Name of Drug Product:	Adapalene Gel 0.1%
Non-Proprietary Name of Drug Substance:	Adapalene
Company Name:	Glenmark Generics Inc.,USA
Dosage Form:	Gel
Strength(s):	0.1%
Route of Administration:	Topical
Proposed Indication(s):	Topical treatment of acne vulgaris

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

What are the nomenclature, molecular structure, molecular formula and molecular weight?

Chemical Name:	6-(4-methoxy-3-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)phenyl)-2-naphthalenecarboxylic acid
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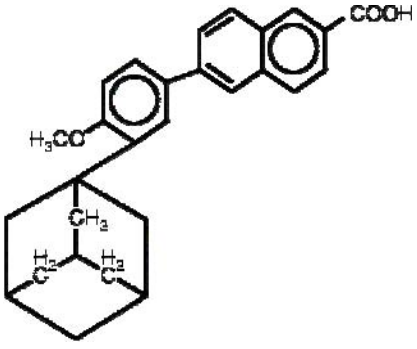
USAN:	Adapalene
Molecular Structure:	
Molecular Formula:	$C_{28}H_{28}O_3$
Molecular Weight:	412.53

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

Acceptable 9/9/09 B. Weitzman

B. Environmental Assessment Or Claim Of Categorical Exclusion

Satisfactory

Adapalene Gel 0.1% to be manufactured by Glenmark Generics Limited, Bardez, Goa, India and marketed by Glenmark Generics Inc., USA will be administered at the same dosage levels, the same duration and for the same indications as NDA 020380 Differin® (Adapalene Gel 0.1%) manufactured by Galderma Laboratories L.P. Therefore, Glenmark Generics Limited, India hereby requests exclusion as specified in 21 CFR 25.31 (a) from the preparation of an environmental assessment.
Glenmark Generics Limited, Bardez, Goa is also in full compliance with applicable local, state, and federal environmental rules and regulations.

III. List Of Deficiencies To Be Communicated

Chemistry Comments to be Provided to the Applicant

ANDA: 91-314 APPLICANT: Glenmark Generics Limited

DRUG PRODUCT: Adapalene Gel 0.1%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)

2.

3.

4.

5.

6.

7.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all available long-term drug product stability data.

2. Information related to bioequivalency is under review. After the review is completed, any deficiencies found will be communicated to you under separate covers.

3. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 91-314
ANDA DUP 91-314
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-627 /Liang-Lii Huang, Ph.D. /9-3-2009

HFD-627/ James Fan, Team Leader/9-15-2009

HFD-617/N. Patel, PM/10-14-2009

F/T: np

V:\Chemistry Division I\Team 3\FIRMSAM\GLENMARK\LTRS&RVS\91-314 rev1.doc

October 20, 2009

TYPE OF LETTER: NOT APPROVABLE -MINOR/

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91314	ORIG-1	GLENMARK GENERICS INC USA	ADAPALENE

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

/s/

LIANG LII HUANG
10/22/2009

JAMES M FAN
10/23/2009

NITIN K PATEL
10/23/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091314Orig1s000

STATISTICAL REVIEWS

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

ANDA/Serial Number:	91-314
Drug Name:	Generic version of Adapalene Gel, 0.1%
Indication(s):	Topical treatment of acne vulgaris
Reference Listed Drug:	Differin® 0.1% Gel (Galderma Laboratories)
Applicant:	Glenmark Generics Inc. USA
Date(s):	February 6, 2009
Biometrics Division:	DB6
Statistical Reviewer:.	Mohamed Nagem, Ph.D.
Concurring Reviewers:	Stella Grosser, Ph.D., Team Leader
Medical Division:	Clinical team in OGD
Clinical Team:	Nicole Lee, Pharm. D.
Keywords:	inflammatory and non-inflammatory lesion count

Objectives of the study

The primary objective of the study was to establish the bioequivalence of the test product, Glenmark Generics Inc. USA, Adapalene Gel, 0.1%, and the reference product, Galderma Laboratories, Inc., Differin® Topical Gel (adapalene 0.1%), and to show superiority of the two active treatments to the vehicle gel, in the treatment of acne vulgaris.

Remarks

The sponsor submitted SAS datasets and programs to the Electronic Document Room (EDR), CDER on February 6, 2009. The statistical analyses used information from datasets stored in "http://edr.fda.gov:7777/edr/EDR_Main.jsp".

Study Design (Protocol # GLK609)

This was a 3-arm parallel-group double-blind study in patients with moderate to severe Acne Vulgaris. The three gels were the test product (Glenmark Pharmaceuticals, Ltd.), the reference product (Differin® 0.1% Gel of Galderma Laboratories, Inc.), and the placebo arm without an active drug (Glenmark Pharmaceuticals's vehicle gel).

A total of 750 patients (300 test, 300 reference, and 150 vehicle) was randomized into the study. Patients were enrolled and randomly assigned to three treatment groups in a ratio of 2:2:1 and were to receive one of the following three treatments:

1. Test Product Group: Adapalene Gel 0.1% (Glenmark Pharmaceuticals, Ltd.), Lot Number: Q15727001, Expiration Date: November 2009.
2. Reference Group: Differin® 0.1% Gel (Galderma Laboratories), Lot Number: 052827 Expiry Date: August 2010.

3. Vehicle Gel Group: Vehicle without active drug (Glenmark Pharmaceuticals) Lot #: 040604.

For all treatment groups the patient instructions for administration of the study drug were the same. Patients were told to apply the study drug as a thin layer to the entire face every evening after washing their face with the hypo-allergenic soap provided and rinsing and gently drying the area for 84 days.

The sponsor's study (protocol # GLK609) was reviewed to evaluate bioequivalence of the test product and the reference product. The sponsor's primary endpoints for this study are:

(1) The mean percent change from baseline in inflammatory lesion count, and (2) The mean percent change from baseline in non-inflammatory lesion count, on Day 84. The sponsor's proposed primary endpoints were evaluated for bioequivalence and secondary parameters were considered as supportive information.

Inclusion Criteria: Subjects with the following characteristics were eligible for inclusion in the study:

Inclusion Criteria

1. Male or non-pregnant, non-lactating female, 12-40 years of age inclusive.
2. Signed informed consent form and met all criteria of current FDA regulations.
3. Female of child bearing potential agreed to abstain from sexual intercourse or use a reliable method of contraception during the study (e.g., condom, IUD, oral, transdermal, injected or implanted hormonal contraceptives).
4. Had moderate to severe facial acne which was defined as having at least 20 but no more than 60 inflammatory lesions (papules + pustules), and at least 25 and no more than 100 non-inflammatory lesions (open and closed comedones), with no more than 2 nodules. Had a Baseline Physician's Global Assessment (PGA) score of 3,4 or 5.

Exclusion Criteria

1. More than 2 facial nodular lesions, any nodules present were documented but were not included in the inflammatory lesion count.
2. Active cystic acne
3. Acne conglobata
4. Significant facial hair such as beards or tattoos or excessive facial scarring that, in the Investigator's opinion would have interfered with the evaluation of the patient's acne.
5. Facial sunburn
6. Any dermatological condition other than acne vulgaris that, in the Investigator's opinion may have interfered with the evaluation of the patient's acne (e.g., rosacea, psoriasis, dermatitis)
7. Females who were pregnant, lactating or likely to become pregnant during the study
8. History of allergy or sensitivity to adapalene or other retinoids or history of any drug hypersensitivity or intolerance which, in the Investigator's opinion, would have compromised the safety of the patient or the study
9. Significant history or current evidence of chronic infectious disease, system disorder, organ disorder or other medical condition that, in the Investigator's opinion would have placed the study participant at undue risk by participation
10. Use of any topical antibiotics or topical steroids used on the face and any oral antibiotics known to treat acne and any systemic steroids within 28 days of the first dosing
11. Chronic use (more than three times per week on average) of any anti-inflammatory products (systemic or topical) within 28 days of the first dosing day. The occasional use of NSAIDs was not a reason for exclusion.
12. Use of oral isotretinoin (Accutane®) within 6 months. Use of topical tretinoin (Retin-A®) or adapalene (Differin®), tazarotene (Tazorac®) or azelaic acid (Azelex®) within 28 days of the first dosing day.
13. Receipt of any drug as part of a research study within 30 days prior to dosing
14. Use of any medicated facial products (soaps, lotions, moisturizers, etc.) or other facial cleansing agents for 14 days prior to study enrollment.
15. Previous participation in this study

Study procedures performed at each visit

Procedure	**Visit 1** Baseline	**Visit 2**[a] 28 Days (± 4 days)	**Visit 3** 56 Days (± 4 days)	**Visit 4** End of Study 84 Days (± 4 days)
Informed Consent/Assent	X			
Medical History	X			
Vital signs	X			X
Pregnancy Test	X			X
Lesion Counts	X	X	X	X
Physician's Global Assessment	X	X	X	X
Concomitant Medication	X	X	X	X
Dispensed Study Medication	X	X	X	
Provide/Review Patient Diary	X	X	X	X
Adverse Events		X	X	X
Evaluation of Patient Compliance to the Protocol		X	X	X
Return of Study Medication		X	X	X
Discharge from Study				X

Outcome variables at visit 4 (Day 84±4)

Lesion Counts:

The same investigator was to assess the subject's facial lesion count by counting the number of facial pustules and papules. "Baseline" for lesion count was defined as the assessment performed on the day that study medication was initially dispensed.

- Change from baseline was calculated as: baseline lesion count – current lesion count (at visit 4).

- Mean percent change from baseline was calculated as:

$$\frac{\text{(Baseline lesion count – Current lesion count (at visit 4))} \times 100\%}{\text{Baseline lesion count}}$$

Physician's Global Assessment (PGA) Scale: The PGA used the following rating scale

0	Normal, clear skin with no evidence of acne vulgaris
1	Skin almost clear, rare non-inflammatory lesions present, with rare non-inflammatory papules (papules must be hyperpigmented, though not pink-red)
2	Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only, no nodular lesions)
3	Several to many comedones and papules/pustules only and there may or may not be 1 small nodular lesion. Non-inflammatory lesions predominate, with multiple inflammatory lesions
4	Many inflammatory lesions, up to many comedones and papules/pustules. There may be a few nodular lesions
5	Highly inflammatory lesions predominate: variable number of comedones, many papules/pustules, and nodular lesions.

The rating scale was static in nature; the assessment was made without reference to any previous assessments for a particular patient.

Primary Endpoints:

The primary endpoints used in this study for determination of bioequivalence of the Test and Reference products were:

- Mean percent change from baseline in inflammatory lesion count at visit 4 (Day 84).
- Mean Percent change from baseline in non-inflammatory lesion count at visit 4 (Day 84).

Secondary Endpoints:

In supportive analyses, efficacy and bioequivalence were assessed using the following secondary endpoints:

- Change from baseline in inflammatory lesion counts
- Change from baseline in non-inflammatory lesion counts
- Mean percent change from baseline in total (inflammatory + non-inflammatory) lesion counts
- Change from baseline in total (inflammatory + non-inflammatory) lesion counts
- Proportion of patients considered a clinical "success" using the PGA. A patient was considered a clinical "success" if their PGA score was a 0 or 1.

Statistical Analysis Methods

Continuous variables: Percent change from baseline of total lesion count at visit 4

Efficacy Analysis

Treatment arms should be similar in PGA scores and lesion counts at the enrollment visit. The efficacy analysis for the mean percent change from baseline in inflammatory lesion counts, non-inflammatory lesion counts, and of total (inflammatory + non-inflammatory) lesion count for each active treatment was performed separately by comparing with the placebo at the (two-sided) 5% level of significance. The active treatment should be more distinguishable from placebo as the study progresses.

Equivalence Analysis

The compound hypothesis to be tested is:

H_0: $\mu_T/\mu_R < \theta_1$ or $\mu_T/\mu_R > \theta_2$ versus H_A: $\theta_1 \le \mu_T/\mu_R \le \theta_2$

In accordance with the standard in Office of Generic Drugs (OGD) for equivalence analyses for continuous endpoints, α=0.05, θ_1=0.80, and θ_2=1.25. Consequently, for "Raw" (i.e. untransformed) endpoints the 90% confidence interval (corresponding to two one-sided tests at level α=0.05, as described by Sasabuchi) based on Fieller's method is calculated for the equivalence test. The null hypothesis H_0 is rejected if the 90% confidence interval for μ_T/μ_R is contained in the [0.80, 1.25] interval. Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products. Calculation of the 90% confidence intervals, using Fieller's method, was facilitated by using the GLM procedure in SAS® (Version 9.1), including the variable treatment and Center in the model.

Rank Methods

Since the mean percent change from baseline in lesion count might be skewed enough that the assumption of normality of distribution may not be appropriate for the data, we also conducted the efficacy and equivalence analyses based on the rank values. The results obtained from the Rank Procedure (SAS Proc Rank) were analyzed using a General linear model, including treatment and center as factors, using the SAS® (Version 9.1) GLM procedure.

```
Proc GLM Data = <dataset name> ;
Class              TRT   SITEID     ;
Model  X =         TRT   SITEID     ;
LSMEANS         TRT/COV E OUT = Out1;
Estimate 'Active - Vehicle '  TRT 1 - 1;
Run;
```

Binary variables: Success/cure rate at visit 4

Efficacy Analysis

The OGD's standard method for binary variables (the success/cure rate) to test for efficacy is the Fisher's exact test. The test was carried out to compare each active treatment to the placebo.

Equivalence Analysis

Based on the usual method used in the OGD for binary outcomes, the 90% confidence interval for the difference in proportions between the test and reference treatments should be contained within -.20 to .20 in order to establish equivalence.
The compound hypothesis to be tested is:

H_0: $p_T - p_R < -.20$, or $p_T - p_R > .20$ versus H_A : $-.20 \leq p_T - p_R \leq .20$
where p_T = Cure rate of the Test product, $\hat{p}_T$ = Sample success rate of the Test product
p_R = Cure rate of the Reference product, $\hat{p}_R$ = Sample success rate of the Reference product
Let n_T = sample size of Test treatment n_R = sample size of Reference treatment

and $se = (\hat{p}_T(1-\hat{p}_T)/n_T + \hat{p}_R(1-\hat{p}_R)/n_R)^{1/2}$

The 90% confidence interval for the difference in proportions between test and reference was calculated as follows, using Yates' correction:

$L = (\hat{p}_T - \hat{p}_R) - 1.645\ se - (1/n_T + 1/n_R)/2$
$U = (\hat{p}_T - \hat{p}_R) + 1.645\ se + (1/n_T + 1/n_R)/2$

We reject H_0 if $L \geq -.20$ and $U \leq .20$.
Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

Analysis Populations

Two analysis populations were defined in the FDA medical reviewer's report:

- Modified Intent-to-Treat (MITT): All subjects who were enrolled, received at least one dose of study medication, and had at least one post-baseline visit.

- Per-Protocol (FDA PP): All subjects in the MITT population, who met the inclusion/exclusion criteria, completed the final study visit (End of study visit 4) within Day 80 to Day 88, and did not take any prohibited concomitant medications or have any other significant protocol violation.

The determination of clinical equivalence of the two active treatments was to be assessed using the FDA's Per Protocol population (FPP), while the superiority comparisons of the two active treatments to placebo were to be assessed using the FDA's Modified Intent-to-treat population (MITT).

The following changes to the FDA's MITT population were made per the Clinical reviewer's request:

- ***Clinical Reviewer's Comment:*** *Per the Clinical reviewer comments, the following patients should be excluded from the PP population because they used Prohibited medication before or during the study period (See page 24 of the Clinical review):* (b) (6) *Investigational Acne Drug* (b) (6) *and Penicillin* (b) (6) (b) (6)

- *Per the Clinical reviewer comments, the following patients* (b) (6) *should be excluded from the PP population due to baseline inclusion criteria violation, however this reviewer verified that subject* (b) (6) *was not part of this study and subjects* (b) (6) *met baseline inclusion and therefore were not excluded from the study population because of baseline entry criteria.*

Statistical Analysis Results

A total of 750 patients was enrolled. The MITT population included 710 patients. The PP population included 584 patients. Table 1 gives the patient disposition.

Table 1 – Patient disposition

Population	Test (N = 300)	Reference (N = 300)	Vehicle (N = 150)	Total (N = 750)
Subjects Enrolled	300 (100%)	300 (100%)	150 (100%)	750 (100%)
Patients Excluded from MITT	16 (5%)	16 (5%)	8 (5%)	40 (5%)
Total Patients in the MITT	284 (95%)	284 (95%)	142 (95%)	710 (95%)
Patients Excluded from PP	51 (17%)	48 (16%)	27 (18%)	126 (17%)
Total Patients in the PP	233 (78%)	236 (79%)	115 (77%)	584 (78%)

The PGA score and the total lesion count at baseline were not statistically significantly different across treatment groups. The Cochran- Mantel-Haenszel Statistic for general association was far from significance for the PGA, as was the ANOVA analysis for the total lesion count. Table 2 describes the baseline lesion count and the PGA scores in the MITT population.

Table 2 - Population distributions at baseline

Baseline Parameter	Test (N = 284)	Reference (N = 284)	Vehicle (N = 142)	p-value
Lesion count at baseline (Papules + pustule)				
MAX	150	154	151	
MEAN	80	81	79	0.70 [1]
MIN	47	45	48	
STD	26	27	26	
PGA Score at Baseline				
0	0	0	0	
1	0	0	0	
2	0	0	0	0.31 [2]
3	192	211	103	
4	86	70	35	
5	6	3	4	

[1] p-value for treatment comparisons based on a two-way analysis of variance model with covariates: treatment and site.
[2] Cochran-Mantel-Haenszel Statistics for General Association.

Demographic characteristics:

The MITT population consisted of 424 patients (59.7%) who are white, 220 (31%) who are Black, 26 (3.7%) who are Asian, and 40 (5.6%) who are of other ethnicity. There was no statistically significant race difference across treatment groups (p-value = 0.83). The mean age of patients was 20. Table 3 describes the demographic characteristics for the MITT population.

Table 3 - Demographic characteristics of the MITT population

Age	**Test (N = 284)**	**Reference (N = 284)**	**Vehicle (N = 142)**	p-value
MAX	46	40	41	0.021 [1]
MIN	12	11	12	
MEAN	19	19	21	
STD	6	6	7	
Race				0.83 [2]
Caucasian	161 (57%)	177 (62%)	86 (61%)	
Black	96 (34%)	81 (29%)	43 (30%)	
Asian	9 (3%)	11 (4%)	6 (4%)	
Others	18 (6%)	15 (5%)	7 (5%)	
Female	170 (60%)	159 (56%)	81 (57%)	0.64 [2]
Male	114 (40%)	125 (44%)	61 (43%)	

[1] p-value for treatment comparisons based on a two-way analysis of variance model with factors of treatment and site.
[2] Cochran-Mantel-Haenszel Statistics for General Association (Based on Table Scores).

Efficacy results: Table 4 summarizes the efficacy results based on the primary and secondary endpoints for the MITT analysis population.

The Test and the Reference product group mean percent change from baseline in inflammatory and non-inflammatory lesion counts at visit 4 (primary endpoints) were statistically significantly better than that of the vehicle. The p-values are < 0.001 for the Test vs. Vehicle and the Reference vs. Vehicle comparisons for both the untransformed ("Raw") and Rank values.

In addition, analyses based on secondary endpoints - change from baseline in inflammatory, non-inflammatory, and total (inflammatory + non-inflammatory) lesion counts at visit 4, and the percent change in total lesion count show the superiority of the Test and Reference group products over the vehicle, with p-values < 0.001 for both the untransformed ("Raw") and Rank values. The efficacy analyses based on the Clinical Cure rates (secondary endpoints) showed the superiority of the Test and Reference product over the Vehicle in the MITT population; the two-sided Fisher's exact tests yielded p-values < 0.05.

Table 4- Efficacy Analyses: MITT Population

Efficacy Analyses (MITT Population)	Test vs. Vehicle			Reference vs. Vehicle		
Raw Data at visit 4:	Test LS Mean	Vehicle LS Mean	p-value	Reference LS Mean	Vehicle LS Mean	p-value
Mean Percent change from baseline in Inflammatory Lesion Count	57.19	37.04	< **0.001**	61.36	37.77	< **0.001**
Change from baseline in Inflammatory Lesion Count	17.85	9.15	< **0.001**	18.75	9.32	< **0.001**
Mean Percent change from baseline in Non-Inflammatory Lesion Count	44.98	32.97	< **0.001**	50.97	34.30	< **0.001**
Change from baseline in Non-Inflammatory Lesion Count	22.02	13.47	< **0.001**	24.99	13.80	< **0.001**
Mean Percent change from baseline in Total Lesion Count	50.39	34.93	< **0.001**	55.13	35.93	< **0.001**
Change from baseline in Total Lesion Count	39.87	22.62	< **0.001**	43.74	23.12	< **0.001**
Rank Data at visit 4:						
Mean Percent change from baseline in Inflammatory Lesion Count	NA	NA	< **0.001**	NA	NA	< **0.001**
Change from baseline in Inflammatory Lesion Count	NA	NA	< **0.001**	NA	NA	< **0.001**
Mean Percent change from baseline in Non-Inflammatory Lesion Count	NA	NA	< **0.001**	NA	NA	< **0.001**
Change from baseline in Non-Inflammatory Lesion Count	NA	NA	< **0.001**	NA	NA	< **0.001**
Mean Percent change from baseline in Total Lesion Count	NA	NA	< **0.001**	NA	NA	< **0.001**
Change from baseline in Total Lesion Count	NA	NA	< **0.001**	NA	NA	< **0.001**
Clinical Cure Rate at visit 4	Treatment arm			p-value		
	Test	Reference	Vehicle	Test vs. Vehicle	Reference vs. Vehicle	
Rate 1 (PGA ≤ 1)	37% (105/284)	43% (121/284)	23% (33/142)	0.004	< 0.001	
Rate 2 (PGA ≤ 2)	70% (200/284)	76% (215/284)	51% (72/142)	< 0.001	< 0.001	
Rate 3 (PGA Reduction by Score of 2)	44% (126/284)	49% (138/284)	28% (40/142)	0.002	< 0.001	

[1] p-values for treatment groups comparisons based on ANOVA model with treatment and center as factors.
[2] p-values for treatment groups comparisons based on the two-sided Fisher's exact test.

Table 5 presents the distribution of individual PGA scores at visit 4 for the three treatment groups for the MITT analysis population.

Table 5 - PGA Score at visit 4: MITT Population

PGA Score at visit 4	**Test (N = 284)**	**Reference (N = 284)**	**Vehicle (N = 142)**
0	7	6	4
1	98	115	29
2	95	94	39
3	76	57	38
4	7	11	29
5	1	1	3
6	0	0	0
p-value [1]	< 0.001	< 0.001	

[1] vs. vehicle; Cochran-Mantel-Haenszel Statistics for General Association (Based on Table Scores).

Equivalence results: Table 6 summarizes the clinical equivalence results in the FDA PP (FPP) population.

The Test and Reference products passed the equivalence test for the untransformed ("Raw") and Rank values of the mean percent change from baseline in inflammatory and non-inflammatory lesion counts at visit 4 (primary endpoints). In addition, the Test and Reference products were found to be clinically equivalent for change from baseline in inflammatory, non-inflammatory, and change and mean percent change in total lesion counts for both the untransformed ("Raw") and Rank values at visit 4 (Day 84) for the PP population.
The clinical equivalence test based on the secondary endpoint, Clinical Cure rates, also provided supportive evidence of the clinical equivalence of the Test and the Reference products.

Table 6- Bioequivalence Analyses: PP Population

Raw Data at visit 4:	Test LS Mean	Reference LS Mean	The 90% CI for the Ratio μ_T/μ_R	Pass the Bioequivalence Test?
Mean Percent change from baseline in Inflammatory Lesion Count	*58.95*	*62.29*	*(0.89 , 1.01)*	*YES*
Change from baseline in Inflammatory Lesion Count	*17.58*	*18.23*	*(0.89 , 1.04)*	*YES*
Mean Percent change from baseline in Non-Inflammatory Lesion Count	*46.36*	*49.59*	*(0.86 , 1.01)*	*YES*
Change from baseline in Non-Inflammatory Lesion Count	*21.32*	*23.90*	*(0.81 , 0.98)*	*YES*
Mean Percent change from baseline in Total Lesion Count	*51.94*	*54.83*	*(0.89 , 1.01)*	*YES*
Change from baseline in Total Lesion Count	*38.90*	*42.12*	*(0.86 , 1.00)*	*YES*
Rank Data at visit 4:				
Mean Percent change from baseline in Inflammatory Lesion Count	*NA*	*NA*	*(0.933 , 1.000)*	*YES*
Change from baseline in Inflammatory Lesion Count	*NA*	*NA*	*(0.900 , 1.009)*	*YES*
Mean Percent change from baseline in Non-Inflammatory Lesion Count	*NA*	*NA*	*(0.896 , 0.956)*	*YES*
Change from baseline in Non-Inflammatory Lesion Count	NA	NA	(0.867 , 0.867)	YES
Mean Percent change from baseline in Total Lesion Count	*NA*	*NA*	*(0.938 , 0.998)*	*YES*
Change from baseline in Total Lesion Count	*NA*	*NA*	*(0.889 , 0.889)*	*YES*
Clinical Cure Rate at visit 4	Test	Reference	The 90% CI for the Test minus Reference	Is the 90% CI within (-20%,20%)?
Rate 1 (PGA ≤ 1)	42% (97/233)	47% (112/236)	(-13.8 , 2.1)	YES
Rate 2 (PGA ≤ 2)	77% (179/233)	81% (191/236)	(-10.7 , 2.5)	YES
Rate 3 (PGA Reduction by Score of 2)	50% (116/233)	54% (128/236)	(-12.5 , 3.6)	YES

Comments on the Sponsor's Analyses

- According to the sponsor, because the data were highly skewed, the data was analyzed using the non-parametric one sided Wilcoxon rank sum test. Although this method is similar in some ways to our use of the rank transformation method, it does not take possible center effects into account.
- The sponsor's analyses were based on different ITT and PP populations than those used by this reviewer.

Conclusions

Efficacy:

Our analysis showed that, for both the Test and Reference products in the MITT population, the mean percent change from baseline in inflammatory and non-inflammatory lesion counts at visit 4 (primary endpoints) were statistically significantly better than those of the vehicle, based on analyses of untransformed ("Raw") and rank values (p-values < 0.001).

Secondary analyses based on the mean percent change and the change from baseline in total lesion count and change from baseline in inflammatory and non-inflammatory lesion counts showed supportive evidence of the superiority of the Reference product over the Vehicle, for both untransformed ("Raw") and rank values in the MITT population. Secondary analyses based on the Clinical Cure rates at visit 4 in the MITT population showed supportive evidence of the superiority of the Test and Reference products over the Vehicle.

Equivalence:

The Test and Reference products were found to be equivalent for the mean percent change from baseline in inflammatory and non-inflammatory lesion counts (Primary endpoint, Table 6) for untransformed ("Raw") and rank values. They were also found to be equivalent for all the secondary endpoints --- change from baseline for inflammatory, non-inflammatory and change and percent change from baseline for the total lesion counts at visit 4 for untransformed and rank values.

In addition the equivalence test for the secondary endpoint, Clinical Cure rate at visit 4, passed for the PP population.

_____
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This Review Includes 14 pages.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91314	ORIG-1	GLENMARK GENERICS INC USA	ADAPALENE

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

/s/

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091314Orig1s000

BIOEQUIVALENCE REVIEWS

Review of a Bioequivalence Study with Clinical Endpoints

ANDA 091314

Adapalene Gel, 0.1%
Glenmark Generics Inc., USA

Nicole Lee, Pharm.D.
Clinical Reviewer
Office of Generic Drugs

Date of Review: June 24, 2010

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Table of Contents

Table of Contents **2**

Executive Summary **4**

I. Recommendation on Approval **5**

II. Summary of Clinical Findings **5**

A. Brief Overview of Clinical Program 5

B. Comparative Efficacy 5

C. Comparative Safety 5

Clinical Review **6**

I. Introduction and Background **6**

A. Drug Product 7

B. Reference Listed Drug 7

C. Regulatory Background 8

II. Description of Clinical Data and Sources **9**

III. Clinical Review Methods **10**

A. Overview of Materials Consulted in Review 10

B. Overview of Methods Used to Evaluate Data Quality and Integrity 10

C. Were Trials Conducted in Accordance with Accepted Ethical Standards. 11

D. Evaluation of Financial Disclosure 11

IV. Review of Bioequivalence **11**

A. Brief Statement of Conclusions 11

B. General Approach to Review of the Comparative Efficacy of the Drug . 11

C. Detailed Review of Bioequivalence Studies with Clinical Endpoints 12

D. Bioequivalence Conclusion 23

V. Comparative Review of Safety 24

A. Brief Statement of Conclusions 24

B. Description of Adverse Events 24

VI. Relevant Findings From Division of Scientific Investigations, Statistics and/or Other Consultant Reviews 25

VII. Formulation 28

VIII. Conclusion and Recommendation 28

A. Conclusion 28

B. Recommendation 28

Review of a Bioequivalence Study with Clinical Endpoints for ANDA 091314

Executive Summary

The sponsor conducted a randomized, double-blind, multiple-site, placebo-controlled, parallel-group study to demonstrate that Glenmark Generics Inc., USA's (Glenmark's) Adapalene Gel, 0.1% is safe and bioequivalent to Differin® Gel in the treatment of acne vulgaris.

The sponsor's statistical analysis of the per protocol (PP) population shows the mean percent change from baseline in inflammatory lesions to be 66.56% for the Glenmark (test) product and 70.54% for the RLD. For non-inflammatory lesions, the result was 57.29% for the test product and 60.57% for the RLD. The 90% Confidence Interval (CI) of the test to reference ratio of mean percent reduction from baseline to Week 12 was within the bioequivalence limits of (0.80, 1.25) for both the inflammatory and non-inflammatory lesion counts.

In the intent-to-treat (ITT) population, the placebo group showed a 43.71% reduction from baseline in inflammatory lesions and a 41.1% reduction in non-inflammatory lesions. The sponsor's analysis concluded that the mean percent change from baseline for both the test and reference groups was statistically superior to that of the placebo group, with a p value of <0.0001 for the inflammatory lesions and a p value of <0.0001(test vs. placebo) and <0.0021 (reference vs. placebo) for the non-inflammatory lesions. Therefore, according to the sponsor's analysis, the study was sensitive enough to detect a difference between the products at the lower end of the dose/response curve.

According to the FDA statistical analysis, the mean percent change from baseline in inflammatory lesions using raw data was 58.95% for the test product and 62.29% for the reference product in the PP population. The 90% Confidence Interval (CI) of the test to reference ratio of the mean percent reduction from baseline to Week 12 was (0.89, 1.01). The mean percent change from baseline in non-inflammatory lesions using raw data was 46.36% for the test product and 49.59% for the reference product in the PP population. The 90% Confidence Interval (CI) of the test to reference ratio of the mean percent reduction from baseline to Week 12 was (0.86, 1.01).

The FDA analysis of the mITT population showed that the mean percent change from baseline in inflammatory lesions using raw data was 57.19% for the test product and 37.04% for the vehicle product with a p-value of <0.001. For the RLD, the mean percent change from baseline in inflammatory lesions using raw data was 61.36% vs. 37.77% for the vehicle, with a p-value of <0.001. The mean percent change from baseline in non-inflammatory lesions using raw data was 44.98% for the test product and 32.97% for the vehicle product with a p-value of <0.001. For the RLD, the result was 50.97% vs. 34.30% for the vehicle product, with a p-value of <0.001.

In addition, the sponsor's analysis of the Investigator's Global Evaluation showed clinical success in 37% of the test patients, 43% of reference patients, and 23% of placebo patients. The test-reference difference was -6%, with a 90% CI of (-12.73, +1.46), within the usual BE limits for a dichotomous endpoint. Both test and reference were superior to placebo with P=0.0043 for the test and p<0.0001 for the reference. According to the FDA statistical analysis, the Investigator's Global Evaluation showed clinical success in 42% of the test patients, 47% of reference patients, and 23% of placebo patients. The 90% CI of (-13.8, 2.1) was within the usual BE limits for a dichotomous endpoint.

According to the sponsor, a total of 750 patients enrolled into the study, of which 710 patients were included in the sponsor's Intent-To-Treat (ITT) population and 592 patients were included in the sponsor's Per Protocol (PP) population analyses.

I. Approval Recommendation

The FDA statistical analysis confirms that the data submitted to ANDA 091314, using the primary endpoint of mean percent reduction in inflammatory and non-inflammatory lesion counts from baseline to Week 12 demonstrates bioequivalence of Glenmark's Adapalene Gel, 0.1% with the reference listed drug, Galderma Laboratories L.P.'s Differin® Gel. Therefore, from a bioequivalence perspective, the test product is recommended for approval.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Adapalene Gel, 0.1% is a prescription topical retinoid-like compound. It is indicated for the treatment of acne vulgaris. Glenmark conducted a clinical endpoint study, enrolling 750 patients, to establish the bioequivalence of their proposed Adapalene Gel, 0.1% to the RLD, Differin® Gel, in the treatment of acne vulgaris. All patients were randomized to receive either the Glenmark product (Test), Differin® (Reference) or Placebo.

B. Comparative Efficacy

The recommended primary endpoint of this study is the mean percent reduction from baseline in inflammatory and non-inflammatory lesion counts at Week 12.

According to the sponsor's analysis, the mean percent reduction from baseline in inflammatory lesion count at Week 12 in the PP population was 66.56% in the test group and 70.54% in the reference group. The 90% CI for the test to reference ratio of the means was within the bioequivalence limits of (0.80, 1.25). The mean percent reduction from baseline in non-inflammatory lesion count at Week 12 in the PP population was 57.29% in the test group and 60.57% in the reference group. The 90% CI for test to reference ratio of the means was within the bioequivalence limits of (0.80, 1.25). Both active products were demonstrated by the sponsor's analysis to be superior to placebo with regard to the mean percent reduction from baseline in inflammatory and non-inflammatory lesion counts, demonstrating that the study was sensitive enough to detect differences in product performance at the lower end of the dose-response curve.

C. Comparative Safety

The safety data submitted in this ANDA show that the test product did not cause any worse adverse events compared to the reference product in the treatment of acne vulgaris. A total of 280 patients reported 403 adverse events during the study. One hundred twenty-eight (128) (42.67%) patients reported 186 adverse events in the test group, 110 (36.67%) patients reported 161 adverse events in the reference group, and 42 (28.0%) patients reported 56 adverse events in the placebo group. The adverse events reported by more than 2% of patients in any one treatment group were application site paraesthesia, application site dryness, application site exfoliation, application site pruritus, dysmenorrhea, headache, myalgia, nasopharyngitis, toothache and xerosis.

Reviewer's comment: *The rate of overall AE reporting was 6 % higher with use of the test product than with the reference. However, the study was not designed to evaluate statistical significance of such reports, and this small difference is not likely to be meaningful. The largest number of reports was for application site dryness in 20% of test patients vs. 17% of reference patients. The only difference in the ingredients of the test and reference products is* (b) (4) *absence of hydrochloric acid in the test product. Therefore, there is no evidence that the safety profiles of the two products would be different.*

Clinical Review

I. Introduction and Background

The Office of Generic Drugs (OGD) has determined that the design of bioequivalence trials for topical acne products should take into consideration the basis of approval for the RLD.

The current standard for NDA approval of a product indicated for the treatment of acne vulgaris is statistical superiority over placebo for reduction in both inflammatory and non-inflammatory lesions counts and a statistically larger success proportion on the Physicians Global Assessment (PGA). It is recognized that the change from baseline in total lesion count is strongly influenced by the change in the lesion type that shows the largest effect. The Division of Dermatology and Dental Products (DDDP) has recommended that topical generic products for the treatment of acne vulgaris show equivalent performance in reduction of both inflammatory and non-inflammatory lesion types. However, in a consultation dated January 29, 2004, it was agreed that the more subjective Investigator's Global analysis could be removed from the study to simplify future study design for 505(j) applications for the acne indication. The OGD has decided to designate the PGA as a secondary endpoint to support the evaluation of bioequivalence.

The OGD does not require that a generic product must show equivalent performance on an endpoint for which the RLD did not show superiority over placebo. The requirement for demonstration of superiority over placebo in a clinical endpoint bioequivalence study is not intended for establishing efficacy of the generic product. Equivalent efficacy and safety of a generic product is assumed if the product is bioequivalent to the RLD. Superior performance compared to placebo is needed to show that the study design is sufficiently sensitive to demonstrate a difference between products. The study should demonstrate equivalent effectiveness for the endpoint(s) upon which efficacy was established for the RLD and also

demonstrate that the test product is no worse than the RLD for the additional endpoints for which the RLD did not demonstrate superiority over placebo. Therefore, in the case of Differin® Gel, the firm must show equivalence for percent reduction in both inflammatory and non-inflammatory lesion counts, because the reference product demonstrated statistical superiority over vehicle in regards to mean percent change from baseline at Week 12 for both inflammatory and non-inflammatory lesion counts.

Prior to 2004, the OGD requested percent change from baseline in lesion counts as the primary efficacy variable for acne studies. However, the standard for approval of an NDA for acne vulgaris treatment was established as numeric change from baseline in lesion counts. In an attempt to be consistent with the NDA study recommendations, the OGD requested that generic sponsors present the change from baseline as both numerical and percent change. Although most of the ANDAs submitted for acne vulgaris treatments have met the 90% confidence interval criteria for bioequivalence for both numerical change and percent change from baseline, some generic sponsors have communicated that a larger study population is required to meet BE limits for numerical change from baseline than for percent change from baseline. Furthermore, the OGD has observed wider confidence intervals for numerical change from baseline than for percent change from baseline in numerous studies recently submitted with a primary endpoint of change from baseline in lesion counts. The OGD currently believes that it may not be reasonable to require that numeric change from baseline lesion counts meet the usual BE limits, and we find no clinical or statistical reason to believe that reliance on the percent change from baseline would result in approval of a product that is not therapeutically equivalent. Therefore, the OGD has decided that the previously recommended endpoint of percent change from baseline in lesion counts is the preferred primary endpoint. The numeric change from baseline will be evaluated as a secondary endpoint to support the evaluation of bioequivalence.

A. Drug Product

1. Drug Established Name: Adapalene Gel, 1%
2. Drug Class: Topical acne agent

B. Reference Listed Drug (RLD)

1. RLD Name: Differin®
2. NDA Number: 20-380
3. NDA Firm: GALDERMA LABORATORIES L.P.
4. Date of Approval: May 31, 1996
5. Approved Indication(s): Topical treatment of acne vulgaris.

6. Dose, Route of Administration and Regimen:
   The product labeling recommends applications once a day to affected areas after washing in the evening before retiring. A thin film of the gel should be applied, avoiding eyes, lips, and mucous membranes.

7. Description of the reference drug, including pertinent safety or dosing considerations:

Adapalene is a retinoid-like compound. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization and inflammatory processes. Adapalene binds to specific retinoic acid nuclear receptors but does not bind to the cytosolic receptor protein. It is suggested that topical adapalene may normalize the differentiation of follicular epithelial cells resulting in decreased microcomedone formation. Absorption through human skin is low. Only trace amounts of parent substance (< 0.25 ng/mL) have been found in the plasma of acne patients following chronic topical application in controlled clinical trials.

Exposure to sunlight, including sunlamps, should be minimized during the use of adapalene. Patients who normally experience high levels of sun exposure, and those with inherent sensitivity to the sun, should be warned to exercise caution. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided. Some adverse events, such as erythema, scaling, dryness, pruritis and burning will occur in 10-40% of patients. Pruritis or burning immediately after application also occurs in approximately 20% of patients. Safety and effectiveness for use below the age of 12 has not been established.

During the early weeks of therapy, an apparent exacerbation of acne may occur. This is due to the action of the medication on previously unseen lesions and should not be considered a reason to discontinue therapy. Therapeutic results should be noticed after eight to twelve weeks of treatment.

8. Brief Discussion about the indication

Acne vulgaris is a common skin condition that can affect people of all ages, although teenagers develop acne most often. (b) (4) [redacted]

C. Regulatory Background

For the approval of Differin® Gel, a total of five clinical studies were conducted with Adapalene 0.1% Gel in acne vulgaris patients, two of which were vehicle-controlled studies. The other three studies were conducted in comparison to tretinoin gel. The primary endpoint in all of the studies was mean percent reduction at week 12 in inflammatory and non-inflammatory lesions. Total lesions and the Global Acne Grade were considered secondary and supportive.

The first vehicle-controlled study (C-89-61), in only 180 patients, failed to statistically show that Adapalene was superior to vehicle ($p > 0.05$) at week 12 in the treatment of non-inflammatory, inflammatory, and total lesions of mild to moderate acne vulgaris.

The second vehicle-controlled study (9105-CD271G-EV) enrolled 256 patients and provided statistical evidence to support the sponsor's claim that Adapalene Gel is therapeutically better than vehicle in the treatment of non-inflammatory and inflammatory lesions and also for total lesions with $p < 0.05$.

The other three NDA clinical studies all used active controls containing tretinoin gel instead of vehicle as a comparator. The first study (CR 88051), which was a dose-ranging study in 89 patients, showed that Adapalene Gel was not equivalent (not within 95% CI) to Retin-A (tretinoin gel) in the reduction of non-inflammatory and inflammatory lesions at week 12, but was equivalent (within 95% CI) in the reduction of total lesions and the Global Acne Grade.

The second study (CR 89064) enrolled 268 patients and demonstrated that Adapalene Gel was equivalent to Retin-A Gel in the reduction of non-inflammatory lesions, total lesions and Global Acne Grade, but not in the reduction of inflammatory lesions.

The third study (CR 89-32), in 323 patients, demonstrated that Adapalene Gel was statistically better than Retin-A Gel in the reduction of non-inflammatory and total lesions. In the reduction of inflammatory lesions, Adapalene Gel was equivalent to Retin-A Gel. Overall, the studies demonstrated that Adapalene Gel was better tolerated than Retin-A Gel.

No INDs, Protocols, and/or Control Documents were submitted by this sponsor.

Several INDs, Protocols, and/or Control Documents have been submitted by other sponsors

One ANDA (090962) has been approved for the same product, adapalene 0.1% gel. Other applications for this drug product and for adapalene 0.1% cream have been submitted, including some that failed to meet the necessary criteria to be received for review.

II. Description of Clinical Data and Sources

A. CRO: Novum Pharmaceutical Research Services

A. Study Period

1. First subject dosed: March 21, 2008
2. Last subject completed: October 27, 2008

B. Study Centers, Investigators and Enrollment

Site Number	Investigator	Location	Number Enrolled
1	Zoe Diana Draelos, MD	High Point, NC	30
2	Robert B. Rhoades, MD	Medical Parameters Martinez, GA	56
3	Steve Sitar, MD	Orange County Clinical Trials Anaheim, CA	50
4	Peter L. Winters, MD	Indianapolis, IN 46250	29
5	Paul H. Ratner, MD, MBA	San Antonio, TX 78229	13
6	Harry H. Sharata, MD, PhD	Madison, WI	20
7	Opted not to participate in study		
8	Cecil M. Farrington, Jr., MD	Salisbury, NC	35
9	Hector Wiltz, MD, CCTI	FXM Research Corporation Miami, FL	100
10	Ines Mendez-Moguel, MD	Belize City, Belize	100
11	Julitta Bradley, MD	Belize City, Belize	100
12	Edward L. Patterson, Jr., MD	Phoenix, AZ	30
13	Charles E. Griff, MD	West Palm Beach, FL	37
14	Eugene W. Monroe, MD	Milwaukee, WI	21
15	Karl G. Heine, MD	Henderson, NV	23
16	Michael H. Gold, MD	Nashville, TN	23
17	Alicia R. Barba, MD	Miami, FL	14
18	Walter K. Nahm, MD, PhD	San Diego, CA	0
19	James Spencer, MD, MS	Saint Ptersburg, FL	19
20	Debra Chih-Fen Liu, MD	Winston, Salem, NC	20
21	Oscar De Valle, MD	Houston, TX	30

III. Clinical Review Methods

A. Overview of Materials Consulted in Review

Original Submission:
February 6, 2009 (Electronic submission and vol. 1.4)

B. Overview of Methods Used to Evaluate Data Quality and Integrity

Division of Scientific Investigations Report:
No DSI was requested because of recent acceptable inspections for the following same sites:

Zoe D. Draelos, MD,PA, ANDA 090962 for adapalene gel, 02/01/2010, NAI
(b) (4)
Hector Wiltz, MD, CCTI, ANDA 065443 for clinda/benzoyl peroxide gel, 01/7/2008, VAI (no Form 483 issued)
Ines Mendez-Moguel, MD, ANDA 090824 for adapalene cream, 04/1/2010, NAI
Julitta Bradley, MD, ANDA 090824 for adapalene cream, 04/1/2010, NAI

C. Were Trials Conducted in Accordance with Accepted Ethical Standards

According to the study report, the IRB used in the study complies with the requirements of FDA 21 CFR, Parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards). These principles govern the IRB to ensure that the rights and welfare of human subjects are protected in accordance with intent of the Belmont Report (*Ethical Principles and Guidelines for the Protection of Human Subjects of Research*), of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, and the Declaration of Helsinki.

D. Evaluation of Financial Disclosure

The Sponsor certified that, in compliance with 21 Code of Federal Regulations (CFR) Part 54, no financial arrangements with the Principal Investigators or Sub-Investigators have been made where the study outcome could affect compensation. In addition, the Principal Investigators and Sub-Investigators have no proprietary interest in the tested product, do not have a significant equity interest in the sponsor of the covered study, and have not received significant payment of other sorts. Form FDA 3454 has been submitted.

IV. Review of Bioequivalence

A. Brief Statement of Conclusions

According to the sponsor's results, the study data meet the bioequivalence limits of the test/reference ratio of the mean percent change from baseline in both inflammatory and non-inflammatory lesion counts. The study also demonstrates superiority of both the active products over placebo with regard to percent reduction from baseline in inflammatory and non-inflammatory lesions at Week 12. The study is therefore shown to be sensitive enough to detect a difference between products at the lower end of the dose/response curve.

B. General Approach to Review of the Comparative Efficacy of the Drug

The sponsor conducted one clinical study. The sponsor's study was reviewed to evaluate the comparative efficacy and safety of the proposed drug. The electronic and paper submission of the ANDA was reviewed in detail.

C. Detailed Review of Bioequivalence Studies with Clinical Endpoints

1. **Protocol Number**: GLK609

2. **Title**: A Randomized, Double-Blind, Multiple-Site, Placebo-Controlled, Parallel Design, Clinical Study to Evaluate the Bioequivalence of Adapalene Gel 0.1% (Glenmark Pharmaceuticals, Ltd.) Compared to Differin® (adapalene 0.1%) Topical Gel (Galderma Laboratories) in Patients with Moderate to Severe Acne Vulgaris

3. **Objectives:** The objective of this study was to evaluate the efficacy and safety of the test formulation of Adapalene Gel, 0.1% as compared to the already marketed formulation, Differin® (adapalene 0.1%) Topical Gel, in patients with acne vulgaris.

   The efficacy of both the test and reference gels was compared for superiority to a placebo gel for all primary and secondary endpoints.

4. **Study Design:** The study was a randomized, double-blind, multiple-site, placebo-controlled, parallel designed clinical study comparing two formulations of adapalene 0.1% topical gel. Patients were randomly assigned in a 2:2:1 ratio to the test product, reference product or placebo, respectively. The patients completed four visits (baseline, Week 4, Week 8 and Week 12).

   a. Treatments

      i. **Test**: Adapalene Gel 0.1% (Glenmark Pharmaceuticals, Ltd.)
         Lot Number: Q15727001
         Expiration Date: November 2009
      ii. **Reference**: Differin® 0.1% Gel (Galderma Laboratories)
         Lot Number: 052827
         Expiry Date: August 2010
      iii. **Placebo**: Gel base only (Glenmark Pharmaceuticals, Ltd.)
         Lot Number: QP15727001
         Expiration Date: November 2009

   b. Drug Application

      For all treatment groups the patient instructions for administration of the study drug were the same. Patients were told to apply the study drug as a thin layer to the entire face every evening after washing their face with the hypo-allergenic soap provided and rinsing and gently drying the area for 84 days.

   c. Study Population

      i. Inclusion Criteria:
         (a) Male or non-pregnant, non-lactating female, 12-40 years of age inclusive

(b) Signed informed consent form, which meets all criteria of current FDA and HIPAA regulations. For patients under the age of majority in the state they are enrolled, the patient's parent or legal guardian was required to sign the consent form and the patient signed an IRB approved "assent to participate" form.
(c) If female and of child bearing potential, patient must have been prepared to abstain from sexual intercourse or use a reliable method of contraception during the study (e.g., condom, IUD, oral, injected or implanted hormonal contraceptives). Patients on hormonal contraceptives must have been on the same hormonal contraceptive for three months prior to the baseline visit and continued on throughout the duration of the study.
(d) Moderate to severe facial acne as defined as: at least 20 but no more than 60 facial inflammatory lesions (papules and pustules) and at least 25 but no more than 100 non-inflammatory lesions (open and closed comedones) and have a PGA score of 3, 4 or 5.

ii. Exclusion Criteria:
(a) More than 2 facial nodular lesions, any nodules present were documented but were not included in the inflammatory lesion count
(b) Active cystic acne
(c) Acne conglobata
(d) Significant facial hair such as beards or tattoos or excessive facial scarring that, in the Investigator's opinion would have interfered with the evaluation of the patient's acne
(e) Facial sunburn
(f) Any dermatological condition other than acne vulgaris that, in the Investigator's opinion may have interfered with the evaluation of the patient's acne (e.g., rosacea, psoriasis, dermatitis)
(g) Females who were pregnant, lactating or likely to become pregnant during the study
(h) History of allergy or sensitivity to adapalene or other retinoids or history of any drug hypersensitivity or intolerance which, in the Investigator's opinion, would have compromised the safety of the patient or the study
(i) Significant history or current evidence of chronic infectious disease, system disorder, organ disorder or other medical condition that, in the Investigator's opinion would have placed the study participant at undue risk by participation
(j) Use of any topical antibiotics or topical steroids used on the face and any oral antibiotics known to treat acne and any systemic steroids within 28 days of the first dosing
(k) Chronic use (more than three times per week on average) of any anti-inflammatory products (systemic or topical) within 28 days of the first dosing day. The occasional use of NSAIDs was not a reason for exclusion.
(l) Use of oral isotretinoin (Accutane®) within 6 months. Use of topical tretinoin (Retin-A®) or adapalene (Differin®), tazarotene (Tazorac®) or azelaic acid (Azelex®) within 28 days of the first dosing day.

(m) Receipt of any drug as part of a research study within 30 days prior to dosing
(n) Use of any medicated facial products (soaps, lotions, moisturizers, etc.) or other facial cleansing agents for 14 days prior to study enrollment.
(o) Previous participation in this study

d. Procedures/Observations

Table 1 – Study Flow Chart (per Sponsor)

Procedure	**Visit 1** Baseline	**Visit 2**[a] 28 Days (± 4 days)	**Visit 3** 56 Days (± 4 days)	**Visit 4** End of Study 84 Days (± 4 days)
Informed Consent/Assent	X			
Medical History	X			
Vital signs	X			X
Pregnancy Test	X			X
Lesion Counts	X	X	X	X
Physician's Global Assessment	X	X	X	X
Concomitant Medication	X	X	X	X
Dispensed Study Medication	X	X	X	
Provide/Review Patient Diary	X	X	X	X
Adverse Events		X	X	X
Evaluation of Patient Compliance to the Protocol		X	X	X
Return of Study Medication		X	X	X
Discharge from Study				X

e. Restrictions

The following concomitant medications were not allowed while enrolled in the study.

- Any antibiotics known to treat acne, or systemic steroids or nasal steroids used more than three times per week were not allowed during the course of the study.
- Any topical antibiotics or topical steroids used on the face.
- Chronic use (more than three time per week on average) of any systemic anti-inflammatory agents, other than the occasional use of NSAIDs
- Isotretinoin or tretinoin
- Any other treatments, prescription or over the counter products for the treatment of acne including medicated and/or astringent washes, soaps, pads or moisturizers (other than the non-antibacterial soap provided)
  - Patients were provided with a mild, non-antibacterial, cleansing soap (b) (4) for use to wash their face prior to each drug application.
  - Patients were provided with a standardized, non-antibacterial, non-

acnegenic, moisturizing agent (b) (4) for use in case they experience dry skin on the face

- Patients were advised to avoid exposure to sunlight for a duration that would require application of sunscreen. If this cannot be avoided patients were provided with a non-acnegenic sunscreen, (b) (4) (b) (4)
- Patients were questioned about all prescription and OTC concomitant medication use (including vitamins or non food nutritional supplements) at each study visit. All concomitant medications (including use of the moisturizer or sunscreen if needed) were recorded in the patient's study chart. Any patient who violated any of the listed restrictions was dropped from continued participation in the study by the Investigator.

Reviewer's comments:

- *Any patient who took any additional medication for the treatment of acne during the study because of lack of treatment effect should be included in the PP population as a treatment failure, and LOCF should be used for analysis of lesion counts. If such medications were taken without regard to treatment status, then the patient should be excluded from the analyses.*
- *Patients who took a restricted concomitant medication that was not for the treatment of acne should be excluded from the PP population but included in the ITT population using LOCF.*

f. Safety measures

Throughout the study, patients were questioned about adverse events and concomitant medication use. The event, start and stop date, outcome, severity, relationship to study drug and any concomitant medication use were reviewed and evaluated by the Investigator for each event. Adverse events were coded into MedDRA terminology during data entry.

g. Endpoints

i. **Primary Endpoints:** The sponsor's primary bioequivalence efficacy variables were:

(a) mean percent change from baseline in inflammatory lesion count at Day 84 for the PP population

(b) mean percent change from baseline in non-inflammatory lesion count at Day 84 for the PP population

ii. **Secondary Endpoints**: The sponsor's secondary efficacy variables were:

(a) Mean numerical reduction from baseline in inflammatory lesion counts

(b) mean numerical reduction from baseline in non-inflammatory lesion counts

(c) proportion of patients considered a clinical "success" using the PGA

Reviewer's comments:

- *The recommended primary endpoints for this bioequivalence study are the mean **percent** change from baseline for **both** inflammatory (papules and*

pustules) and non-inflammatory (open and closed comedones) lesion counts at week 12. The absolute/numeric change from baseline is considered supportive information and is evaluated as a secondary endpoint.

- *The FDA statistician was requested to analyze the percent change in inflammatory (sum of papules and pustules) and non-inflammatory lesion counts. If the test and reference products fail to be superior to the placebo then the FDA statistician was also requested to analyze the numeric change in inflammatory (sum of papules and pustules) and non-inflammatory lesion counts. A formal analysis of the other secondary endpoints was not requested.*

h. Physician's Global Assessment

The PGA used the following rating scale.

Table 2: Physician's Global Assessment (per sponsor)

Grade	Description
0	Normal, clear skin with no evidence of acne vulgaris
1	Skin almost clear, rare non-inflammatory lesions present, with rare non-inflammatory papules (papules must be hyperpigmented, though not pink-red)
2	Some non-inflammatory lesions are present, with few inflammatory lesions (papules/pustules only, no nodular lesions)
3	Several to many comedones and papules/pustules only and there may or may not be 1 small nodular lesion. Non-inflammatory lesions predominate, with multiple inflammatory lesions
4	Many inflammatory lesions, up to many comedones and papules/pustules. There may be a few nodular lesions
5	Highly inflammatory lesions predominate: variable number of comedones, many papules/pustules, and nodular lesions.

The rating scale was static in nature and was performed without reference to any previous assessments for a particular patient.

A patient was considered a clinical "success" if their PGA score was a 0 or 1.

i. Statistical analysis plan

No interim analysis was planned during the study nor was any conducted.

i. **Patient Populations**

(a) Per-Protocol (PP) Population – The PP population included patients that met the inclusion/exclusion criteria, completed the study according to the protocol, and whose final visit was within 80 to 88 days inclusive of their first dosing day. Patients who requested to be dropped from the study because of lack of efficacy, or were discontinued from the study by the Investigator because of lack of efficacy and patients discontinued for insufficient therapeutic response.

(b) Intent-to-Treat (ITT) Population – The ITT population included all patients in the PP population plus all patients who used the study drug on at least one occasion and had at least one post-baseline evaluation. If the people did not complete the study, the patient's lesion count and PGA assessment will be carried forward for the primary analysis of superiority and for analysis of bioequivalence as appropriate.

D. ©Safety Population – All 750 patients who were randomized were included in the safety analysis.

ii. **Distribution of Data** – The primary efficacy data were to be tested by the sponsor for normal distribution using Kolmogorov-Smirnov testing. If it was ascertained that the distribution was not normal then non-parametric testing, specifically the Wilcoxon Rank-Sum test, was to be employed.

iii. **Bioequivalence** (per sponsor) – The primary measures of bioequivalence were to be evaluated using the Per Protocol Population. The two primary endpoints of the study are the mean percent reduction in non-nodular inflammatory lesion count (papules and pustules) at Week 12 and the mean percent reduction in noninflammatory lesion count (open and closed comedones) compared with baseline at Week 12. Although the number of nodules at each visit was recorded, it was not included in the analysis of inflammatory lesions for efficacy analysis.

If the 90% CI for the test/reference ratio in the mean percent reduction from baseline in inflammatory lesion count and mean percent reduction from baseline in non-inflammatory lesion count were within 80-125%, then bioequivalence of the test to reference product was considered to be proven for the primary endpoints.

Secondary measures of bioequivalence were determined by the sponsor using the ITT population. The secondary analysis comprised three endpoints; mean numerical reduction in inflammatory lesion count, mean numerical reduction in non-inflammatory lesion counts and the proportion of patients who are considered a "clinical success" or "clinical failure" at Week 12 in the test and reference groups.

If the 90% CI for the test to reference ratio in the mean numerical change from baseline in both inflammatory and non-inflammatory lesion counts were within 80-125% then bioequivalence was supported. For the proportion of clinical success, if the 90% CI (with Yates Correction Factor) of the difference between the proportion of patients considered a "clinical success" in the test and the reference product groups was contained within the range -20% to +20% then bioequivalence was supported.

iv. **Efficacy –** The ITT population was to be used by the sponsor to evaluate the superiority of both the test and reference product over placebo for all primary and secondary endpoints. If both the test and reference were found to be statistically superior ($p<0.05$) to placebo based on the sponsor's analysis of mean percent reduction from baseline in both inflammatory and non-inflammatory lesion counts at Week 12 using a two-sided t-test, then both the test and reference products were to be deemed by the sponsor to be more effective than the placebo in reducing inflammatory and non-inflammatory lesion counts.

The ITT population was also to be used by the sponsor to assess all three secondary endpoints for superiority: mean numerical reduction from baseline in inflammatory and non-inflammatory lesion counts and "clinical success/failure" using the PGA score.

v. **Baseline** – Baseline comparability of all treatment groups was compared by the sponsor. The groups were compared for basic demographics (age, gender, ethnicity, race), number of inflammatory lesions (papules and pustules), number of nodules, number of non-inflammatory lesions (open and closed comedones) and PGA score.

5. Study Conduct

a. Compliance

All patients were provided with a dosing diary in which they were required to record the date and time of study drug use. At Visits, 2, 3 and 4, the patients' diaries were reviewed for compliance with the dosing requirements of the study protocol. Four (4) patients (3 in the test group and 1 in the reference group) failed to use the drug at least 75% of the required time or more than 125% of the required time and were excluded from the PPP, but included in the ITT population.

b. Randomization

The randomization was generated (b) (4) until after the database had been locked. It was not provided to the statistician until after the last patient had completed the study and the database had been locked. At each site, patients were randomized into one of three groups: test, reference or placebo in a 2:2:1 ratio, respectively. Randomization was performed according to a computer-generated randomization scheme. One six digit patient number was assigned to each patient, where the first two digits were the site identifier number and the last 4 digits were the four digit randomization number.

At the completion of the study each investigative site was provided a copy of the complete randomization in a sealed envelope in case it would be required during an FDA inspection.

c. Blinding/Packaging

Blinding of study tubes was achieved by applying opaque tape over the tubes of

study drug. All study drug was dispensed in identical plain boxes with standardized labeling. The patient was requested not to discuss the appearance of the tubes or study drug with the Investigator. Each study site had at least one "Independent Dispenser". The role of the "Independent Dispenser" was to dispense new and collect used study medication from the patients and to ensure the medication logs were reported correctly. They were not involved in collecting any efficacy data in the study thus ensuring the integrity of the study blind. The blind was accidentally broken at Site #04, Dr. Winters, (b) (6) The patient kit was resealed and was not dispensed. The blind was not broken on any other occasion during the study.

d. Reserve Samples

Each site was required to pick at least one block of study drug at random as retention drug samples. The blocks were selected prior to the first patient being enrolled at the site. If the site received any additional study drug shipments additional blocks were selected from each shipment. Each investigative site signed a statement confirming they would retain these drug supplies according to 21 CFR 320.38 and 320.63.

e. Study Population

Table 3 below provides a summary of the patient disposition in the study.

Table 3: Summary of Patient Disposition (per Sponsor)

	Test	Reference	Placebo	Total
Number of Patients Randomized	**300**	**300**	**150**	**750**
Patients Included in Safety Analyses	**300**	**300**	**150**	**750**
Patients Included in Intent-to-Treat Analyses	**284**	**284**	**142**	**710**
Patient Excluded from Per Protocol Analyses	**47**	**45**	**26**	**118**
Inc/Exc not met	3	2	1	6
Final Study Visit out of Window	17	21	11	49
Restricted Med not for acne	2	4	3	9
Dosing Non-Compliance	3	1	0	4
Lost to Follow-up	9	9	5	23
Withdrew Consent	8	5	6	19
Adverse Event	4	1	0	5
Other	1	2	0	3
Patients Included in Per-Protocol Analyses	**237**	**239**	**116**	**592**
Restricted Med for Acne	0	1	0	1
Insufficient Therapeutic Response	0	3	1	4

Reviewer's Comments:

- *The FDA statistician was asked to exclude the following patients from both the ITT and PP populations for not meeting inclusion/exclusion criteria:*

- *Any patient with baseline lesion counts outside the inclusion criteria (combined papules/pustules should be ≥20 and ≤60 and combined open and closed comedones should be ≥25 and ≤ 100).*
- *Any patient with baseline nodule count ≥3.*
- *Any patient with baseline PGA score less than 3.*

- *The following patients should also be excluded from the PP population for the reasons noted:*
  - *Prohibited medication use before or during the study period: Amoxicillin* (b) (6) *Investigational Acne Drug* (b) (6) *and Penicillin* (b) (6)
  - *All patients who are outside of the designated ±4 day visit window for Visit 4.*

f. Baseline Patient Characteristics (per sponsor)

There were no clinically relevant differences between the treatment groups for any of the baseline evaluations.

Table 4: Patient Demographic Characteristics for the Safety Population (per Sponsor)

	Test	Reference	Placebo
Number of Patients	300	300	150
Age in years (mean ± SD)	19.3 ± 6.1	19.3 ± 6.1	20.9 ± 7.1
Gender (number, %)			
Male	120 (40)	134 (44.67)	64 (42.67)
Female	180 (60)	166 (55.33)	86 (57.33)
Ethnicity (number, %)			
Hispanic/Latino	114 (38)	130 (43.33)	58 (38.67)
Not Hispanic/Latino	186 (62)	170 (56.67)	92 (61.33)
Race (number, %)			
White	170 (56.67)	185 (61.67)	92 (61.33)
Native Hawaiian/ Other Pacific Islander	1 (0.33)	0	1 (0.67)
Black/African American	102 (34)	86 (28.67)	44 (29.33)
Asian	9 (3)	12 (4)	6 (4)
Other	16 (5.33)	17 (5.67)	7 (4.67)
Physician's Global Assessment			
3	205 (68.33)	223 (74.33)	110 (73.33)
4	89 (29.67)	74 (24.67)	36 (24)
5	6 (2)	3 (1)	4 (2.67)
Inflammatory Lesion Count (mean ± SD)	31.9 ± 10.2	31.8 ± 10.4	31.2 ± 10.1
Non-Inflammatory Lesion Count (mean ± SD)	48.1 ± 19.0	49.7 ± 19.6	47.9 ± 18.2
Number of Nodules (mean ± SD)	0.18 ± 0.47	0.16 ± 0.45	0.19 ± 0.53

6. Results

Primary Endpoints (Equivalence-PPP) per sponsor

Mean Percent Reduction in Inflamed Lesion Count on Day 84

	N	% Reduction	T/R	Lower 90% CI	Upper 90% CI
Test	237	66.56%		≥0.80	≤1.25
Ref	239	70.54%	0.94	P<0.0001, Ho≤0.80 x Ref	P<0.0001, Ho≥ 1.25 x Ref

Mean Percent Reduction in Non-inflamed Lesion Count on Day 84

	N	% Reduction	T/R	Lower 90% CI	Upper 90% CI
Test	237	57.29%		≥0.80	≤1.25
Ref	239	60.57%	0.95	P<0.0001, Ho:≤0.80 x Ref	P<0.0001, Ho:≥ 1.25 x Ref

FDA Bioequivalence Analyses: PP Population

Raw Data at visit 4	**Test LS Mean**	**Reference LS Mean**	**90% CI**	**Pass the BE Test?**
Mean Percent Change from Baseline in Inflammatory Lesion Count	58.95	62.29	(0.89, 1.01)	YES
Mean Percent change from baseline in Non-Inflammatory Lesion Count	46.36	49.59	(0.86, 1.01)	YES
Rank Data at visit 4				
Mean Percent Change from Baseline in Inflammatory Lesion Count	NA	NA	(0.933, 1.000)	YES
Mean Percent change from baseline in Non-Inflammatory Lesion Count	NA	NA	(0.896, 0.956)	YES

Primary Endpoints (Placebo Comparison-ITT) per sponsor

Mean Percent Reduction in Inflamed Lesion Count on Day 84

	N	% Reduction		
Test	284	63.65%	Test v. Placebo	p<0.0001
Reference	284	67.32%	Ref v. Placebo	p<0.0001
Placebo	142	43.71%		

Mean Percent Reduction in Non-inflamed Lesion Count on Day 84

	N	% Reduction		
Test	284	52.69%	Test v. Placebo	p<0.0021
Reference	284	57.86%	Ref v. Placebo	p<0.0001
Placebo	142	41.10%		

FDA Placebo Comparison: MITT Population

	Test vs. Vehicle			Reference vs. Vehicle		
Raw Data at visit 4	**Test LS Mean**	**Vehicle LS Mean**	**p-value**	**Reference LS Mean**	**Vehicle LS Mean**	**p-value**
Mean Percent Change from baseline in Inflammatory Lesion Count	57.19	37.04	<0.001	61.36	37.77	<0.001
Mean Percent Change from Baseline in Non-Inflammatory Lesion Count	44.98	32.97	<0.001	50.97	34.30	<0.001
Rank Data at visit 4						
Mean Percent Change from Baseline in Inflammatory Lesion Count	NA	NA	<0.001	NA	NA	<0.001
Mean Percent Change from Baseline in Non-Inflammatory Lesion Count	NA	NA	<0.001	NA	NA	<0.001

Secondary Endpoints (Equivalence-ITT) per sponsor

Mean Numerical Reduction in Inflamed Lesion Count on Day 84

	N	Reduction	T/R	Lower 90% CI	Upper 90% CI
Test	284	20.89		≥0.80	≤1.25
Ref	284	21.65	0.96	P=0.0001, Ho:≤0.80 x Ref	P<0.0001, Ho:≥ 1.25 x Ref

Mean Numerical Reduction in Non-Inflamed Lesion Count on Day 84

	N	Reduction	T/R	Lower 90% CI	Upper 90% CI
Test	284	25.93		≥0.80	≤1.25
Ref	284	28.76	0.90	P=0.0103, Ho:≤0.80 x Ref	P<0.0001, Ho:≥ 1.25 x Ref

Percent of Patients Considered a Clinical Success on Day 84

	N	% Clinical Success	T/R	Lower 90% CI	Upper 90% CI
Test	284	36.97%			
Ref	284	42.61%	-5.63	-12.73	1.46

FDA Secondary Endpoint Bioequivalence Analyses: PP Population

Raw Data at visit 4	**Test LS Mean**	**Reference LS Mean**	**90% CI**	**Pass the BE Test?**
Change from Baseline in Inflammatory Lesion Count	17.58	18.23	(0.89, 1.01)	YES

Change from Baseline in Non-Inflammatory Lesion Count	21.32	23.90	(0.81, 0.98)	YES
Rank Data at visit 4				
Change from Baseline in Inflammatory Lesion Count	NA	NA	(0.900, 1.009)	YES
Change from Baseline in Non-Inflammatory Lesion Count	NA	NA	(0.867, 0.867)	YES
Clinical Cure rate at visit 4	**Test**	**Reference**	**90% CI**	**Pass the BE Test?**
PGA ≤1	42%	47%	(-13.8, 2.1)	YES

Secondary Endpoints (Placebo Comparison-ITT) per sponsor

Mean Numerical Reduction in Inflamed Lesion Count on Day 84

	N	Reduction		
Test	284	20.89	Test v. Placebo	p<0.0001
Reference	284	21.65	Ref v. Placebo	p<0.0001
Placebo	142	12.23		

Mean Numerical Reduction in Non-Inflamed Lesion count on Day 84

	N	Reduction		
Test	284	25.93	Test v. Placebo	p<0.0001
Reference	284	28.76	Ref v. Placebo	p<0.0001
Placebo	142	17.46		

Percent of Patients Considered a Clinical Success on Day 84

	N	% Clinical Success		
Test	284	36.97%	Test v. Placebo	p=0.0043
Ref	284	42.61%	Ref v. Placebo	p<0.0001
Placebo	142	23.24%		

FDA Secondary Endpoints Placebo Comparison: MITT Population

	Test vs. Vehicle			**Reference vs. Vehicle**		
Raw Data at visit 4	**Test LS Mean**	**Vehicle LS Mean**	**p-value**	**Reference LS Mean**	**Vehicle LS Mean**	**p-value**
Change from Baseline in Inflammatory Lesion Count	17.85	9.15	<0.001	18.75	9.32	<0.001

Change from Baseline in Non-Inflammatory Lesion Count	22.02	13.47	<0.001	24.99	13.80	<0.001
Rank Data at visit 4						
Change from Baseline in Inflammatory Lesion Count	NA	NA	<0.001	NA	NA	<0.001
Change from Baseline in Non-Inflammatory Lesion Count	NA	NA	<0.001	NA	NA	<0.001
Clinical Cure Rate visit 4	**Test**	**Reference**	**Vehicle**	**Test vs. Vehicle**	**Reference vs. Vehicle**	
PGA ≤1	37%	43%	23%	0.004	<0.001	

E. Bioequivalence Conclusion

Both the Sponsor's statistical analysis and the FDA's statistical analysis show the 90% CI for test to reference ratio of the mean percent reduction from Baseline in inflammatory and non-inflammatory lesion counts to be within the established bioequivalence limits of (0.80, 1.25).

The mean percent reduction from Baseline in inflammatory and non-inflammatory lesion counts of both products were demonstrated by both the Sponsor's analysis and the FDA analysis to be superior to placebo, demonstrating that the study was sensitive enough to detect differences in product performance at the lower end of the dose-response curve.

V. Comparative Review of Safety

A. Brief Statement of Conclusions

This study showed similar adverse events (AEs) with use of the test and reference products.

No deaths or serious AEs were reported during the course of the study. Five patients (4 Test, 1 Reference, and 0 Placebo) were discontinued from the study due to AEs. The type and frequency of AEs were similar across treatment groups.

B. Description of Adverse Events

A total of 280 patients reported 403 adverse events during the study. One hundred twenty-eight (128) (42.67%) patients reported 186 adverse events in the test group, 110 (36.67%) patients reported 161 adverse events in the reference group, and 42 (28.0%) patients reported 56 adverse events in the placebo group. The adverse events reported by more than 2% of patients in any one treatment group were the following:

Adverse Events Reported by more than 2% of patients

ADVERSE EVENT	Number (%)		
	Test	**Reference**	**Placebo**
APPLICATION SITE PARAESTHESIA	20(6.67)	12 (4.00)	0 (0.00)
APPLICATION SITE DRYNESS	61 (20.33)	50 (16.67)	16 (10.67)
APPLICATION SITE EXFOLIATION	7 (2.33)	3 (1.00)	1 (0.67)
APPLICATION SITE PRURITUS	9 (3.00)	6 (2.00)	0
DYSMENORRHEA	4 (1.33)	7 (2.33)	3 (2.00)
HEADACHE	20 (6.67)	12 (4.00)	5 (3.33)
MYALGIA	0	0	4 (2.67)
NASOPHARYNGITIS	4 (1.33)	6 (2.00)	2 (1.33)
TOOTHACHE	2 (0.67)	1 (0.33)	3 (2.00)
XEROSIS	8 (2.67)	2 (0.67)	0

Reviewer's comment: *The rate of overall AE reporting was 6 % higher with use of the test product than with the reference. However, the study was not designed to evaluate statistical significance of such reports, and this small difference is not likely to be meaningful. The largest number of reports was for application site dryness in 20% of test patients vs. 17% of reference patients. The only difference in the ingredients of the test and reference products is* (b) (4) *absence of hydrochloric acid in the test product. Therefore, there is no evidence that the safety profiles of the two products would be different.*

VI. Relevant Findings from Division of Scientific Investigations, Statistics and/or Other Consultant Reviews

A. Division of Scientific Investigations

A DSI inspection was not requested because of a recent acceptable inspection history for the following same sites:

Zoe D. Draelos, MD,PA, ANDA 090962 for adapalene gel, 02/01/2010, NAI
(b) (4)
Hector Wiltz, MD, CCTI, ANDA 065443 for clinda/benzoyl peroxide gel, 01/7/2008, VAI (no Form 483 issued)
Ines Mendez-Moguel, MD, ANDA 090824 for adapalene cream, 04/1/2010, NAI
Julitta Bradley, MD, ANDA 090824 for adapalene cream, 04/1/2010, NAI

B. Statistics

The following comments were forwarded to the FDA statistician:

1. The recommended primary endpoints are the mean percent change from baseline for both inflammatory (papules and pustules) and non-inflammatory (open and closed comedones) lesion counts at week 12. The absolute/numeric change from baseline is considered supportive information and is evaluated as a secondary endpoint. The difference between the products for the clinical success rate on the PGA is a secondary endpoint. The FDA statistician is requested to analyze the percent change in inflammatory (sum of papules and pustules only) and non-inflammatory lesion

counts. If your analysis does not confirm equivalence for the primary endpoint or superiority of the active products over the placebo, then please also analyze the numeric change in inflammatory (sum of papules and pustules) and non-inflammatory lesion counts.

2. Please evaluate the data distribution to determine whether a rank analysis method is needed for evaluation of these data. If so, please conduct your analysis accordingly.

3. FDA generally accepts a visit window of ± 4 days. Therefore, the visit window for Visit 4 (Week 12, Day 84) should be within ± 4 days to be included in the PP population. Therefore, those patients who were outside of the ± 4-day visit window for Visit 4 should be excluded from the PP population unless they were discontinued for lack of treatment response. Patients who were outside of the designated visit window for other visits need not be excluded from the PP population unless there were other reasons for exclusion.

4. The FDA statistician is asked to exclude the following patients from both the ITT and PP populations for not meeting the following inclusion/exclusion criteria:
    - Baseline lesion counts outside the inclusion criteria (combined papules/pustules should be ≥20 and ≤60 and combined open and closed comedones should be ≥25 and ≤ 100).
    - Baseline nodule count ≥3:
    - Had PGA score less than 3.

5. The following patients should be excluded from the PP population for the reasons noted:
    - Prohibited medication use before or during the study period: Amoxicillin (b) (6) Investigational Acne Drug (b) (6) and Penicillin (b) (6)
    - All patients who are outside of the designated +/- 4 days for Visit 4, unless the patient discontinued from the study due to lack of treatment response.

6. All patients that discontinued from the study due to lack of treatment response should be included in the PP population as treatment failures, using LOCF for the lesion counts.

The following tables summarize the FDA statistical analyses:

Efficacy Analysis: MITT Population

	Test vs. Vehicle			Reference vs. Vehicle		
Raw Data at visit 4	Test LS Mean	Vehicle LS Mean	p-value	Reference LS Mean	Vehicle LS Mean	p-value
Mean Percent Change from baseline in Inflammatory Lesion Count	57.19	37.04	<0.001	61.36	37.77	<0.001

Change from Baseline in Inflammatory Lesion Count	17.85	9.15	<0.001	18.75	9.32	<0.001
Mean Percent Change from Baseline in Non-Inflammatory Lesion Count	44.98	32.97	<0.001	50.97	34.30	<0.001
Change from Baseline in Non-Inflammatory Lesion Count	22.02	13.47	<0.001	24.99	13.80	<0.001
Rank Data at visit 4						
Mean Percent Change from Baseline in Inflammatory Lesion Count	NA	NA	<0.001	NA	NA	<0.001
Change from Baseline in Inflammatory Lesion Count	NA	NA	<0.001	NA	NA	<0.001
Mean Percent Change from Baseline in Non-Inflammatory Lesion Count	NA	NA	<0.001	NA	NA	<0.001
Change from Baseline in Non-Inflammatory Lesion Count	NA	NA	<0.001	NA	NA	<0.001
Clinical Cure Rate at visit 4	Test	Reference	Vehicle	Test vs. Vehicle	Reference vs. Vehicle	
PGA ≤1	37%	43%	23%	0.004	<0.001	

Bioequivalence Analyses: PP Population

Raw Data at visit 4	Test LS Mean	Reference LS Mean	90% CI	Pass the BE Test?
Mean Percent Change from Baseline in Inflammatory Lesion Count	58.95	62.29	(0.89, 1.01)	YES
Change from Baseline in Inflammatory Lesion Count	17.58	18.23	(0.89, 1.01)	YES
Mean Percent change from baseline in Non-Inflammatory Lesion Count	46.36	49.59	(0.86, 1.01)	YES
Change from Baseline in Non-Inflammatory Lesion Count	21.32	23.90	(0.81, 0.98)	YES
Rank Data at visit 4				
Mean Percent Change from Baseline in Inflammatory Lesion Count	NA	NA	(0.933, 1.000)	YES
Change from Baseline in	NA	NA	(0.900,	YES

Inflammatory Lesion Count			1.009)	
Mean Percent change from baseline in Non-Inflammatory Lesion Count	NA	NA	(0.896, 0.956)	YES
Change from Baseline in Non-Inflammatory Lesion Count	NA	NA	(0.867, 0.867)	YES
Clinical Cure rate at visit 4	Test	Reference	90% CI	Pass the BE Test?
PGA ≤1	42%	47%	(-13.8, 2.1)	YES

VII. Formulation

Component	Function	Test (% w/w)	Reference*
Adapalene	Active Ingredient	0.10	0.1%
Carbomer 940	(b) (4)	(b) (4)	
Propylene Glycol, USP			
Poloxamer 182			
Edetate Disodium, USP			
Methylparaben, NF			
Sodium Hydroxide, NF			
Hydrochloric Acid (b) (4)	Adjust pH		
Purified Water, USP	(b) (4)		

*per FDA internal database for NDA 020380

Reviewer's Comment: *The test and reference formulations are very similar. The only difference is that the test formulation does not include hydrochloric acid,* (b) (4) *This difference is unlikely to change the safety or efficacy of this product, and this study shows no meaningful difference in AE reporting.*

VIII. Conclusion and Recommendation

A. Conclusion

The data presented in this ANDA 091314 demonstrates that Glenmark's Adapalene Gel, 0.1% is bioequivalent to the reference listed drug, Differin Gel, 0.1%. The FDA statistical review confirms that the 90% CI of the mean percent change from baseline between the test and reference products at week 12 is within (0.80, 1.25) for both inflammatory and non-inflammatory lesions of acne vulgaris. The test and reference products also demonstrate superiority over placebo at week 12, demonstrating that the study is sensitive enough to detect differences in product performance at the lower end of the dose response curve.

B. Recommendation

This application is recommended for approval from a bioequivalence standpoint.

_____ _____
Nicole Lee, Pharm.D. Date
Clinical Reviewer
Office of Generic Drugs

_____ _____
Dena R. Hixon, M.D. Date
Associate Director for Medical Affairs
Office of Generic Drugs

_____ _____
Dale P. Conner, Pharm.D. Date
Director
Division of Bioequivalence I
Office of Generic Drugs

COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:091314 APPLICANT: Glenmark Generics Inc., USA.

DRUG PRODUCT: Adapalene Gel, 0.1%

The Clinical Review Team has completed its review and has no further questions at this time.

The data submitted to ANDA 091314 using the primary endpoint of mean percent reduction in inflammatory and non-inflammatory lesion counts from baseline to Week 12, are adequate to demonstrate bioequivalence of Glenmark's Adapalene Gel, 0.1% with the reference listed drug, Differin Gel, 0.1%.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91314	ORIG-1	GLENMARK GENERICS INC USA	ADAPALENE

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

/s/

NICOLE LEE
06/30/2010

DENA R HIXON
06/30/2010
I concur.

DALE P CONNER
06/30/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 091314Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA #91-314 ApplicantGlenmark Generics Ltd.
Drug Name/Strength: Adapalene Gel, 0.1%

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **CGMP** ☐

REVIEWER:

1. **Martin Shimer** Date 7/1/10
Chief, Reg. Support Branch Initials rlw/for

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD =
Differin Gel NDA#20-380
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked N/A
If Para. IV Certification- did applicant Nothing Submitted
Notify patent holder/NDA holder Yes ☐ No ☐ Written request issued
Was applicant sued w/in 45 days:Yes ☐ No ☐ Study Submitted
Has case been settled: Yes ☐ No ☐ Date settled:

Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes
Type of Letter:Full Approval.
Comments:ANDA submitted on 2/9/2009, BOS=Differin Gel 0.1% NDA 20-380, PIII to '720 and '440. ANDA ack for filing on 2/9/2009 (LO dated 4/20/2009). Both the '720 and '440 patents expired on 5/31/2010. ANDA is now eligible for immediate Full Approval.

2. Project Manager, Trang Tran Team 3 Date7/1/10
Review Support Branch InitialsTT

Original Rec OAI ☐
Date of Application2/6/09
Date Acceptable for Filing2/9/09
Patent Certification (type)III
Date Patent/Exclus.expires5/31/2010 ☐
☐

Citizens' Petition/Legal Case Yes
(If YES, attach email from PM to CP coord) No ☐

Priority Approval ☒
(If yes, prepare Draft Press Release, Email ☒
it to Cecelia Parise)

☒

Suitability Petition/Pediatric Waiver Yes ☒
Pediatric Waiver Request:

☐
☐

Comments:

3.

Date_____ Date7/1/10
Name/Initials_____ Name/Initials rlw/for

REMS required? REMS acceptable?
☐Yes ☒No ☐Yes ☐No ☒n/a

Comments:
FPL found acceptable for approval 9/9/09.

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 7/1/10
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials rlw/for
Comments:There are no unexpired patents listed in the current "Orange Book" for this drug product..

5. Div. Dir./Deputy Dir. Date6/30/10
Chemistry Div. I Initials PS

Comments:cmc ok.

6. Frank Holcombe **First Generics Only** Date 7/1/10
Assoc. Dir. For Chemistry Initials rlw/for
Comments: (First generic drug review)
N/A. Pliva's ANDa 90-962 for this drug product was approved on 6/2/10.

7. Vacant Date_____
Deputy Dir., DLPS Initials_____
RLD = Differin Gel, 0.1%
Galderma Laboratories, LP NDA 20-380

8. Peter Rickman Date 7/1/10
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐
Comments: Bioequivalence studies with a clinical endpoint found acceptable for approval. Bio study sites had acceptable DSI inspection histories. Statistical review found acceptable 6/23/10. Office-level bio endorsed 6/30/10.

Final-printed labeling (FPL) found acceptable for approval 9/9/09. No new changes to RLD labeling as documented on approval summary for ANDA 90-824.

CMC found acceptable for approval (Chemistry Review #2).

OR

8. Robert L. West Date 7/1/10
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments:Acceptable EES dated 4/16/09 (Verified 7/1/10). No "OAI" Alerts noted.

There are no patents or exclusivity currently listed in the "Orange Book" for this drug product.

This ANDA is recommended for approval.

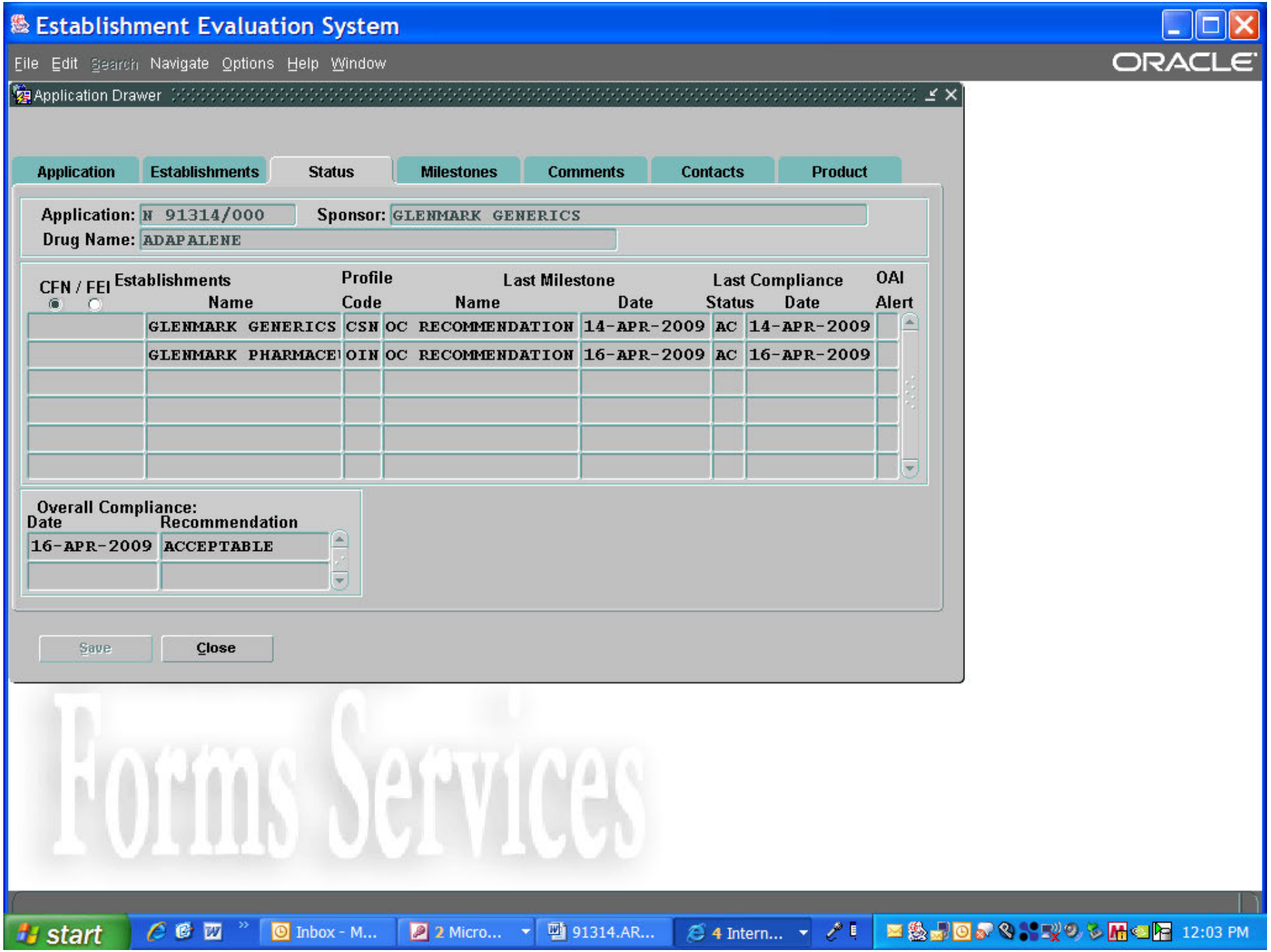
9. Keith Webber Date 7/1/10
Deputy Director, OPS Initials rlw/for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Trang Tran Team 3 Date7/1/10
Initials TT

Applicant notification:
7/1/10Date notified of approval by phone
7/1/10Date approval letter faxed

FDA Notification:
7/1/10Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
_____Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

EER DATA: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ORACLE
Application Drawer
Application
Establishments
Status
Milestones
Comments
Contacts
Product
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Sponsor: GLENMARK GENERICS
Drug Name: ADAPALENE
CFN / FEI
Establishments Name
Profile Code
Last Milestone Name
Last Milestone Date
Last Compliance Status
Last Compliance Date
OAI Alert
GLENMARK GENERICS CSN OC RECOMMENDATION 14-APR-2009 AC 14-APR-2009
GLENMARK PHARMACE OIN OC RECOMMENDATION 16-APR-2009 AC 16-APR-2009
Overall Compliance:
Date
Recommendation
16-APR-2009 ACCEPTABLE
Save
Close
Forms Services
start
Inbox - M...
2 Micro...
91314.AR...
4 Intern...
12:03 PM

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91314	ORIG-1	GLENMARK GENERICS INC USA	ADAPALENE

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

/s/

TRANG Q TRAN
07/01/2010

QUALITY DEFICIENCY - MINOR

ANDA 091314

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Glenmark Generics Inc., USA TEL: (201) 684-8017

ATTN: William R. McIntyre FAX: (201) 831-0080

FROM: Nitin Patel FDA CONTACT PHONE: (240) 276-8548

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated February 6, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Adapalene Gel, 0.1%.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **2** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

Chemistry Comments to be Provided to the Applicant

ANDA: 091314 APPLICANT**:** Glenmark Generics Inc., USA

DRUG PRODUCT: Adapalene Gel, 0.1%

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. (b) (4)
2.
3.
4.
5.
6.
7.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all available long-term drug product stability data.

2. Information related to bioequivalency is under review. After the review is completed, any deficiencies found will be communicated to you under separate covers.

3. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval.

Sincerely yours,

{see appended electronic signature page}

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-91314	ORIG-1	GLENMARK GENERICS INC USA	ADAPALENE

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

/s/

JAMES M FAN
10/31/2009

Telephone Fax

ANDA 91-314

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8984

TO: Glenmark Pharmaceuticals Inc, USA

TEL: (202)684-8017

ATTN: William McIntyre

FAX: (202)831-0080

FROM: Beverly Weitzman

:

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for adapalene gel, 0.1%

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

Labeling Comments

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 91-314

Date of Submission: February 6, 2009

Applicant's Name: Glenmark Generics Inc., USA

Established Name: Adapalene Gel, 0.1%

Labeling Deficiencies:

1. **CONTAINER** (45 *g):*
   a. Revise your storage statement to read as "Stored at 20° - 25°C (68° - 77°F) [See USP Controlled Room Temperature]" Protect from freezing.
   b. *P*lease assure that your container label is of actual size, color and clarity when submitting in final printed labeling.
2. **CARTON** (45 g):
   a. **Principal panels**: Repeat the statement of route of administration and "NOT FOR OPHTHALMIC USE" appearing on the side panel, such that is appears with prominence on each of the principal display panels.
   b. Recommend adding the statement "Keep out of reach of children".
   c. See CONTAINER comment (a).
3. **INSERT:** Satisfactory in DRAFT

Revise your labeling, as instructed above, and submit final printed labeling electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with that of your last submission with all differences annotated and explained.

{See appended electronic signature page}

_____
Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

JOHN F GRACE
08/20/2009
for Wm Peter Rickman

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
*** **A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ ***

ANDA #: 91-314 **FIRM NAME**: GLENMARK GENERICS LIMITED

PIV: NO **Electronic or Paper Submission:** PAPER (CTD FORMAT)

RELATED APPLICATION(S): NA

First Generic Product Received? NO

DRUG NAME: ADAPALENE

DOSAGE FORM: GEL, 0.1%

Random Queue: 3

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☒ **BCE**	
☐ **BST**	☐ **BDI**	

Chem Team Leader: Fan, Jim Chem PM: Rosalyn Adigun Labeling Reviewer: Beverely Weitzman
Bio PM: Diana Solana

Letter Date: FEBRUARY 6, 2009 **Received Date**: FEBRUARY 9, 2009

Comments: EC - 1 YES **On Cards:** YES
Therapeutic Code: 4029041 ACNE AGENTS

Archival copy: PAPER (CTD FORMAT) **Sections** I
Review copy: YES E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Iain Margand Date 4/14/2009	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**

Supervisory Concurrence/Date: _____ **Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:
*****See attached Clinical Team review*****

Requested clarification who is the applicant for the ANDA. 356h states Glenmark USA, however there is a U.S. Agent LOA for Glenmark USA to act on the behalf of Glenmark Limited in India.
Per Dr. McIntyre, Glenmark USA is the applicant, the U.S. LOA was placed in the application unintentionally.

Contact: William McIntyre 201-684-8017

MODULE 1
ADMINISTRATIVE

ACCEPTABLE

1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: FEBRUARY 6, 2009	☒
1.2.1	**Form FDA 3674 (PDF) YES** Box "B"	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) YES Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) NA	☒
1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s) '440, '720 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☒ PIV ☐ (Statement of Notification) ☐ 3. Expiration of Patent(s): 5/31/2010 a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES no exclusivities	☒
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient Y b. Type III DMF authorization letter(s) for container closure Y 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) NA	☒

1.12.11	**Basis for Submission** NDA# : 20-380 Ref Listed Drug: DIFFERIN Firm: GALDERMA LABORATORIES, L.P. ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same 2. Active ingredients Adapalene 3. Inactive ingredients 4. Route of administration Topical 5. Dosage Form Gel 6. Strength 0.1%	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): NA	☐
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) Y **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained Y **1.14.1.3** 1 package insert (content of labeling) submitted electronically Y ***Was a proprietary name request submitted? No (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained Y **1.14.3.3** 1 RLD label and 1 RLD container label Y	☒

MODULE 2
SUMMARIES ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF Y** **Word Processed e.g., MS Word** Y A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** Y **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P** **Drug Product** **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF** Y **Word Processed e.g., MS Word** Y **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary Table 4. Bioanalytical Method Validation Table 6. Formulation Data **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies Table 3. Statistical Summary of the Comparative BA Data **2.7.1.4 Appendix** **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies	☒

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) Y 2. Function or Responsibility Y 3. Type II DMF number for API DMF# 18756 4. CFN or FEI numbers	☒
3.2.S.3	**Characterization**	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) Y **3.2.S.4.2 Analytical Procedures** Y **3.2.S.4.3 Validation of Analytical Procedures** Y 1. Spectra and chromatograms for reference standards and test samples see 3.2.S.4.4 2. Samples-Statement of Availability and Identification of: a. Drug Substance Y b. Same lot number(s) Y **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) Y 2. Applicant certificate of analysis Y **3.2.S.4.5 Justification of Specification** Y	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems** Refer to DMF # 18756	☐
3.2.S.7	**Stability** Refer to DMF# 18756	☐

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1. Unit composition Y 2. Inactive ingredients and amounts are appropriate per IIG Q1/Q2 per OND Chem review formulation (see below)	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report	☒
3.2.P.3	**Manufacture** **3.2.P.3.1 Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. Function or Responsibility YES 4. CFN or FEI numbers **3.2.P.3.2 Batch Formula** Y **3.2.P.3.3 Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process Y 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified (b) (4) 3. If sterile product: Aseptic fill / Terminal sterilization N/A 4. Reprocessing Statement Y **3.2.P.3.4 Controls of Critical Steps and Intermediates** Y **3.2.P.3.5 Process Validation and/or Evaluation** Y 1. Microbiological sterilization validation 2. Filter validation (if aseptic fill) N/A	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified Y **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) Y 2. Suppliers' COA (specifications and test results) Y **3.2.P.4.2 Analytical Procedures** Y **3.2.P.4.3 Validation of Analytical Procedures** Y **3.2.P.4.4 Justification of Specifications** Applicant COA Y	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** Y **3.2.P.5.2 Analytical Procedures** Y **3.2.P.5.3 Validation of Analytical Procedures** Y Samples - Statement of Availability and Identification of: 1. Finished Dosage Form Y 2. Same lot numbers Y **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form lot# Q15727001 **3.2.P.5.5 Characterization of Impurities** Y **3.2.P.5.6 Justification of Specifications** Y	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) Y 2. Components Specification and Test Data Y 3. Packaging Configuration and Sizes 45 g laminated tube 4. Container/Closure Testing Y 5. Source of supply and suppliers address Y	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted Y 2. Expiration Dating Period 24 months **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments Y **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data Y 2. Batch numbers on stability records the same as the test batch Q15727001	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available)** **3.2.R.2.S Comparability Protocols** **3.2.R.3.S Methods Validation Package NO** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☐

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation see attached Theoretical Yield Actual Yield Packaged Yield **3.2.R.1.P.2 Information on Components** N/A **3.2.R.2.P Comparability Protocols** N/A **3.2.R.3.P Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5

CLINICAL STUDY REPORTS

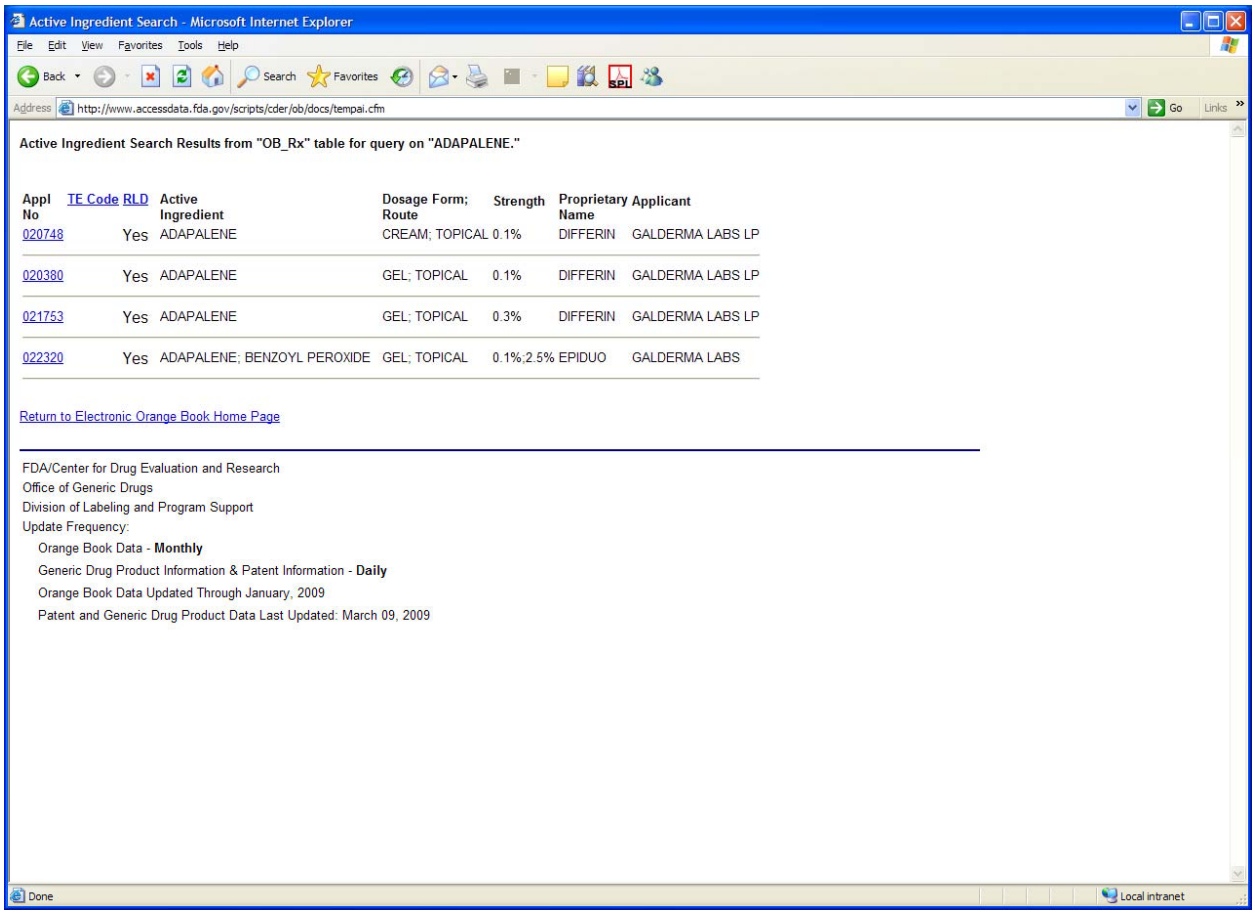
ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☐
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) N/A b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** Q15727001 **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒

	5.3.1.2 Comparative BA/BE Study Reports 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. Summary Bioequivalence tables: Table 10. Study Information Table 12. Dropout Information Table 13. Protocol Deviations **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 11. Product Information Table 16. Composition of Meal Used in Fed Bioequivalence Study **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples **5.3.7** **Case Report Forms and Individual Patient Listing**	☒
5.4	**Literature References**	☐
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) NA 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted: NA 3. In-Vitro Dissolution: NA	☐
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** YES BIO/STU (CLINICAL) OK per Clinical Team 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted YES SENT TO EDR	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 8/11/2008


Active Ingredient Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm
Go Links
Active Ingredient Search Results from "OB_Rx" table for query on "ADAPALENE."
Appl No | TE Code | RLD | Active Ingredient | Dosage Form; Route | Strength | Proprietary Name | Applicant
020748 | | Yes | ADAPALENE | CREAM; TOPICAL | 0.1% | DIFFERIN | GALDERMA LABS LP
020380 | | Yes | ADAPALENE | GEL; TOPICAL | 0.1% | DIFFERIN | GALDERMA LABS LP
021753 | | Yes | ADAPALENE | GEL; TOPICAL | 0.3% | DIFFERIN | GALDERMA LABS LP
022320 | | Yes | ADAPALENE; BENZOYL PEROXIDE | GEL; TOPICAL | 0.1%;2.5% | EPIDUO | GALDERMA LABS
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through January, 2009
Patent and Generic Drug Product Data Last Updated: March 09, 2009
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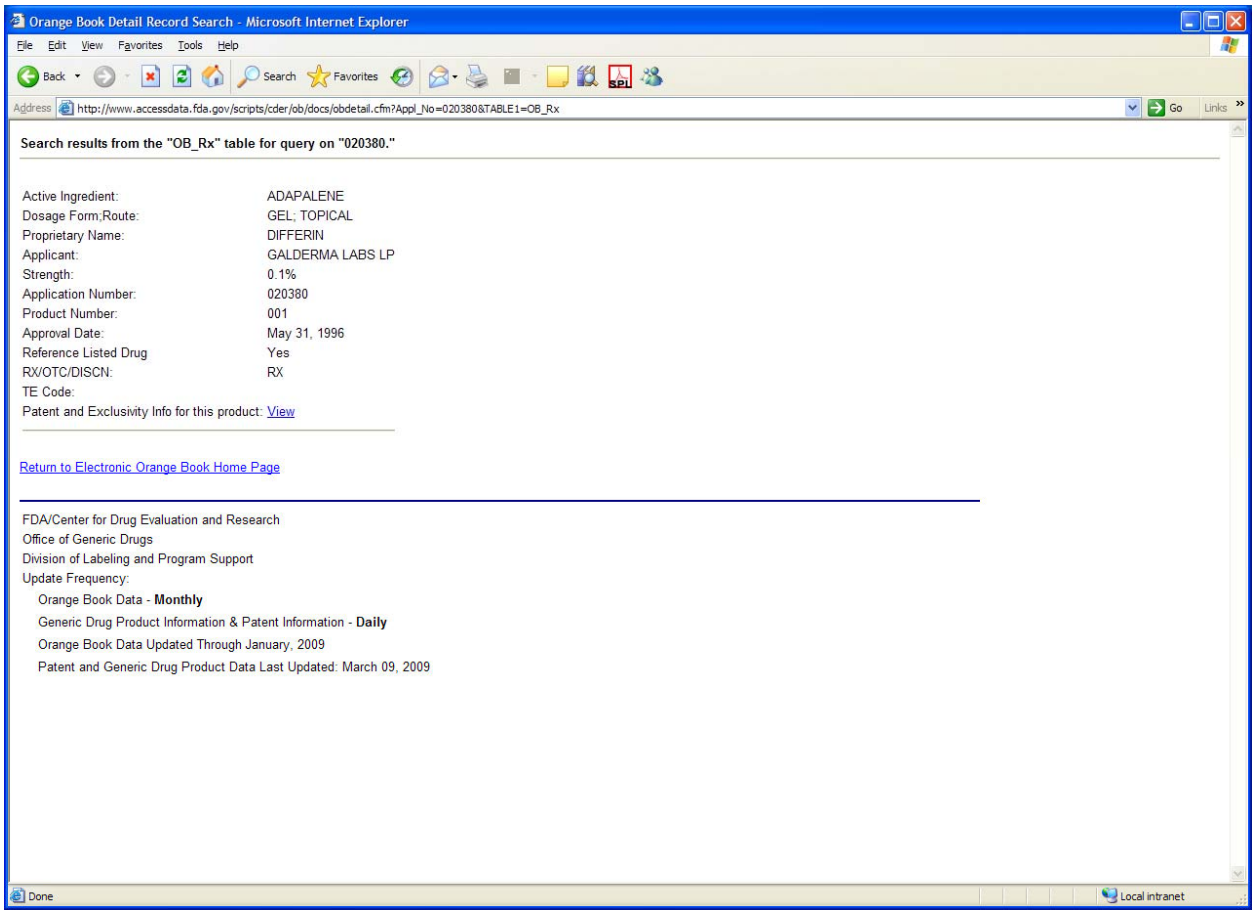
Local intranet


Orange Book Detail Record Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=020380&TABLE1=OB_Rx
Go Links
Search results from the "OB_Rx" table for query on "020380."
Active Ingredient: ADAPALENE
Dosage Form;Route: GEL; TOPICAL
Proprietary Name: DIFFERIN
Applicant: GALDERMA LABS LP
Strength: 0.1%
Application Number: 020380
Product Number: 001
Approval Date: May 31, 1996
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
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Patent and Generic Drug Product Data Last Updated: March 09, 2009
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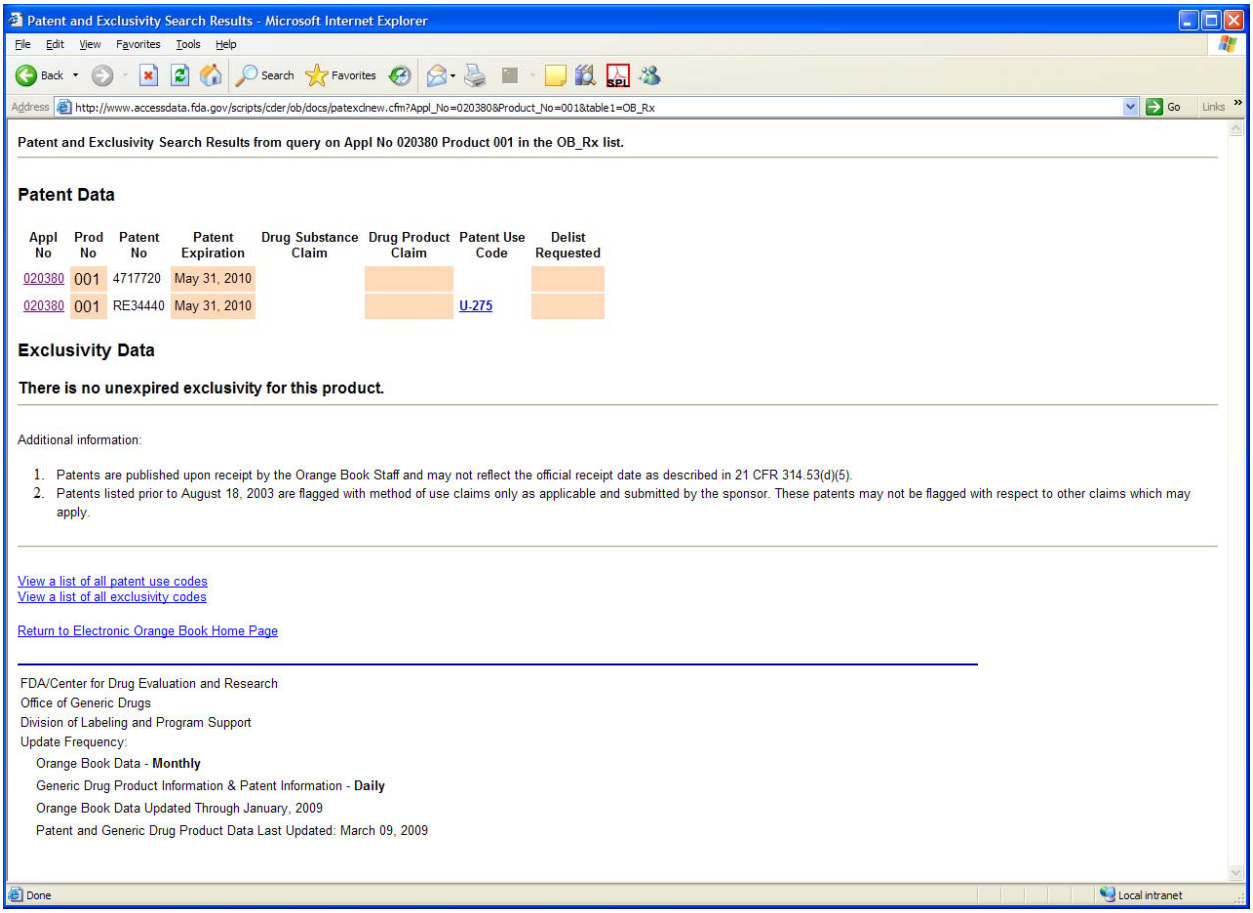

Following this page, 4 Pages Withheld in Full as (b)(4)

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	X				Novum study #70744002 Protocol #GLK609
Summary of Study	X				
Clinical Site (s)	X				
Study Investigator (s)	X				
List of subjects included in PP/ (M)ITT populations per treatments	X				
List of subjects excluded/ from PP/ (M)ITT per treatments	X				
Reasons for discontinuation from the study if discontinued	X				
Adverse Events	X				
Concomitant Medications	X				
Individual subject's scores/data per visit	X				
Pre-screening of Patients	X				
IRB Approval	X				
Consent Forms	X				
Randomization Schedule	X				
Protocol Deviations	X				
Case Report Forms	X				
PD Data Disk (or Elec Subm)	X				
Study Results	X				
Financial Disclosure	X				

Clinical Raw Data/ Medical Records	X				
Composition	X				
BioStudy Lot Numbers	X				
Date of Manufacture	X				
Exp. Date of RLD	X				
Statistical Reports	X				
Defined BE endpoints	X				
Summary results provided by the firm indicate studies pass BE criteria	X				See below for comments
Summary results provided by the firm indicate superiority of the active treatments over the vehicle/placebo	X				See below for comments
Waiver requests for other strengths / supporting data		X			N/A

Comments to be conveyed to the sponsor
Your application is acceptable for filing.

Comments <u>not to be conveyed</u> to the sponsor:
Patients with a clinical diagnosis of moderate to severe acne vulgaris, defined as: at least 20 but no more than 60 facial inflammatory lesions (papules and pustules) with no more than 2 nodules and at least 25 but no more than 100 non-inflammatory lesions (open and closed comedones) and had a PGA score of 3, 4 or 5, were eligible for inclusion in the study.

The sponsor states that non-parametric testing, Wilcoxon Rank-Sum test, was performed for the primary endpoint analysis because the distribution of their data was not normal. The 90% CIs for the test/reference ratio of the mean percent change from baseline in inflammatory (papules and pustules) lesion count and non-inflammatory (open and closed comedones) lesion count in the PP population at Day 84 were within the established bioequivalence limits of 80 to 125%. Both test and reference products were shown to be superior to the vehicle with regard to the primary endpoint. Nodules were not included in the sponsor's analysis of inflammatory lesions.

The 90% CIs for the test/reference ratio of the mean reduction from baseline in inflammatory and non-inflammatory lesion counts in the PP population at Day 84 were also within the established bioequivalence limits of 80 to 125%. Both test and reference products were shown to be superior to the vehicle.

The sponsor also evaluated the proportion of patients with a clinical success based on a PGA. Success was defined by the sponsor as a PGA score of 0 (normal) or 1 (skin almost clear) at their final evaluation. Patients with a PGA score higher than 1 was considered a "clinical failure".

The sponsor's summary of the result is shown below.

Primary and secondary analyses: Change from baseline in inflammatory and non-inflammatory lesion counts at Day 84

Table 3 Statistical Summary of the Comparative Bioavailability Data

A Randomized, Double-Blind, Multiple-Site, Placebo-Controlled, Parallel Design, Clinical Study to Evaluate the Bioequivalence of Adapalene Gel 0.1% (Glenmark Pharmaceuticals, Ltd.) Compared to Differin® (adapalene 0.1%) Topical Gel (Galderma Laboratories) in Patients with Moderate to Severe Acne Vulgaris Study No. 70744002				
Non-Parametric Analysis 90% Confidence Intervals				
Parameter	Ho: Test ≤ 0.8*Ref	Ho: Test ≥ 1.25*Ref		
Mean Percent Reduction in Inflamed Lesion Count (PPP)	<.0001	<.0001		
Mean Percent Reduction in Non-Inflamed Lesion Count (PPP)	<.0001	<.0001		
Mean Numerical Reduction in Inflamed Lesion Count (ITT)	0.0001	<.0001		
Mean Numerical Reduction in Non-Inflamed Lesion Count (ITT)	0.0103	<.0001		
Non-Parametric Analysis Superiority Testing				
Parameter	Test vs Placebo	Reference vs Placebo		
Mean Percent Reduction in Inflamed Lesion Count (ITT)	<.0001	<.0001		
Mean Percent Reduction in Non-Inflamed Lesion Count (ITT)	0.0021	<.0001		
Mean Numerical Reduction in Inflamed Lesion Count (ITT)	<.0001	<.0001		
Mean Numerical Reduction in Non-Inflamed Lesion Count (ITT)	<.0001	<.0001		
Normal Distribution Analysis 90% Confidence Intervals				
Parameter	Test	Reference	Ratio	90% Confidence Interval
Mean Percent Reduction in Inflamed Lesion Count (PPP)	66.56	70.54	94.65	88.49-100.80
Mean Percent Reduction in Non-Inflamed Lesion Count (PPP)	57.29	60.57	93.82	86.28-101.36
Mean Numerical Reduction in Inflamed Lesion Count (ITT)	20.89	21.65	95.81	88.78-102.84
Mean Numerical Reduction in Non-Inflamed Lesion Count (ITT)	25.93	28.76	88.74	80.26-97.23
			Difference	
Clinical Success (ITT)	36.97	42.61	-5.63	-12.73-1.46

Table 3 Statistical Summary of the Comparative Bioavailability Data (continued)

A Randomized, Double-Blind, Multiple-Site, Placebo-Controlled, Parallel Design, Clinical Study to Evaluate the Bioequivalence of Adapalene Gel 0.1% (Glenmark Pharmaceuticals, Ltd.) Compared to Differin® (adapalene 0.1%) Topical Gel (Galderma Laboratories) in Patients with Moderate to Severe Acne Vulgaris Study No. 70744002				
Normal Distribution Analysis Superiority Testing				
Parameter	Test vs Placebo	Reference vs Placebo		
Mean Percent Reduction in Inflamed Lesion Count (ITT)	<.0001	<.0001		
Mean Percent Reduction in Non-Inflamed Lesion Count (ITT)	0.0024	<.0001		
Mean Numerical Reduction in Inflamed Lesion Count (ITT)	<.0001	<.0001		
Mean Numerical Reduction in Non-Inflamed Lesion Count (ITT)	<.0001	<.0001		
Clinical Success (ITT)	0.0043	<.0001		

The sponsor's formulation is provided below.

Adapalene Gel 0.1%			
Ingredient (s)	**Specification**	**Function**	**Quantity % w/w**
Adapalene	(b) (4)	Active	0.10
Edetate Disodium	USP	(b) (4)	
Carbomer 940 (b) (4)	NF		
Methylparaben	NF		
Propylene Glycol	USP		
Polaxamer 182	(b) (4)		
Sodium Hydroxide	NF		
Purified Water[1]	USP		

(b) (4)

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

/s/

Martin Shimer

4/20/2009 02:07:28 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 91-314

Glenmark Generics Inc., USA
Attention: William McIntyre, Ph.D.
750 Corporate Drive
Mahwah, NJ 07430

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Adapalene Gel, 0.1%

DATE OF APPLICATION: February 6, 2009

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 9, 2009

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Rosalyn Adigun
Project Manager
240-276-8518

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Martin Shimer
4/20/2009 02:07:11 PM
Signing for Wm Peter Rickman

CLINICAL REVIEW TEAM CHECKLIST FOR GENERIC ANDA
FOR APPLICATION COMPLETENESS

ANDA# 91-314_____ **FIRM NAME**___Glenmark Generics Inc. USA_____

DRUG NAME __Adapalene Gel, 0.1%_____

DOSAGE FORM __topical gel_____

Requested by: _Washington, Edward_____ Date: _3/10/09_____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Clinical Review Team
X	**Study meets statutory requirements**
	Study does NOT meet statutory requirements
	Waiver meets statutory requirements
	Waiver does NOT meet statutory requirements
	Reason:

RECOMMENDATION: **_ X __COMPLETE** **_ __INCOMPLETE**

Reviewed by:

_____ Date: _____
Reviewer
Carol Y. Kim, Pharm.D.
Clinical Reviewer

_____ Date: _____
Dena R. Hixon, M.D.
Associate Director for Medical Affairs

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	X				Novum study #70744002 Protocol #GLK609
Summary of Study	X				
Clinical Site (s)	X				
Study Investigator (s)	X				
List of subjects included in PP/ (M)ITT populations per treatments	X				
List of subjects excluded/ from PP/ (M)ITT per treatments	X				
Reasons for discontinuation from the study if discontinued	X				
Adverse Events	X				
Concomitant Medications	X				
Individual subject's scores/data per visit	X				
Pre-screening of Patients	X				
IRB Approval	X				
Consent Forms	X				
Randomization Schedule	X				
Protocol Deviations	X				
Case Report Forms	X				
PD Data Disk (or Elec Subm)	X				
Study Results	X				
Financial Disclosure	X				

Clinical Raw Data/ Medical Records	X				
Composition	X				
BioStudy Lot Numbers	X				
Date of Manufacture	X				
Exp. Date of RLD	X				
Statistical Reports	X				
Defined BE endpoints	X				
Summary results provided by the firm indicate studies pass BE criteria	X				See below for comments
Summary results provided by the firm indicate superiority of the active treatments over the vehicle/placebo	X				See below for comments
Waiver requests for other strengths / supporting data		X			N/A

Comments to be conveyed to the sponsor

Your application is acceptable for filing.

Comments <u>not to be conveyed</u> to the sponsor:

Patients with a clinical diagnosis of moderate to severe acne vulgaris, defined as: at least 20 but no more than 60 facial inflammatory lesions (papules and pustules) with no more than 2 nodules and at least 25 but no more than 100 non-inflammatory lesions (open and closed comedones) and had a PGA score of 3, 4 or 5, were eligible for inclusion in the study.

The sponsor states that non-parametric testing, Wilcoxon Rank-Sum test, was performed for the primary endpoint analysis because the distribution of their data was not normal. The 90% CIs for the test/reference ratio of the mean percent change from baseline in inflammatory (papules and pustules) lesion count and non-inflammatory (open and closed comedones) lesion count in the PP population at Day 84 were within the established bioequivalence limits of 80 to 125%. Both test and reference products were shown to be superior to the vehicle with regard to the primary endpoint. Nodules were not included in the sponsor's analysis of inflammatory lesions.

The 90% CIs for the test/reference ratio of the mean reduction from baseline in inflammatory and non-inflammatory lesion counts in the PP population at Day 84 were also within the established bioequivalence limits of 80 to 125%. Both test and reference products were shown to be superior to the vehicle.

The sponsor also evaluated the proportion of patients with a clinical success based on a PGA. Success was defined by the sponsor as a PGA score of 0 (normal) or 1 (skin almost clear) at their final evaluation. Patients with a PGA score higher than 1 was considered a "clinical failure".

The sponsor's summary of the result is shown below.

Primary and secondary analyses: Change from baseline in inflammatory and non-inflammatory lesion counts at Day 84

Table 3 Statistical Summary of the Comparative Bioavailability Data

A Randomized, Double-Blind, Multiple-Site, Placebo-Controlled, Parallel Design, Clinical Study to Evaluate the Bioequivalence of Adapalene Gel 0.1% (Glenmark Pharmaceuticals, Ltd.) Compared to Differin® (adapalene 0.1%) Topical Gel (Galderma Laboratories) in Patients with Moderate to Severe Acne Vulgaris Study No. 70744002				
Non-Parametric Analysis 90% Confidence Intervals				
Parameter	Ho: Test ≤ 0.8*Ref	Ho: Test ≥ 1.25*Ref		
Mean Percent Reduction in Inflamed Lesion Count (PPP)	<.0001	<.0001		
Mean Percent Reduction in Non-Inflamed Lesion Count (PPP)	<.0001	<.0001		
Mean Numerical Reduction in Inflamed Lesion Count (ITT)	0.0001	<.0001		
Mean Numerical Reduction in Non-Inflamed Lesion Count (ITT)	0.0103	<.0001		
Non-Parametric Analysis Superiority Testing				
Parameter	Test vs Placebo	Reference vs Placebo		
Mean Percent Reduction in Inflamed Lesion Count (ITT)	<.0001	<.0001		
Mean Percent Reduction in Non-Inflamed Lesion Count (ITT)	0.0021	<.0001		
Mean Numerical Reduction in Inflamed Lesion Count (ITT)	<.0001	<.0001		
Mean Numerical Reduction in Non-Inflamed Lesion Count (ITT)	<.0001	<.0001		
Normal Distribution Analysis 90% Confidence Intervals				
Parameter	Test	Reference	Ratio	90% Confidence Interval
Mean Percent Reduction in Inflamed Lesion Count (PPP)	66.56	70.54	94.65	88.49-100.80
Mean Percent Reduction in Non-Inflamed Lesion Count (PPP)	57.29	60.57	93.82	86.28-101.36
Mean Numerical Reduction in Inflamed Lesion Count (ITT)	20.89	21.65	95.81	88.78-102.84
Mean Numerical Reduction in Non-Inflamed Lesion Count (ITT)	25.93	28.76	88.74	80.26-97.23
			Difference	
Clinical Success (ITT)	36.97	42.61	-5.63	-12.73-1.46

Table 3 Statistical Summary of the Comparative Bioavailability Data (continued)

A Randomized, Double-Blind, Multiple-Site, Placebo-Controlled, Parallel Design, Clinical Study to Evaluate the Bioequivalence of Adapalene Gel 0.1% (Glenmark Pharmaceuticals, Ltd.) Compared to Differin® (adapalene 0.1%) Topical Gel (Galderma Laboratories) in Patients with Moderate to Severe Acne Vulgaris Study No. 70744002				
Normal Distribution Analysis Superiority Testing				
Parameter	Test vs Placebo	Reference vs Placebo		
Mean Percent Reduction in Inflamed Lesion Count (ITT)	<.0001	<.0001		
Mean Percent Reduction in Non-Inflamed Lesion Count (ITT)	0.0024	<.0001		
Mean Numerical Reduction in Inflamed Lesion Count (ITT)	<.0001	<.0001		
Mean Numerical Reduction in Non-Inflamed Lesion Count (ITT)	<.0001	<.0001		
Clinical Success (ITT)	0.0043	<.0001		

The sponsor's formulation is provided below.

Adapalene Gel 0.1%			
Ingredient (s)	**Specification**	**Function**	**Quantity % w/w**
Adapalene	(b) (4)	Active	0.10
Edetate Disodium	USP	(b) (4)	
Carbomer 940 (b) (4)	NF		
Methylparaben	NF		
Propylene Glycol	USP		
Polaxamer 182	(b) (4)		
Sodium Hydroxide	NF		
Purified Water[1]	USP		

(b) (4)

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/s/

Dena Hixon
4/3/2009 10:06:22 AM
I concur.