

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-087

CHEMISTRY REVIEW(S)

MEMORANDUM

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

DATE: January 16, 2009
TO: NDA 22-087 CMC Review #1
FROM: Jane Chang
Review Chemist, ONDQA
SUBJECT: Update of Labeling Information
NDA 22-087, Vectical (calcitriol) Ointment

Recommendation and Conclusion on Approvability:

The recently revised labels, submitted via the 1/15/2009 email, are acceptable and, therefore, the previous "Approval" recommendation (Chemistry Review #1 Addendum) from the chemistry, manufacturing and controls perspective remains the same.

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Chemistry Assessment

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

A. Labeling & Package Insert

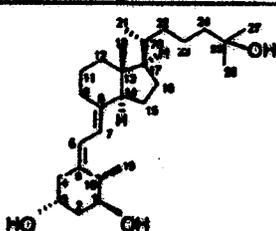
Revised mock-up labels for immediate and carton containers (100 g package size only) as well as package insert were provided through emails on January 12, 2009, January 14, 2009, and January 15, 2009 to the Project Manager, Emelia Annum. The information is summarized below.

1. Package Insert (provided in the 1/15/2009 email)

1) Dosage Forms and Strengths

Labeling Item	Information provided
Dosage Form	ointment
Strength	3 micrograms calcitriol per gram of ointment (3 mcg/g)

2) Description

Labeling Item	Information Provided
Proprietary name	VECTICAL
Established name	calcitriol*
Route of Administration	topical
Dosage Form	ointment
Qualitative ingredient information	Other components of the ointment are mineral oil, dl- α -tocopherol, and white petrolatum.**
Pharmacological/therapeutic class	vitamin D analog
Chemical name, structural formula, molecular weight	 <p>Chemical name: (5Z,7E)-9,10-seccholesta-5,7,10(19)-triene-1α,3β,25-triol*** Molecular weight: 416.64</p>
Other important chemical/physical properties	VECTICAL ointment is a white or almost white crystalline solid. It is practically insoluble in water, freely soluble in alcohol and soluble in fatty oils.

*Not provided in the package insert (PI) sent via the 1/12/2009 email.

**The names "dl- α -tocopherol" and "dl- α tocopherol" were used in the PI provided via the 1/12/2009 and 1/14/2009 emails, respectively.

***Chemical name was mistakenly stated to be _____ in the package insert provided via the 1/12/2009 email.

b(4)

3) *How Supplied*

Labeling Item	Information provided
Strength of dosage form	3 mcg/g
Units of dosage form e.g. bottles of 30 tablets	5 g 100 g
NDC number: 5 g tube 100 g tube	0299-2012-05 0299-2012-10
Special handling	Do not freeze or refrigerate.
Storage condition	Store at 25° C (77° F); excursions permitted to 15° - 30° C (59° - 86° F) [See USP Controlled Room Temperature.]

4) *Patient Counseling Information*

Labeling Item	Information provided
Trade name	VECTICAL
Manufacturer's name as qualified by 21 CFR 201.1(h)(5)*	Marketed by: Galderma Laboratories L.P. Fort Worth, Texas 76177 Manufactured by: Galderma Production Canada, Inc. Baie d'Urfé, QC H9X 3S4* Canada Made in Canada. GALDERMA is a registered trademark. (Part Number)**

*A type of [redacted] for "H9X" was present in the PI provided via the 1/12/2009 email.

**A website "www.vectical.com" was included in the PI provided via the 1/14/2009 email.

b(4)

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2. Labels (provided in the 1/15/2009 email)

1) Immediate Container

Labeling Item	Information provided
Trade name	Vectical
Establish name (size at least one half of trade name)	calcitriol
Strength	3 mcg/g
Net contents	100 g
Lot number per 21 CFR 201.18	on crimp
Expiration date per 21 CFR 201.17	on crimp
"Rx only" statement per 21 CFR 201.100(b)(1)	provided
Storage (not required)	Store at controlled room temperature 68°-77 °F (20° - 25°C) with excursions permitted between 59° - 86° F (15° - 30°C). Do not freeze or refrigerate.
NDC number (requested but not required per 21 CFR 201.2)	100 g 0299-2012-10
Bar Code per 21 CFR 201.25(e)(2)	Not provided for immediate container
Name of manufacturer/distributor per 21 CFR 201.1(h)(5)	Marketed by: GALDERMA LABORATORIES, L.P. Fort Worth, TX 76177 USA
Manufacturer's name	Galderma Production Canada Inc. Baie d'Urfé, QC H9X 3S4 Canada Made in Canada GALDERMA is a registered trademark. P51449-1*
Others	For topical use only. Not for ophthalmic, oral or intravaginal use. Each gram contains: calcitriol 3 mcg in an ointment base consisting of mineral oil, dl- α -tocopherol, and white petrolatum.**

*A website "www.vectical.com" was included in the label provided via the 1/14/2009 email.

**The names "dl- α -tocopherol" and "dl- α tocopherol" were used in the labels provided via the 1/12/2009 and 1/14/2009 emails, respectively.

1 Page(s) Withheld

 Trade Secret / Confidential (b4)

 ✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

2) *Cartons*

Labeling Item	Information provided
Trade name	Vectical
Establish name (size at least one half of trade name)	calcitriol
Strength	3 mcg/g
Net quantity of dosage form	100 g
Lot number per 21 CFR 201.18	Provided on flap panel
Expiration date per 21 CFR 201.17	Provided on flap panel
"Rx only" statement per 21 CFR 201.100(b)(1)	provided
"See package insert for complete prescribing information"	provided
"Keep out of reach of children" (optional)	Not provided
Qualitative ingredient information	Each gram contains: calcitriol 3 mcg in an ointment base consisting of mineral oil, dl- α -tocopherol, and white petrolatum.*
Storage	Store at controlled room temperature 68°-77 °F (20° - 25°C) with excursions permitted between 59° - 86° F (15° - 30°C). Do not freeze or refrigerate.
NDC number per 21 CFR 207.35(b)(3)(i)	100 g 0299-2012-10
Bar Code per 21 CFR 201.25(c)(2)	Provided
Name of manufacturer/distributor per 21 CFR 201.1(h)(5)	Marketed by: GALDERMA LABORATORIES, L.P. Fort Worth, TX 76177 USA Manufactured by: Galderma Production Canada Inc. Baie d'Urff, QC H9X 3S4 Canada Made in Canada GALDERMA is a registered trademark. P51459-1**

*The names "dl- α -tocopherol" and "dl- α tocopherol" were used in the labels provided via the 1/12/2009 and 1/14/2009 emails, respectively.

**A website "www.vectical.com" was included in the label provided via the 1/14/2009 email.

The carton label provided on 1/15/2009 is shown below.

b(4)

Evaluation: The package insert labeling information provided via the 1/12/2009 email is acceptable except for the following items:

Section 11 DESCRIPTION:

1. Lack of established name
2. Typo in the chemical name.

Section 17 PATIENT COUNSELING INFORMATION:

1. Typo in the address of manufacturer.

The following recommendations were made to the clinical team in the 1/13/2009 email:

Section 11 DESCRIPTION:

1. Added established name after the tradename, i.e. VECTICAL (calcitriol) ointment.
2. Revise the chemical name to "(5Z,7E)-9,10-secocholesta-5,7,10(19)-triene-1 α ,3 β ,25-triol".
3. Delete _____ in the statement _____

That is, the statement should be changed to "Other components of the ointment are mineral oil, dl- α -tocopherol, and white petrolatum."

b(4)

Section 17 PATIENT COUNSELING INFORMATION:

The correct address is:

Manufactured by:

Galderma Production Canada, Inc.

Bate d'Urfé, QC H9X 3S4

Canada

It should be noted that the applicant agreed to use dl- α -tocopherol instead of vitamin E in the labeling. The applicant accepted the recommendation and the recommended changes have been reflected in the package insert provided via the 1/14/2009 email with the exception of deletion of hyphen between a and tocopherol. See additional comment below.

The carton and container labels submitted via the 1/12/2009 email are not acceptable for the following reasons:

b(4)

The above comments were conveyed to the applicant in the 1/14/2009 teleconference (am). The applicant agreed to all recommendations stated above for the carton and container labels. In addition, the applicant suggested using a "," between "Ointment" and the strength "3 mcg/g", which will be presented at the same line as the established name. This reviewer stated that a "," should not be used on the carton and container labels between the established name and strength. This position is concurred by the Branch Chief, Dr. Moo-Jhong Rhee, and the Division Director, Dr. Elaine Morefield. The applicant agreed not to use "," between "Ointment" and the strength "3 mcg/g" in the 1/14/2009 pm teleconference.

After the 1/14/2009 pm teleconference, revised package insert and carton and container labels, which incorporated the recommended changes, were submitted via email on 1/14/2009. However, a website "www.vectical.com" was added in the package insert and carton and container labels. Based on the verbal communication with the Medical Officer, Dr. Patricia Brown, a website in the labeling is considered to be promotional information and is not acceptable.

In addition, the name for "dl- α -tocopherol" was changed to "dl- α tocopherol" (a space between a and tocopherol without a hyphen) in the package insert, carton and container labels. This is inconsistent with the nomenclature used by IUPAC. The following comments were sent to the applicant on 1/15/2008 via email:

- 1. The website listed on the carton and container labels and package insert should be deleted.*
- 2. A hyphen should be used for "dl- α -tocopherol" in the package insert (Section 11 Description), container and carton labels. This is to be consistent with the*

*nomenclature used in IUPAC (<http://www.chem.amul.ac.uk/iupac/misc/toc.html>).
The Greek symbols are always preferred when the font is available for use
because otherwise the name would be too long.*

*These recommendations were all incorporated into the package insert and carton and container
labels submitted via email on 1/15/2009. Therefore, acceptable labels have been provided.*

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/s/

Jane Chang
1/16/2009 11:27:38 AM
CHEMIST

Moo-Jhong Rhee
1/16/2009 02:20:00 PM
CHEMIST
Chief, Branch III

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MEMORANDUM

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

DATE: October 22, 2008

TO: NDA 22-087 CMC Review #1

FROM: Jane Chang
Review Chemist, ONDQA

SUBJECT: Update of EER Status
NDA 22-087, Tradename (calcitriol) Ointment

Recommendation and Conclusion on Approvability:

All manufacturing and testing facilities were found to be acceptable by the Office of Compliance as recommended by S. Adams on October 20, 2008. The EER Summary Report is attached.

From a chemistry, manufacturing, and controls review perspective, this NDA may be approved.

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FDA CDER RES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 22087/000
Org Code : 540
Priority :

Sponsor: GALDERMA LABS
14501 NORTH FREEMAY
FORT WORTH, TX 76177

Stamp Date : 27-SEP-2006
PDUFA Date : 27-OCT-2008
Action Goal :
District Goal: 29-AUG-2008

Brand Name : SILKIS OINTMENT
Estab. Name:
Generic Name: CALCITRIOL OINTMENT 3
MICROGRAMS/GRAM
Dosage Form: (OINTMENT)
Strength : 3 MICROGRAM/GRAM

FDA Contacts: L. CHASEY
J. CHANG
S. DING

Project Manager (NFC-60) 301-827-8675
Review Chemist 301-796-1973
Team Leader 301-796-1349

Overall Recommendation: ACCEPTABLE on 20-OCT-2008 by S. ADAMS (NFD-325) 301-796-3193

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

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile : OEN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 31-JAN-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

b(4)

DMF No: AADA:

Responsibilities: []
Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 16-JAN-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : FEI :

b(4)

21-OCT-2008

FDA CDER ERS
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Page 2 of 2

DMF No:

AADA:

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 20-OCT-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

b(4)

Establishment : CPN : FEI :

DMF No: AADA:

b(4)

Responsibilities:

Profile : OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 31-JAN-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

b(4)

Establishment : CPN : FEI :

DMF No: AADA:

b(4)

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 31-JAN-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

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/s/

Jane Chang
10/22/2008 09:35:36 AM
CHEMIST

Moo-Jheng Rhee
10/22/2008 09:37:36 AM
CHEMIST
Chief, Branch III

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NDA 22-087

**Tradename
(Calcitriol) Ointment
3 mcg/g**

Galderma

Jane L. Chang, Ph.D.

Review Chemist

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

**For Division of Dermatologic and Dental Drug Products
HFD-540**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	4
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.....	10
C. Basis for Approvability or Not-Approval Recommendation	10
III. Administrative.....	10
A. Reviewer's Signature.....	10
B. Endorsement Block.....	10
C. CC Block.....	10
Chemistry Assessment	11
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	11
S DRUG SUBSTANCE	11
S.1 General Information.....	11
S.2 Manufacture	12
S.3 Characterization	14
S.4 Control of Drug Substance.....	16
S.5 Reference Standards or Materials	31
S.6 Container Closure System.....	31
S.7 Stability	32
P DRUG PRODUCT	34
P.1 Description and Composition of the Drug Product.....	34
P.2 Pharmaceutical Development.....	35
P.3 Manufacture	44
P.4 Control of Excipients	58
P.5 Control of Drug Product	61
P.6 Reference Standards or Materials	76
P.7 Container Closure System.....	76
P.8 Stability	78
A APPENDICES	88

NDA 22-087 CMC REVIEW

- A.1 Facilities and Equipment (biotech only) 88
- A.2 Adventitious Agents Safety Evaluation 88
- A.3 Novel Excipients 88

- R REGIONAL INFORMATION 88
 - R.1 Executed Batch Records 88
 - R.2 Comparability Protocols 88
 - R.3 Methods Validation Package 88

- II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 89
 - A. Labeling & Package Insert 89
 - 1. Package Insert 89
 - 2. Labels 90
 - 3. Drug Listing Data Elements in Structured Product Labeling 94
 - B. Environmental Assessment Or Claim Of Categorical Exclusion 96

- III. List Of Deficiencies 97

Appears This Way
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Chemistry Review Data Sheet

1. NDA 22-087
2. REVIEW #: 1
3. REVIEW DATE: 09-OCT-2008
4. REVIEWER: Jane L. Chang
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Pre-NDA Meeting	14-JUN-2006
FDA Fax CMC Comments Post pre-NDA Meeting	16-JUN-2006
Original Submission	25-SEP-2006
Amendment (BC)	20-NOV-2006
11/14/2006 Telecon discussing in vitro release testing	29-NOV-2006
11/20/2006 Telecon discussing in vitro release testing	01-DEC-2006
Refuse-To-File Letter	22-NOV-2006
Meeting Briefing Package	04-FEB-2007
Refuse-To-File 3/13/2007 Telecon Minutes	20-MAR-2007
CMC Advice Letter	29-JUN-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission (RS)	21-DEC-2007
Amendment (BL)	29-APR-2008
Amendment (BC)	11-AUG-2008
Amendment (BC)	13-AUG-2008
Amendment (BC)	02-SEP-2008
Amendment (BC)	08-SEP-2008

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Galderma Laboratories, L.P.
Address:	14501 North Freeway Fort Worth, Texas 76177
Representative:	Paul Clark Director
Telephone:	817-961-5336

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Tradename (not yet finalized)
- b) Non-Proprietary Name: calcitriol ointment
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3 (New Dosage Form)
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment of plaque-type psoriasis

11. DOSAGE FORM: Ointment

12. STRENGTH/POTENCY: 3 mcg/g

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx OTC

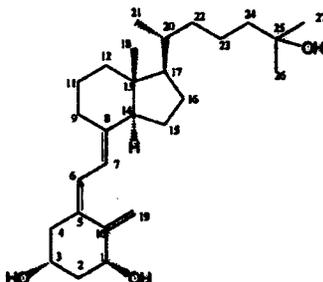
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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



(5Z, 7E)-9,10-secocholesta-5,7,10(19)-triene-1 α ,3 β ,25-triol
 CAS Number: 32222-06-3 C₂₇H₄₄O₃ MW = 416.64

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF # ⁴	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
					adequate	6/5/2008	By J. Chang
					N/A	N/A	See Page 77
					adequate	5/10/1995	reviewer unknown
					adequate	1/10/2007	By J. Pinto
					adequate	9/5/2006	By J. Chang
					N/A	N/A	See Page 77

*LOA letters dated 11/19/2007, 8/29/2006, and 2/16/2006 were provided for DMF# respectively.

**DMF formerly held by _____

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)

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NDA 22-087 CMC REVIEW

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	62,151	Calcitriol Ointment 3 µg/g

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending*		
Pharm/Tox	N/A		
Biopharm	N/A		
Methods Validation	N/A, according to the current ONDQA policy**		
Office of Drug Safety	Not recommended***	4/3/2008	J. Park
EA	Categorical exclusion (see review)	4/2/2008	J. Chang
Microbiology	N/A		

*At the completion of this review, inspection for the drug substance testing facility _____ is still pending. The other manufacturing facilities are found to be acceptable.

**The analytical procedures and their validations were reviewed and found to be adequate. Methods validation packages will not be sent to FDA laboratories because the methods do not meet the "method validation request criteria" according to the current ONDQA policy that was announced on 1/12/05.

***DMETS concurs with DDMAC's objection to the proposed proprietary name, Silkis, based on promotional concerns.

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Executive Summary Section

The Chemistry Review for NDA 22-087

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Therefore, this NDA may be approved pending resolution of the following issue:

- An acceptable overall recommendation from the Office of Compliance. Inspection of the drug substance testing facility, _____, is still pending.

b(4)

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

None

II. Summary of Chemistry Assessments

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

(1) Drug Product

Calcitriol ointment 3 µg/g is a single-phase, white translucent semi-solid product indicated for the topical treatment of plaque-type psoriasis. The formulation is achieved by _____

b(4)

Acceptable specification has been provided to ensure product identity, strength, purity, and quality. The specification includes description, microscopic analysis, identification (calcitriol by NP-HPLC and vitamin E by NP-HPLC), assays of calcitriol (NP-HPLC) and vitamin E (NP-HPLC), homogeneity (NP-HPLC), related substances (NP-HPLC), viscosity, minimum fill, and microbial limits.

Executive Summary Section

Acceptable information was provided for container closure system for tube sizes _____ 100 g proposed for marketing and a 5g size intended for samples. _____

Acceptable stability data were provided for three clinical batches (_____ scale) used for pivotal Phase 3 studies and for 18 packaged batches (from 3 bulk drug product batches, each at _____ scale) manufactured for process validation in the intended manufacturing site. The data included up to 9 months at $40^{\circ}\text{C}\pm 2^{\circ}\text{C}/75\%\pm 5\%\text{RH}$ and 36 months at $25^{\circ}\text{C}\pm 2^{\circ}\text{C}/60\%\pm 5\%\text{RH}$ for the clinical batches and up to 6 months at $40^{\circ}\text{C}\pm 2^{\circ}\text{C}/75\%\pm 5\%\text{RH}$ and 30 months at $25^{\circ}\text{C}\pm 2^{\circ}\text{C}/60\%\pm 5\%\text{RH}$ for the validation batches. Calcitriol ointment 3 $\mu\text{g}/\text{g}$ remained within specification after 30 months at $25^{\circ}\text{C}/60\%\text{RH}$ for the three validation batches, with no noticeable change observed for any parameter, except viscosity. A slight tendency to decrease was observed for vitamin E content throughout time, however, all the values remained within specification. Similar trend was also observed for the three clinical batches. That is, after 36 months at $25^{\circ}\text{C}/60\%\text{RH}$, no noticeable change was observed on clinical batches for any parameter. _____

b(4)

A photostability study was conducted on one clinical batch. The results obtained did not show any significant change. The formulation in its packaging was stable regarding light exposure. Freeze/thaw and cold/warm cycling studies were conducted on two clinical batches. _____, which showed a

_____ all other attributes were within the specification.

b(4)

b(4)

The stability data support the proposed expiration dating period of 36 months for calcitriol ointment 3 $\mu\text{g}/\text{g}$ when stored at 25°C (77°F), excursions permitted to $15\text{--}30^{\circ}\text{C}$ ($59\text{--}86^{\circ}\text{F}$).

(2) Drug Substance

Calcitriol is a well-established compendial drug substance whose structure has been fully elucidated. Calcitriol is marketed in various formulations since 1978. These formulations include oral capsules (0.25 μg and 0.5 μg , NDA 18-044 for management of secondary hyperparathyroidism in chronic renal failure and hypocalcemia in dialysis patients and patients with postsurgical idiopathic, or pseudohypoparathyroidism), an injectable solutions (0.001 and 0.002 mg/mL , NDA 18-874 for management of hypocalcemia in patients on chronic renal dialysis), and oral solution (1 $\mu\text{g}/\text{mL}$, NDA 21-068 for the treatment of secondary hyperparathyroidism in patients with moderate to severe chronic renal failure who are not yet undergoing dialysis).

Executive Summary Section

The drug substance is manufactured by _____ Details of the manufacturing process and control of materials and calcitriol are provided in _____'s DMF# _____. This DMF has been reviewed by this reviewer and found to be adequate to support the NDA. In addition to the tests listed in the USP monograph (with the exception for the specified impurity _____)

b(4)

_____ testing for residual solvents and pre-calcitriol are included in the drug substance specification.

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

Calcitriol Ointment should be applied to affected areas of the body, twice daily, morning and evening for 8 weeks or until cleared. The maximum daily dose should not exceed _____

b(4)

Calcitriol Ointment is to be stored at controlled room temperature 25°C (77°F). When stored under the specified conditions, an expiration dating period of 36 months can be expected.

C. Basis for Approvability or Not-Approval Recommendation

Adequate data have been submitted to ensure the drug product's identity, strength, quality, purity, potency, and stability as a topical product for its intended use. This NDA may be approved pending resolution of the following issue:

- An acceptable overall recommendation from the Office of Compliance. Inspection of the drug substance testing facility _____ is still pending.

b(4)

III. Administrative

- A. **Reviewer's Signature**
electronically signed in DFS
- B. **Endorsement Block**
electronically signed in DFS
- C. **CC Block**
entered electronically in DFS

88 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Jane Chang
10/9/2008 02:35:25 PM
CHEMIST

Moo-Jhong Rhee
10/9/2008 02:59:09 PM
CHEMIST
Chief, Branch III

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**Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II**

OND Division: Division of Dermatology and Dental Products
NDA: 22-087
Applicant: Galderma Laboratories, LP.
Stamp Date: Dec. 27, 2007
PDUFA Date: Oct 27, 2008
Trademark: Silkis (calcitriol) ointment, 3 µg/g
Established Name: Calcitriol
Dosage Form: Ointment
Route of Administration: Topical
Indication: Plaque psoriasis

PAL: Shulin Ding

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

Summary and Critical Issues

A. Summary

The NDA is the resubmission of NDA 22-087 which was originally submitted in September, 2006 and received a refusal-to-file (RTF) action. The reason for the RTF action was that no data were provided to link the designated commercial manufacturing site and process to those of Phase 3 clinical supplies. Therefore, the quality and bioavailability of the commercial batches were not assured. Subsequent to the refusal-to-file action, the Agency agreed that the applicant could use in-vitro release test (IVRT) results to bridge the site/process changes, and comments were forwarded to the applicant for the proposed IVRT study protocol.

A complete initial quality assessment has already been conducted in Y2006 and filed in DFS when NDA 22-087 was first submitted. CMC summary and critical review issues for the proposed product can be found there. The present quality assessment, Initial Quality Assessment #2, focuses only on new information which was not present in Y2006 submission.

There is only two new pieces of information in the resubmitted NDA 22-087. One is an update in establishment information. The other is the requested IVRT results. There are no changes in formulation, excipient controls, packaging, manufacturing process, commercial batch size, drug substance supplier, and drug product manufacturer.

There are more stability data provided in the resubmission to support an expiry period of 36 months at controlled room temperature of 68-77°F (20-25°C), excursion permitted to

15-30°C. The data provided include long term (25°C/60% RH) data of 30 months and accelerated temperature (40°C/75% RH) data of 6 months from 3 commercial scale batches. The registration stability program covers _____ suppliers and provides each fill size at least 3 batches of data.

b(4)

B. Critical Issues for Review

Link between Commercial Batches to Phase 3 Supplies

- The designated commercial batch manufacturing site is located in Canada. It is a different site from the Phase 3 batch manufacturing site (in France), and there are also process changes. The Canadian site has not produced any clinical batches.

In-vitro drug release test results are provided in the resubmission to demonstrate "sameness" between the batches produced at the designated commercial site and Phase 3 batches. The IVRT results need to be carefully reviewed. The applicant mentioned that the initial comparison on bulk failed the test although other comparisons pass.

Other critical review issues can be found in the Initial Quality Assessment conducted in Y2006.

C. Comments for 74-Day Letter

None

D. Comments/Recommendation:

The application is fileable from the CMC and quality perspective. The major review issue is whether the IVRT results adequately demonstrate "sameness" between the batches produced at the designated commercial site and Phase 3 batches.

Manufacturing facilities for Drug substance and drug product are located in Europe and Canada. GMP inspection requests have been submitted.

Shulin Ding
Pharmaceutical Assessment Lead

Moo-Jhong Rhee
Chief, Branch III

Filing Checklists

A. Administrative Checklists

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

B. Technical Checklists

1. Drug Substance Referenced to DMF _____

b(4)

		Does the section contain synthetic scheme with in-process parameters?	Not applicable.
		Does the section contain structural elucidation data?	Not applicable.
		Does the section contain specifications?	Not applicable.
		Does the section contain information on impurities?	Not applicable.
		Does the section contain validation data for analytical methods?	Not applicable.
		Does the section contain container and closure information?	Not applicable.
		Does the section contain stability data?	Not applicable.

2. Drug Product

x		Does the section contain manufacturing process with in-process controls?	
x		Does the section contain quality controls of excipients?	
x		Does the section contain information on composition?	
x		Does the section contain specifications?	
x		Does the section contain information on degradation products?	
x		Does the section contain validation data for analytical methods?	
x		Does the section contain information on container and closure systems?	
x		Does the section contain stability data with a proposed expiration date?	
x		Does the section contain information on labels of container and cartons?	
x		Does the section contain tradename and established name?	

C. Review Issues

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

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/s/

Shulin Ding
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Moo-Jhong Rhee
1/28/2008 10:13:05 AM
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Chief, Branch III

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**Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II**

OND Division: Division of Dermatology and Dental Products
NDA: 22-087
Applicant: Galderma Laboratories, LP.
Stamp Date: Sep 27, 2006
PDUFA Date: July 27, 2007
Trademark: Silkis (calcitriol) ointment, 3 µg/g
Established Name: Calcitriol
Dosage Form: Ointment
Route of Administration: Topical
Indication: Plaque psoriasis

PAL: Shulin Ding

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

Summary and Critical Issues:

A. Summary

The drug substance, calcitriol, is referenced to DMF _____, held by _____
DMF _____ has been reviewed multiple times (last review dated Jan 4, 2006), and deemed
adequate to support referenced submissions. b(4)

The drug product, Silkis™ (calcitriol) ointment 3 µg/g, is a white, translucent ointment. The drug
is fully solubilized in the ointment base. The product is packaged in _____
aluminum tubes at fill sizes of 5 grams, _____ and 100 grams. The 5 g size is the sample size. b(4)

The to-be-marketed formulation is the same formulation used in pivotal clinical trials and
registration stability batches. The formulation contains the following excipients: white
petrolatum, EP; mineral oil USP; and Vitamin E, USP. Note that the white petrolatum used in the
proposed formulation conforms to EP not USP.

The proposed commercial manufacturing scale is _____ The manufacturing process consists of
the following steps: _____

_____ b(4)

Stability data provided in the initial submission to support an expiry period of 36 months at
controlled room temperature of 68-77°F (20-25°C), excursion permitted to 15-30°C, include long
term (25°C/60% RH) data of 18-36 months and accelerated temperature (40°C/75% RH) data of

6-9 months from 3 pilot-scale batches and three commercial-scale batches. Each fill size has at least 3 batches of data.

B. Critical issues for review

Link between Commercial Batches to Phase 3 Supplies

- The designated commercial batch manufacturing site is located in Canada. It is a different site from the Phase 3 batch manufacturing site (in France), and there are also process changes. The Canadian site has not produced any clinical batches.

For topical products, in-vitro drug release test is one of the requirements in order to demonstrate "sameness" for batches produced at different sites or with different processes. The in-vitro drug release comparison is not provided in the NDA. This omission is, therefore, a filing issue.

Container/Closure System Qualification

- The primary container/closure system, _____ aluminum tubes, is referenced to _____ DMF _____ and _____ DMF _____. The applicant provides no information regarding test results on the container/closure system per USP<661> physicochemical tests and light transmission test. There is no mentioning of leaching/sorption studies and USP<87> Biological tests – plastics and other polymers.

b(4)

USP test results may reside in the two referenced DMFs. If not, this omission is a significant review issue. The extremely low drug concentration of this product renders the product vulnerable to the effect of leaching and sorption.

C. Comments for 74-Day Letter

Issues:

- The absence of in-vitro drug release comparison between commercial process batches made at the Canadian site and those made at the Phase 3 manufacturing site using the Phase 3 process.
- The manufacturing changes _____, are not supported.
- The establishment information provided in the NDA may be incomplete. The function of each facility and CFN numbers are not provided. It is uncertain where the testing sites are for the proposed drug substance and drug product.
- The absence of container/closure qualification test results such as USP<661>.

b(4)

To resolve the issues the applicant should:

1. Conduct an in-vitro drug release study, and compare the drug release profile of the commercial process batches with that of a comparable-age batch made at the Phase 3 manufacturing site using the Phase 3 process. The study should include a comparison among all proposed fill sizes.
2. The manufacturing changes / _____ need to be supported by in-vitro drug release results (see #1).
3. Provide complete establishment information.
4. Provide in the NDA container/closure qualification test results (such as USP<661>) or indicate where the data reside.

b(4)

D. Comments/Recommendation:

The application is not fileable from the CMC and quality perspective. The submission of data supporting the manufacturing process at the designated commercial manufacturing site is a filing requirement (21CFR 314.101 (d)(3)).

The designated commercial manufacturing site and process are different from those of Phase 3 clinical supplies. Bridging data to support these changes are missing. Specifically, there are no in-vitro drug release results in the NDA. 21CFR 314.50 (d)(1) (ii)(a) requires dissolution data to ensure quality and bioavailability of the product.

This issue has been discussed in teleconferences with the NDA applicant. It is apparent that they do not have this piece of data available, and the in vitro drug release method has not been developed. In addition, it is unclear whether suitable batches exist for use in this testing or new batches will need to be made. The drug, calcitriol, is known to be light sensitive and easily oxidizable by air. This will complicate their attempt to develop a method for the in vitro drug release study. There are significant technical hurdles in generating this type of data for this drug in this dosage form. Their ability to generate the required data within an adequate time frame to allow timely review in the review cycle is in doubt.

Therefore, ONDQA recommends a refusal to file.

Shulin Ding
Pharmaceutical Assessment Lead

Elaine Morefield
Division Director

Filing Checklists

A. Administrative Checklists

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

B. Technical Checklists

1. Drug Substance Referenced to DMF ~~_____~~

b(4)

		Does the section contain synthetic scheme with in-process parameters?	Not applicable.
		Does the section contain structural elucidation data?	Not applicable.
		Does the section contain specifications?	Not applicable.
		Does the section contain information on impurities?	Not applicable.
		Does the section contain validation data for analytical methods?	Not applicable.
		Does the section contain container and closure information?	Not applicable.
		Does the section contain stability data?	Not applicable.

2. Drug Product

x		Does the section contain manufacturing process with in-process controls?	
x		Does the section contain quality controls of excipients?	
x		Does the section contain information on composition?	
x		Does the section contain specifications?	
x		Does the section contain information on degradation products?	
x		Does the section contain validation data for analytical methods?	
x		Does the section contain information on container and closure systems?	
x		Does the section contain stability data with a proposed expiration date?	
x		Does the section contain information on labels of container and cartons?	
x		Does the section contain tradename and established name?	

C. Review Issues

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

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Elaine Morefield
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