CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-212

MICROBIOLOGY REVIEW(S)

J. LOTUS

REVIEW FOR HFD-540
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #1 OF NDA

SEP 24 1999

September 24, 1999

A. 1. NDA 21-112

SPONSOR Hill Dermaceuticals, Inc.
2650 So. Mellonville Avenue
Sanford, FL 32773

2. PRODUCT NAMES: —— Cream

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Topical Cream

4. METHOD(S) OF STERILIZATION: NA

5. PHARMACOLOGICAL CATEGORY: Cutaneous Melanosis

6. DRUG PRIORITY CLASSIFICATION:

B. 1. DATE OF INITIAL SUBMISSION: March 12, 1999

2. DATE OF AMENDMENT: na

3. RELATED DOCUMENTS: none

4. ASSIGNED FOR REVIEW: September 23, 1999

C. REMARKS: The drug product is a nonsterile, preserved topical cream which has a microbial limit specification.

D. CONCLUSIONS: This submission is recommended for approval on the basis of product quality microbiology.

/S/ 9-24-99

Bryan Riley, Ph.D.

PAC 9/24/99

cc:

HFD 540/Consult File
HFD 540/V. Lutwak
HFD 540/E. Pappas
HFD 805/Consult File
HFD 805/B. Riley

Drafted by: B. Riley, 9/24/99
R/D initialed by: P. Cooney,

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

1 page

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

8/27/99

TO (Division/Office)		FROM:	
Trek Cooney		Vince Lutwak HFD-540	
IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
27,164	21112		March 12, 1999
NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
CREAM			9/27/99

NAME OF FIRM: Hill Pharmaceuticals Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(Specify below)*

MMDO Consult

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILITY STUDIES
- ☐ BASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL– BIOPHARMACEUTICS
- ☐ IN–VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)*
- ☐ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☒ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*

LT in mail - 8/27

MMDO Consult

please cc:
HFD-540/E. Puppis
HFD-540/V. Lutwak

PKLN 8.BSB
301-827-7340

SIGNATURE OF REQUESTER /S/

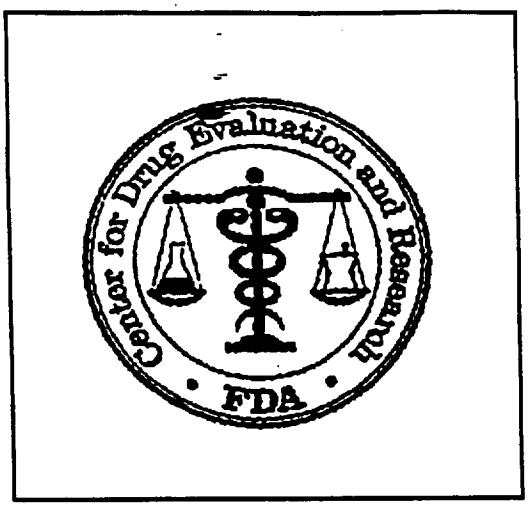
METHOD OF DELIVERY *(Check one)*
☒ MAIL ☐ HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

FACSIMILE TRANSMISSION RECORD



From: Vickey Lutwak, Project Manager

Division of Dermatologic and
Dental Drug Products, HFD-540
Center for Drug Evaluation & Research
Food & Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Phone 301-827-2020 / 2073
Fax 301-827-2075

Date: Sept 24, 1999

To:

Name BRYAN RILEY

Company _____

City _____ State ____

Phone # _____

FAX # 301-827-3084

Number of Pages (INCLUDING COVER PAGE) 2+3

Please telephone (301) 827-2020 IMMEDIATELY if re-transmission is necessary.

NOTE: We are providing the attached information via telephone facsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Additional message: NDA 21-112

BRYAN - Per your request -

Vickey

356h form

	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) LETTER OF RESPONSE

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Rosario G. Ramirez	Rosario G. Ramirez, Regulatory Affairs	21 SEPT. 1999

ADDRESS (Street, City, State, and ZIP Code)	Telephone Number
2650 So. Mellonville Avenue Sanford, FL 32773	(407) 323 - 1887

MESSAGE CONFIRMATION

09/24/99 10:18

NO.	NAME	BOX	GROUP
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DATE	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
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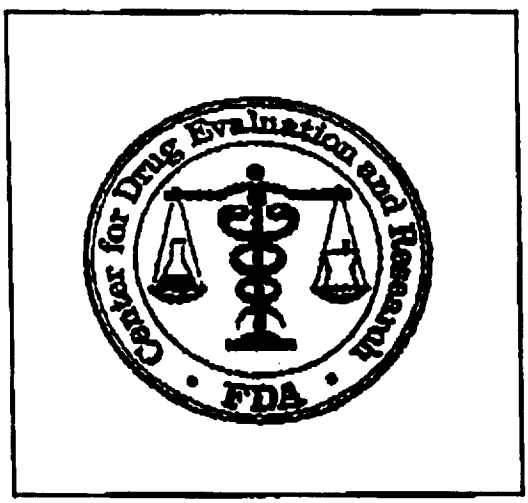
FACSIMILE TRANSMISSION RECORD



From: Vickey Lutwak, Project Manager

Division of Dermatologic and
Dental Drug Products, HFD-540
Center for Drug Evaluation & Research
Food & Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Phone 301-827-2020 / 2073
Fax 301-827-2075

Date: Sept 24, 1999

To:

Name BRYAN RILEY

Company _____

City _____ State _____

Phone # _____

FAX # 301-827-3084

Number of Pages (INCLUDING COVER PAGE) 3

Please telephone (301) 827-2020 IMMEDIATELY if re-transmission is necessary.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Hill Dermaceuticals, Inc.	JULY 24, 2001
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
407-323-1887	407-649-9213
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
2650 South Mellonville Avenue Sanford, Florida 32773	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA 21-112

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Please See Attachment	TRI-LUMA Cream

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Please See Attachment	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Cream	Please See Attachment	Topical

(PROPOSED) INDICATION(S) FOR USE:

Melasma

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION: Full response to Non-Approvable Letter (to NDA)

PROPOSED MARKETING STATUS *(check one)* ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Please See Attachment

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
X	1. Index
X	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
X	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
X	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
X	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
X	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
X	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
X	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
X	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
X	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
X	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
X	17. Field copy certification (21 CFR 314.50 (l)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. Financial Information (21 CFR Part 54)
	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Rosario G Ramirez	Rosario G. Ramirez Director, Medical/Regulatory Affairs	JULY 24, 2001

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2650 So. Mellonville Ave., Sanford, FL 32773	(407) 323-1887

ATTACHMENT to 356h

CHEMICAL NAME

Fluocinolone acetonide: **pregna-1,-4-diene-3,20-dione, 6,9-difluoro-11,21 dihydroxy- 16,17-[(1-methylethylidene)bis(oxy)]-, (6α,11β,16α)-.**

Hydroquinone: **1,4-benzenediol**

Tretinoin: **(*all-E*)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid**

ESTABLISHMENT INFORMATION

Locations of manufacturing, packaging and control sites for drug substances and drug product:

Drug Product: Cream

Location: HILL DERMACEUTICALS, INC.
(Establishment Registration Number: 1036365/ORL)
2650 South Mellonville Avenue
Sanford, Florida 32773

Contact: Jerry Roth

Telephone: (407) 323-1887

Drug Substance: Fluocinolone acetonide USP Drug Master File Number:

Location:

Contact:

Telephone:

Drug Substance: Hydroquinone USP Drug Establishment Registration #

Location:

Contact:

Telephone:

Drug Substance: Tretinoin USP Drug Master File Number

Location:

Contact:

ORIGINAL

Hill Dermaceuticals, Inc.

2500 South Mellonville Avenue • Sanford, Florida 32773 • 407 323-1887 • FAX: 407 849-9213

"The Scalp Company"

ORIG AMENDMENT

— Cream
— , NDA 21-112

BS

September 9, 1999

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850
Attn: Ms. Vickey Lutwak
Project Manager

RE: Additional Information
Diskettes as requested

Enclosed are 2 diskettes. a copy for the statisticians and a desk copy.

I have also enclosed a diskette on the In vivo study on percutaneous absorption of on human volunteers, as desk copy. This is the corrected version, as per changes from the Institutional Review Board. The amended study protocol will be submitted under the IND.
Thank you.

Respectfully,

RG Ramirez

Rosario G. Ramirez
Medical/Regulatory Affairs

ORIGINAL

Hill Dermaceuticals, Inc.

NEW CORRESP

"The Scalp Company"

2650 South Mellonville Avenue • Sanford, Florida 32773 • 407 323 1887 • Fax 407 849 3213

Cream
(NDA 21-112)

September 9, 1999

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850
Attn: Ms. Vickey Lutwak
Project Manager

RE: 120 Days Safety Report

In reference to NDA 21-112 for the drug product containing 0.01% Fluocinolone acetonide, 4.0% Hydroquinone, 0.05% Tretinoin, there are no on-going follow-up or new studies currently in progress. The clinical studies performed for this product have been completed and concluded prior to the submission of the NDA.

This letter is to notify the FDA that the safety analysis on all studies have been reported under the NDA submission, and that the 120-day safety report does not apply.

Rosario G. Ramirez
Medical/Regulatory Affairs

Jerry S. Roth
F

120 days
SEE 9/9/99

ORIGINAL

NEW CORRESP

NC

Hill Dermaceuticals, Inc.

"The Scalp Company"

407-323-1887 • Fax: 407-649-9213
Millennium Avenue • Sanford, Florida 32

___ Cream
___ NDA 21-112

September 13, 1999

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850
Attn: Ms. Vickey Lutwak
Project Manager

RE: 1. Additional Information: Case report forms
Baseline photos

2. Requested Study Drugs

This submission contains the following items:

1. 3 copies of the requested additional case report forms (74 MAH/Torok, 78 CCD/Torok, 02 BJ/Wieder, 53 JNK/Wieder);
2. Baseline photographs included in the Reviewer Copy
3. Samples of the test drugs used in the clinical trials, with active contents identified for each tube.

Photographs were not taken for Dr. Willis' patients. Patients 14 IB, 43 DBF, 49MHJ, 50 CLJ, 59 LEW, 78 MB do not have photos as these patients were from Dr. Willis' study center.

A desk copy of volume 1.3 of the original NDA submission is also submitted for the Microbiology reviewers.

Respectfully,

Rosario G. Ramirez

Rosario G. Ramirez
Medical/Regulatory Affairs

Hill Dermaceuticals, Inc.

2650 South Mellonville Avenue • Sanford, Florida 32773 • 407-323-1887 • Fax: 407-649-9213

"The Scalp Company"

March 19,1999

Jonathan K. Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd. HFD-540
Rockville, MD 20850

RE: NDA 21,112, application for approval of New Drug ~~~ Cream for the treatment of individuals (Skin phototypes II and III) with Cutaneous Melanosis

Dear Dr. Wilkin:

Hill Dermaceuticals, Inc., is submitting a full new drug application for ~~~ NDA 21,112, for the indication, cutaneous melanosis. This application contains all the required sections of a full application, CFR section 314.50

The clinical study conducted for ~~~ consists of well-controlled clinical trials (Study 1--EAST and Study 2--WEST) carried out by independent investigators. The East study was conducted by Isaac Willis, MD of Atlanta, Georgia, Helen Torok, MD of Medina, Ohio and Neil Brody, MD of Manhasset, New York. The West study was conducted by A. Paul Kelly, MD and Joshua Wieder, MD of Los Angeles, California. The clinical trials and statistical analysis reports were written in such a way that the East (Study 1) study is considered one well-controlled trial and the West (Study 2) study as another well controlled trial. The investigators belonging to their respective regions were combined to make up one report. A statistical analysis was also made for all centers combined as one (Studies 1 & 2).

~~~ contains 3 active components, Fluocinolone acetonide 0.01%, Hydroquinone 4.0%, and Tretinoin 0.05%, in a hydrophilic base. The clinical studies performed compared this triple combination product to formulations of any 2 combinations of its active ingredients, i.e. fluocinolone + hydroquinone; fluocinolone + tretinoin; hydroquinone + tretinoin. Statistical analysis showed a significantly better results for than any of the other treatment groups, for both primary efficacy evaluation and secondary efficacy evaluation.
~~~

Safety data collected showed that erythema was the most frequently experienced adverse event, followed by peeling. The frequency of these reactions had very little difference between treatment groups, as these adverse events are expected reactions from the product due to the inherent irritancy property of tretinoin and hydroquinone. It is well to mention that the group experienced mostly mild cases of erythema.

The chemistry, manufacturing and controls section of this submission complied with all the requirements of a full new drug applications, section 314.50 of the Code of Federal Regulations.

Statistical data sets and the proposed package labeling have been placed in disks and will be made available upon your request.

We respectfully request priority review of this submission. We have attached a copy of he application letter to the Health and Human Services pertaining to the application fee. An application fee has been submitted for this NDA.

Should you have any questions concerning this NDA, please call Rosario Ramirez, MD, clinical study coordinator, at 407-323-1887.

Thank you for your continued cooperation.

Sincerely,

Jerry S. Roth
President
Hill Dermaceuticals, Inc.

Hill Dermaceuticals, Inc.

ORIGINAL
NC

2600 South Mellonville Avenue • Sanford, Florida 32773 • 407-323-1887 • Fax: 407-649-9213

VIA FEDERAL EXPRESS

"The Scalp Company"

April 21, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug
Products, HFD-540
Attention: Document Room
9201 Corporate Blvd.
Rockville, MD 20850-3202

Re: ——— (fluocinolone acetonide 0.01%/hydroquinone4%/tretinoin 0.05%)Cream
Your Reference Number: 21-112

To Whom It May Concern:

We have received your letter of April 16, 1999 informing us that you received our new drug application (NDA) for ——— and that it will either be filed on May 21, 1999, or you will notify us to the contrary by May 21, 1999.

For the sake of clarity, we are writing to reiterate that, prior to receiving your April 16 correspondence, we submitted payment in full for the User Fees. Two checks written on Hill Dermaceuticals Licensing Account (Check Nos. 0276 and 0277), payable to The Food and Drug Administration in the amount of $136,141.00 each, were sent via Federal Express to the Mellon Bank in Pittsburg, Pennsylvania. Please refer to the copies which are enclosed.

We would like to further reiterate that we sent a request for a waiver of the pediatric study requirement in the Archival copy Volume 1.1, NDA 21-112, dated March 19, 1999, including supporting information and documentation which appear on the 17th page from the User Fee Cover Sheet (top page), copies of which are enclosed for your reference.

Should you require additional information, or wish to discuss this matter further, please contact me at (800) 344-5707.

Very truly yours,

Jerry S. Roth
President

JSR:med

cc: Mary Jean Kozma-Fornaro - Supervisor, Project Management Staff

ORIGINAL

Hill Dermaceuticals, Inc.

"The Scalp Company"

2650 South Mellonville Avenue • Sanford, Florida 32773 • 407-323-1887 • Fax: 407-649-9213

Cream
NDA 21-112

April 29, 1999

Jonathan K. Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd. , HFD-540
Rockville, MD 20850
Attn: Mr. Ernie Pappas
Chemistry Division

NEW CORRESP
NC

RE: ——— NDA 21-112
Amendment to a Pending Application.

Dear Mr. Pappas:

In response to your request for the location and address of the actual manufacturing plant for Tretinoin USP, we have taken every effort to follow-up and expedite acquisition of this information from ——— representative ——— has kindly provided the address for the manufacturing plant for Tretinoin ——— ———

The attachment to FDA Form 356h has been revised to show the above address for the drug substance Tretinoin. This revision is submitted as supplement to NDA 21-112, ——— Cream. Please advise if there is any other requirement.

Sincerely,

R G Ramirez

Rosario G. Ramirez
Medical/Regulatory Affairs

cc: Ms Mary Jean Kozma-Fornaro

ORIGINAL

Hill Dermaceuticals, Inc.

2050 South Millenville Avenue • Sanford, Florida 32773 • 407-323-1887 • Fax: 407-849-9213

"The Scalp Company"

— Cream
— NDA 21-112

NEW CORRESP

April 29, 1999

NC

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 11 1999
MEGA DOC RM

Jonathan K. Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd. , HFD-540
Rockville, MD 20850
Attn: Ms. Mary Jean Kozma-Fornaro

RE: ——— Cream, NDA 21-112
General Correspondence

Dear Ms. Fornaro:

We would like to verify the pages for the *in-vitro* study (*In vitro* Percutaneous Absorption and Cutaneous Disposition of ——— Cream Across Intact Human Skin) submitted under the Human Pharmacokinetic and Bioavailability Section (biopharm) which is Item 6 in the original NDA submission. The pages for the summary of the *in-vitro* study are **6 0003 - 0004**; the full report for this study is located in pages **6 0021 to 6 0046**.

Item 6 is included in volume 5 of 7 of the archival copy.

Please advise as to acceptability of the submitted information on the biopharmaceutic section for filing purposes. We are also requesting further guidance on the matter of the in vivo study, as discussed earlier in the teleconference. We are presently looking into laboratory facilities for this study.

Thank you for your patience and guidance.

Sincerely,

Rosario G. Ramirez
Med/Regulatory

Jerry Roth

Hill Laboratories

BC ✓ ORIGINAL V. Shedrick F. Pappas

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D MAY 0 3 1999 MEGA DOC RM

April 29, 1999

Mary Jean Kozma-Fornaro
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd. HFD-540
Rockville, MD 20850

Faxed to Jo chemis 4/30 mailed 7/Dec/99

RE: ——— NDA 21,112

Dear Ms. Kozma-Fornaro:

Enclosed is the copy of volume 1.6 of the ——— Cream NDA Submission and another copy of the abbreviated table of contents, to assist Mr. Pappas in finding the room temperature stability information of the clinical investigation formulations of ——— t Cream found in volume 1.6, as promised.

If you have any further questions, please feel free to call. (407) 323-1887

Thank you,

Marianna Arsts

2650 S. Mellonville Avenue
Sanford, Florida 32773

Telephone: 407-323-1887
Fax: 407-649-9213

Hill Laboratories

DRIG NEW CORRES
NC

April 29. 1999

Mary Jean Kozma-Fornaro
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd. HFD-540
Rockville, MD 20850

RE: —— Cream NDA 21,112

Dear Ms. Kozma-Fornaro:

The following is an abbreviated table of contents, which will assist Mr. Pappas in finding the room temperature stability information of the clinical investigation formulations of —— Cream found in volume 1.6.

We are sending a copy of volume 1.6. as well another copy of this abbreviated table of contents to you by Federal Express.

If you have any further questions, please feel free to call. (407) 323-1887

Thank you,

Marianna Arsts

ORIGINAL

2650 S. Mellonville Avenue
Sanford, Florida 32773

Telephone: 407-323-1887
Fax: 407-~~649-9213~~
323-1871

Stability Information for [redacted] Cream Clinical Investigation Formulations

ATTACHMENT to 356h

CHEMICAL NAME

Fluocinolone acetonide: **pregna-1,-4-diene-3,20-dione, 6,9-difluoro-11,21 dihydroxy- 16,17-[(1-methylethylidene)bis(oxy)]-, (6α,11β,16α)-.**

Hydroquinone: **1,4-benzenediol**

Tretinoin: **(*all-E*)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid**

ESTABLISHMENT INFORMATION

Locations of manufacturing, packaging and control sites for drug substances and drug product:

Drug Product: Cream

Location: HILL DERMACEUTICALS, INC.
(Establishment Registration Number: 1036365/ORL)
2650 South Mellonville Avenue
Sanford, Florida 32773

Contact: Jerry Roth

Telephone: (407) 323-1887

Drug Substance: Fluocinolone acetonide USP Drug Master File Number:

Location:

Contact:

Telephone:

Drug Substance: Hydroquinone USP Drug Establishment Registration

Location:

Contact:

Telephone:

Drug Substance: Tretinoin USP Drug Master File Number:

Location:

Contact:

5/10/99 Hon Lum of NJ

1) requested East & West if any data needed separately
2) Need Safety data separated out
3) will find out tomorrow & get with location

Hill Dermaceuticals, Inc.

"The Scalp Company"

CENTER FOR DRUG REC'D MAY 10 1999

— Cream
— NDA 21-112

May 7, 1999

Jonathan K. Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd. , HFD-540
Rockville, MD 20850

RE: — Cream, NDA 21-112
General Correspondence: Response to deficiencies with NDA application.

Dear Dr. Wilkin:

The enclosed archival copy, review copy and desk copy are submitted in response to the deficiencies noted in several sections of the new drug application. The following itemizes the list of deficiency issues addressed in this submission.

In reference to the original submission, the following volume number follow the sequence of the originally submitted 7- volume Archival Copy.

Volume 8 contains:
1. Integrated Summary of Safety Results, as requested.
2. The hard copy of the correspondence faxed to the Agency indicating the volume and page number of the assay test results on the formulations used in the clinical studies. The results contain initial assays and room temperature stability assays.
3. Stability summary forms on the Clinical Study Batch No. 97K065 / K970082.
4. Stability summary forms for the 3 test batches packaged in the 1 ounce tubes and those packaged in the 5 ounce tubes.

Volume 9 contains the full report of the Dermal Safety Studies:
A. Protocol # 0056, Repeat Insult Patch Test comparing — to its vehicle
B. Protocol # 0057, Photocontact Allergenicity Study on —
C. Protocol # 0058, Phototoxicity Study on —
D. Protocol # 0059, Repeat Insult Patch Test comparing each active ingredient in to its vehicle

Hill Dermaceuticals, Inc.

"The Scalp Company"

5000 South Melbourne Avenue • Sanford, Florida 32773 • 407-323-1887 • Fax: 407-649-9213

— Cream
— NDA 21-112

May 10, 1999

Jonathan K. Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd. , HFD-540
Rockville, MD 20850
Attn: Ms. Mary Jean Kozma-Fornaro

RE: — , NDA 21-112
General Correspondence: Disk for Statistical Database.

Dear Ms. Fornaro:

Enclosed, please find the disk for the — , cream clinical efficacy and safety studies statistical database. A printout of this database is included in the submission of May 8, 1999. Nevertheless, I have included another copy of the printout for this disk.

Thank you.

Sincerely,

Rosario G. Ramirez
Medical/Regulatory Affairs

APPEARS THIS WAY ON ORIGINAL

[redacted]

Hill Dermaceuticals, Inc.

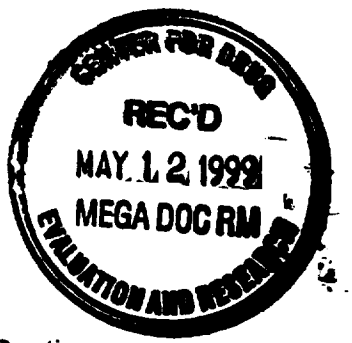
ORIGINAL

"The Scalp Company"

— Cream
— NDA 21-112

May 11, 1999

Jonathan K. Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd. , HFD-540
Rockville, MD 20850
Attn: Biostatistics Department



RE: ——— .n, NDA 21-112
General Correspondence: Safety analysis, Statistical Section

Dear Sir:

Enclosed, please find 3 copies (Archival, Review and Desk copies) of the safety report for East (Study 1) and West (Study 2) studies for the statistical section of NDA 21-112. The summary of the adverse events were presented for each study.

Thank you.

Sincerely,

Rosario G. Ramirez
Medical/Regulatory Affairs

cc: Ms. Mary Jean Kozma-Fornaro
Project Manager Supervisor

Hill Dermaceuticals, Inc.

"The Scalp Company"

2650 South Wekiva Avenue • Sanford, Florida 32773 • 407-323-1887 • Fax: 407-649-9213

ORIGINAL

BM

Cream
NDA 21-112

ORIG AMENDMENT

May 19, 1999

Jonathan K. Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd. , HFD-540
Rockville, MD 20850
Attn: Biostatistics Department

RE: ——— , NDA 21-112
General Correspondence

Dear Dr. Wilkin:

In response to the enclosed letter from the Agency regarding adverse events information and case report forms on the clinical studies, please find tabulated data for:

1. Adverse events information pursuant to Clin guidelines III.B.10.b.5. The adverse events were tabulated according to Investigator.
2. Tabulated absolute number of patients per adverse event.
3. Tabulated safety and efficacy data on the long term follow-up period after 8 weeks double-blind.
4. Resubmission of case report forms with page numbers.

Item number 1 references the page numbers on the case report forms.

Enclosed are 3 copies of the submission. Thank you.

Sincerely,

Rosario G. Ramirez
Medical/Regulatory Affairs

cc: Ms. Mary Jean Kozma-Fornaro

Hill Dermaceuticals, Inc.

"The Scalp Company"

South Mellonville Avenue • Sanford, Florida 32773 • 407 323 1887 • FAX 407 323 3270

June 4, 1999

Mary Jean Kozma-Fornaro
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd. HFD-540
Rockville, MD 20850

Dear Ms. Kozma-Fornaro:

The information requested by Dr. De Camp to continue the chem[illegible]w for [redacted] (NDA 21-112) is as follows:

1. The difference between the tables was the Identification Test for Hydroquinone. It was an editing mistake and a revised table for Vol. 1.3 Page Number: 4 0764 has been included with this letter.

2. To show the compatibility between Hydroquinone, Tretinoin and Fluocinolone Acetonide three different formulations were used. All formulations have the same active ingredient concentrations as in

   A) Tretinoin and Hydroquinone Cream (Red)

   B) Tretinoin and Fluocinolone Acetonide Cream(Blue)

   C) Fluocinolone Acetonide and Hydroquinone Cream (Black)

   These formulations were placed on room temperature stability. There is 12 months stability on each formula and also can be found in the Clinical Data Section. The page numbers are as follows:

   a) Tretinoin and Hydroquinone Cream (Red) ..... 7 0343 to 7 0344

   b) Tretinoin and Fluocinolone Acetonide Cream (Blue).....7 0373 to 7 0374

   c) Fluocinolone Acetonide and Hydroquinone (Black) .....7 0403 to 7 0404

   Additional room temperature stability will be available in June for these formulations and will be submitted.

ORIGINAL

3. Room Temperature long-term stability on _____ is on going. Additional stability data will be available in August and will be submitted.

If you have any further questions, please feel free to call. (407) 323-1887

Thank you,

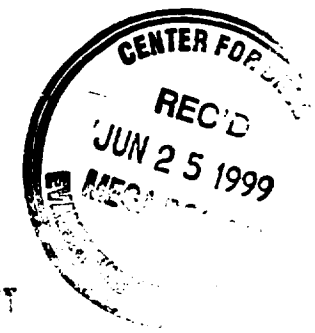
Nancy Puglia

Quality Assurance / Chemical Engineer

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

BC



Hill Dermaceuticals, Inc.

ORIG AMENDMENT

"The Scalp Company"

— Cream
— NDA 21-112

June 23, 1999

Jonathan K. Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd. , HFD-540
Rockville, MD 20850
Attn: Chemistry Department

RE: ——— NDA 21-112
General Correspondence

This submission refers to the information request from the chemistry department, FDA correspondence dated May 26, 1999 (copy enclosed). The response letter from Nancy Puglia (lab manager), and corrected specifications and tests table faxed to the agency on June 4, 1999, are included. Also included is a copy of the original submitted table (vol 1.1, pg 3 0021) for in-process, finished product, and stability specifications and tests.

Enclosed are 3 copies of the submission. Thank you.

Sincerely,

Rosario G. Ramirez
Medical/Regulatory Affairs

cc: Ms. Mary Jean Kozma-Fornaro
Project Manager Supervisor

Ms. Victoria Lutwak
Project Manager

Hill Dermaceuticals, Inc.

"The Scalp Company"

2650 South Mellonville Avenue • Sanford, Florida 32773 • 407-323-1887 • Fax: 407-649-9213

/ NDA 21-112

ORIG NEW CORRES

August 19, 1999

NC

Jonathan K. Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., HFD-540
Rockville, MD 20850
ATTN: Ms. Vickey Lutwak
Project Manager

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
SEP 24 1999
MEGA DOC RM

RE: Response to Chemistry request.

We are requesting comments and advise with the enclosed itemized list. The list includes planned actions as well as actions taken regarding specific issues in the CMC section.

We request further guidance if the information provided is not adequate. We would like a teleconference before August 27. Thank you for your patience and understanding.

Sincerely,

Rosario G. Ramirez
Medical/Regulatory Affairs

Nancy Puglia
Plant Manager / Lab Supervisor

Enc.

ORIGINAL

ORIGINAL

NEW CORRESP

NC

Hill Dermaceuticals, Inc.

"The Scalp Company"

2... South Mellonville Avenue • Sanford, Florida 3...73 • 407-323-1887 • Fax: 407-649-9213

Cream
NDA 21-112

August 27, 1999

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850
Attn: Ms. Vickey Lutwak
Project Manager

RE: Response to faxed request

The requested information, photographs and samples shall be provided no later September 9, 1999. To be included in this submission are the following:

1. Baseline photographs of the patients specified in the list provided by the Agency.
2. Test drug samples, the triad and the 3 dyads.
3. Additional Case Report Forms
4. Electronic format of the statistical report (pages 8 0006 - 8 0027), integrated summary of safety, and the integrated summary of efficacy.
5. Letter on the '120-days safety report'.

At this time, there is no plan to include a patient package insert for this drug product.

Regarding the licensing of the drug product, this information will be forwarded to FDA when it becomes available. Thank you.

Respectfully,

Rosario G. Ramirez

Rosario G. Ramirez
Medical/Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
HILL DERMACEUTICALS, INC	21 SEPTEMBER 1999
TELEPHONE NO. *(Include Area Code)* (407) 323 - 1887	**FACSIMILE (FAX) Number** *(Include Area Code)* (407) 649 - 9213
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 2650 South Mellonville Avenue Sanford, FL 32773 USA	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(if previously issued)*

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Fluocinolone acetonide, Hydroquinone, Tretinoin	—

CHEMICAL/BIOCHEMICAL/BLOOD, PRODUCT NAME *(if any)*	CODE NAME *(if any)*
Please see attachment	N/A

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
1 oz. (28 grams)	0.01% , 4.0% , 0.05%	Topical

(PROPOSED) INDICATION(S) FOR USE:
Cutaneous melanosis

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION :
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION RESPONSE TO FAXED REQUEST

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Please see attachment

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

ORIGINAL

Hill Dermaceuticals, Inc.

"The Scalp Company"
NEW CORRESP
NC

NDA 21-112
Cream

September 24, 1999

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., HFD-540
Rockville, MD 20850
ATTN: Ms. Vickey Lutwak
Project Manager

RE: Proposed Trade Names for the combination drug product:
Fluocinolone acetonide 0.01%, Hydroquinone 4.0%, Tretincin 0.05%
NDA 21-112

The following names are hereby submitted for the above combination drug product: Fluocinolone acetonide 0.01%, Hydroquinone 4.0%, Tretinoin 0.05%, NDA 21-112

1.

2.

Sincerely,

Rosario G. Ramirez

Rosario G. Ramirez
Medical/Regulatory Affairs

... Mt. Holly ville Avenue • Sanford, Florida 32773 • 407-323-1887 • Fax: 407-649-9213

ORIGINAL

BM

Hill Dermaceuticals, Inc.

"The Scalp Company"

NDA ORIG AMENDMENT

NDA 21-112
Cream

September 27, 1999

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., HFD-540
Rockville, MD 20850
ATTN: Ms. Vickey Lutwak
Project Manager

RE: Response to the medical reviewer's request for photographs, and additional case report forms.

The following is a resubmission of the Sept. 13, 1999 sponsor response letter and additional information requested, the archival and 2 copies. This submission includes photographs of specified patients from the clinical studies, and copies of additional requested case report forms.

A copy of the Sept. 13, 1999 sponsor letter and faxed request from the FDA is enclosed. Thank you.

Sincerely,

Rosario G. Ramirez
Medical/Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
SEP 2 8 1999
MEGA DIV. 2M

Enc.

ORIGINAL

Hill Dermaceuticals, Inc.

NEW CORRESP

NC

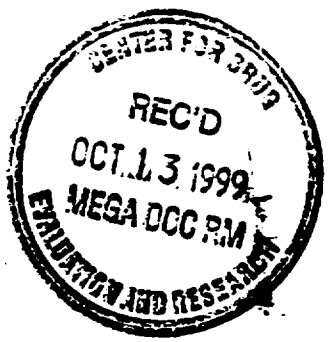
2650 South Merrimac Avenue • Sanford, Florida 32773 • 407-323-1887 • Fax: 407-849-9213

"The Scalp Company"

NDA 21-112

CREAM

October 12, 1999



Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., HFD-540
Rockville, MD 20850
ATTN: Ms. Vickey Lutwak
Project Manager

RE: Requested photographs of all male patients from clinical studies.

As requested in your earlier telephone conversation, photographs of all male patients from the East and West clinical studies are enclosed, the archival and two copies. The following is a list of patient identification numbers, patient initials and appropriate investigator group for the above-mentioned photographs. There were no male patients in Dr. Helen Torok's clinical study group.

Investigator Group	Patient ID #/Patient Initials
Neil Brody, MD	#
Joshua Wieder, MD	
Paul Kelly, MD	

The above selected photographs are from the initial visit. Please do not hesitate to

APPEARS THIS WAY ON ORIGINAL

ORIGINAL
BM

Hill Dermaceuticals, Inc.

"The Scalp Company"

AMENDMENT

NDA 21-112
Cream

October 25, 1999

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., HFD-540
Rockville, MD 20850
ATTN: Ms. Vickey Lutwak
Project Manager

RE: Case Reports, Protocol 24

Enclosed, please find copies of the requested case report documentation, pages 1 and 2, from the East and West studies.

The content of this submission includes all patients enrolled in all 5 study sites, divided according to investigator. The enclosed first 2 pages of each case report are sequentially arranged according to patient number.

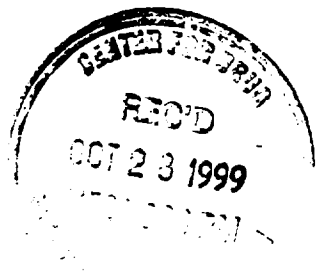
Sincerely,

Rosario G. Ramirez
Medical/Regulatory Affairs

ORIGINAL

ORIG AMENDMENT

Hill Dermaceuticals, Inc.



"The Scalp Company"

NDA 21-112
—— Cream

October 25, 1999

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., HFD-540
Rockville, MD 20850
ATTN: Ms. Vickey Lutwak
Project Manager

RE: Requested Chemistry Information

The executed manufacturing batches placed on primary stability are not the same as the manufactured batch used in the clinical studies.

The batch used in the clinical studies can be found in Archival volume 1.6, Item 7, Appendix 6, starting at page 7 0248. This section includes manufacturing batch records, stability summary forms, certificates of analysis, and initial test results for batch number 97K065 / K970082. We will gladly forward a copy of Appendix 6 section for Mr. Pappas if he so wishes.

The executed manufactured batch size was —— The intended commercial batch size is ——

Sincerely,

Rosario G. Ramirez
Medical/Regulatory Affairs

ORIGINAL

NC

Hill Dermaceuticals, Inc.

"The Scalp Company"

2650 South Mellonville Avenue • Sanford, Florida 32773 • 407-323-1887 • Fax: 407-649-9213

NDA 21-112
Cream

NEW CORRESPONDENCE

October 28, 1999

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., HFD-540
Rockville, MD 20850
ATTN: Ms. Vickey Lutwak
Project Manager

RE: General Correspondence: Requested Information

The tabulated data enclosed is provided in reference to the information request from the Medical officer regarding the clinical studies performed for

The requested information include date of starting, date of completion, and date of data unblinding for Study 24 East, Study 24 West, Contact irritation and sensitization potential – 0056, Photoallergenicity test – 0057, Phototoxicity test – 0058, and Repeat insult patch test – 0059.

Sincerely,

Rosario G. Ramirez
Medical/Regulatory Affairs

ORIGINAL

Hill Dermaceuticals, Inc.

NEW CORRESP

NC

2650 South Mellonville Avenue • Sanford, Florida 32773 • 407-323-1887 • Fax: 407-649-9213

"The Scalp Company"

NDA 21-112
Cream

November 4, 1999

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., HFD-540
Rockville, MD 20850
ATTN: Ms. Vickey Lutwak
Project Manager

RE: Protocol # 24, West Study patient # 100

Enclosed, please find 3 copies (archival plus 2 copies) of the missing case report for patient # 100 of the West study under Dr. A. Paul Kelly. As requested previously, only the first 2 pages of the case report is submitted.

Sincerely,

Rosario G. Ramirez

Rosario G. Ramirez
Medical/Regulatory Affairs

Hill Dermaceuticals, Inc.

ORIGINAL

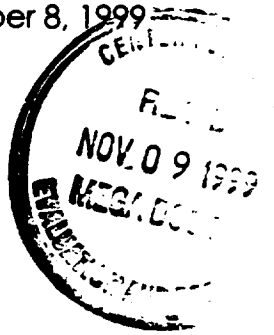
NC

NEW CORRESP

"The Scalp Company"

NDA 21-112
—— Cream

November 8, 1999



Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., HFD-540
Rockville, MD 20850
ATTN: Ms. Vickey Lutwak
Project Manager

RE: Proposed Trade Names for the combination drug product
Fluocinolone acetonide 0.01%, Hydroquinone 4.0%, Tretinoin 0.05%
NDA 21-112

The following names are hereby submitted for the above combination drug product: Fluocinolone acetonide 0.01%, Hydroquinone 4.0%, Tretinoin 0.05%, NDA 21-112 (IND ——

1. **TRILUMA**

2. ——

Sincerely,

Rosario G. Ramirez

Rosario G. Ramirez
Medical/Regulatory Affairs

Hill Dermaceuticals, Inc.

"The Scalp Company"

NDA 21-112
——— Cream

December 16, 1999

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., HFD-540
Rockville, MD 20850
ATTN: Ms. Vickey Lutwak
Project Manager

RE: Additional Information for Chemistry, Manufacturing and Controls Section of NDA 21-112

Reference is made to the CMC section of NDA 21-112 ——— Cream (0.01% Fluocinolone acetonide, 4.0% Hydroquinone, 0.05% Tretinoin), regarding the request for information to demonstrate chemical compatibility of the active ingredients, and to show that the analytical assay methods are stability indicating.

1. Validation of the analytical test methods to assay Tretinoin, Hydroquinone and Fluocinolone acetonide in the presence of potential degradation products, 1,4 benzoquinone, 13-cis-tretinoin, 11-cis-tretinoin, fluocinolone, and 21-methoxy-fluocinolone acetonide.

Although each of the active ingredients in ——— Cream has its own analytical assay method, the validation of each test method verified that the active ingredient being assayed was quantitatively determined with no interference from the degradation products of the tested active ingredient, other active ingredients, degradation products of the other active ingredients, or excipients found in the cream.

2. Validation of the analytical assay method for each active component to demonstrate that the method is stability indicating.

The assay method for the individual active ingredient is specific for the wavelength of the active component, i.e. Fluocinolone acetonide = 254nm, Hydroquinone = 280 nm, and Tretinoin = 365 nm. To establish that each assay method is 'stability indicating', each method was run at 3 different wavelengths, 254 nm / 280 nm / 365 nm, and tested for each active component and their degradation products.

The results of the experimentation demonstrated that each method specific for an active component, e.g. fluocinolone acetonide = 254 nm, verified presence of the active component at a specific retention time, different from retention times of its degradation products, other active ingredients, and degradation products of other active ingredients. (Pages 3 – 7).

Each section of this submission is labeled accordingly for easy access. The chromatographic data are labeled according to the test performed.

We are confident that the information presented satisfies the chemistry questions. Thank you for your continued assistance and cooperation.

Sincerely,

Rosario G. Ramirez
Medical/Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

Hill Dermaceuticals, Inc.

NEW CORRESP

"The Scalp Company"

NDA 21-112
[redacted] Cream

January 5, 2000

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., HFD-540
Rockville, MD 20850
ATTN: Ms. Vickey Lutwak
Project Manager

Oct 21 never submitted ← non-Asked Sponsor ← Submit in Jan

RE: Hard copy submission for requeste[redacted]

Enclosed please find the letter providing ir[redacted] by the Agency, regarding [redacted]y. The letter was sent via facsimile but was inadve[redacted]d as hard copies to the NDA. Herewith submitted are 3 [redacted]d 2 copies, to NDA 21-112, [redacted] team.

Thank you for your kind understanding.

Sincerely,

Rosario G. Ramirez
Medical/Regulatory Affairs

BEST POSSIBLE COPY

Enc.

Hill Dermaceuticals, Inc.

"The Scalp Company"

NDA 21-112
— Cream

October 21, 1999

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., HFD-540
Rockville, MD 20850
ATTN: Ms. Vickey Lutwak
Project Manager

RE: —

— provides the x-ray diffraction (XRD) analys according to USP/NF methodology for magnesium aluminum silicate identification. Magnesium aluminum silicate, also known as *Veegum k*, is one of the components found in the triple combination drug product —

—

A copy of the methodology and results performed by the — can be found in NDA 21-112 Archival volume 1.2, Item 4 CMC, pages 4 0242 to 4 0245.

Sincerely,

Rosario G. Ramirez

Rosario G. Ramirez
Medical/Regulatory Affairs

DOSK COPY

Hill Dermaceuticals, Inc.

"The Scalp Company"

2650 South Mellonville Avenue • Sanford, Florida 32773 • 407-323-1887 • Fax: 407-649-9213

NDA 21-112
[redacted] Cream

October 28, 1999

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., HFD-540
Rockville, MD 20850
ATTN: Ms. Vickey Lutwak
Project Manager

RE: General Correspondence: Requested Information

The tabulated data enclosed is provided in reference to the information request from the Medical officer regarding the clinical studies performed for [redacted]

The requested information include date of starting, date of completion, and date of data unblinding for Study 24 East, Study 24 West, Contact irritation and sensitization potential – 0056, Photoallergenicity test – 0057, Phototoxicity test – 0058, and Repeat insult patch test – 0059.

Sincerely,

Rosario G. Ramirez
Medical/Regulatory Affairs

Attachment to NDA 21-112

General Correspondence Letter
October 28, 1999

Protocol No.	Date Started	Date Completed	Date of Data Unblinding
Study 24, EAST	1 - 31 - 98	2 - 25 - 99	Unblinding of all patients occurred at the 8th week of treatment. Start: 5 – 14 – 98 Last: 9 – 4 - 98
Study 24, WEST	3 - 17 - 98	2 - 23 - 99	Unblinding of all patients occurred at the 8th week of treatment. Start: 5 – 12 – 98 Last: 10 – 1 - 98
Protocol 0056 Contact irritation and sensitization	8 - 25 - 97	10 - 24 - 97	11 - 4 - 97, double-blinded
Protocol 0057 Photoallergenicity test	10 - 3 - 97	12 - 8 - 97	NOT BLINDED
Protocol 0058 Phototoxicity test	9 - 22 - 97	9 - 26 - 97	9 - 26 - 97, single-blinded
Protocol 0059 Repeat insult Patch test	3 - 30 - 98	5 - 15 - 98	5 – 18 – 98, double-blinded

APPEARS THIS WAY
ON ORIGINAL

DERMA-SMOOTHE/FS®
SCALP OIL

DERMA-SMOOTHE/FS®
ATOPIC PAK

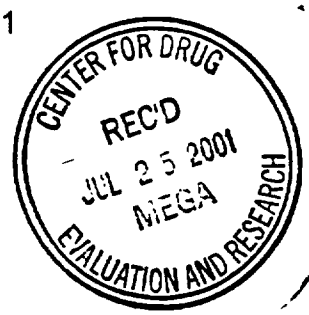
ONE AMENDMENT
A2

Dermaceuticals, Inc.

Specialty Dermatologicals for Children & Adults

NDA 21-112
TRI-LUMA Cream

July 20, 2001



Jonathan Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd. , HFD-540
Rockville, MD 20850
Attn: Ms. Vickey Lutwak
Project Manager

RE: Amendment to a Pending Application
NDA 21-112 TRI-LUMA Cream

Dear Dr. Wilkin :

Hill Dermaceuticals, Inc. is submitting this amendment to a pending application for TRI-LUMA Cream, NDA 21-112, for the indication, melasma of the face. This amendment is in response to the non-approvable (NA) letter (January 21, 2000) to the original NDA submission. The contents of this amendment include the complete response to the deficiencies stated in the NA letter.

Two new adequate and well-controlled clinical trials for a Phase III efficacy and safety study have been conducted. These pivotal clinical studies support clinical and statistical claims of the drug for the treatment of melasma. The 6 months safety data report on more than 300 patients, in accordance with ICH E1A Guideline for Industry, The Extent of Population Exposure to Assess Clinical Safety, is included in this submission. The long-term (12 months) safety studies are presently ongoing. Upon completion, 12 months safety data will be submitted during the review period, prior to approval.

Clinical and statistical assessment of the pivotal efficacy studies show that TRI-LUMA Cream is significantly effective for the treatment of melasma. Superiority (statistical significance) of TRI-LUMA Cream over each dyad was demonstrated based on analysis of success rate as "clearing" of melasma, or score of zero. Safety evaluation, including the 6 months safety data, show that TRI-LUMA has a significantly favorable safety profile in 1029 patients in a total of 8 clinical studies.

ORIGINAL

2650 South Mellonville Avenue • Sanford, FL 32773-9311 • Phone 1.800.344.5707 • Fax 1.407.649.9213

Studies were conducted to assess irritation and sensitization potential of TRI-LUMA cream on more than 200 subjects. A preliminary 21-Day cumulative irritancy study was performed on 25 subjects to assess the irritancy potential of TRI-LUMA compared to the Hydroquinone-Tretinoin (HQ-RA) dyad, and the cream vehicle, under occlusive patch. Data from this preliminary study demonstrated significant irritation from the HQ-RA dyad as compared to TRI-LUMA and the vehicle.

The second study, Modified Draize Sensitization Study, was performed on 225 subjects. The patch used for this study is an occlusive plastic chamber held in place with paper tape. Results from the Modified Draize study showed the HQ-RA dyad to be more irritating than TRI-LUMA or the vehicle.

Separate clinical pharmacology studies were conducted to assess maximum systemic exposure after percutaneous absorption, and to evaluate HPA axis (adrenal) suppression after 8 weeks of daily use. The results of the *in vivo* maximum systemic exposure study demonstrated minimal absorption of the active components of TRI-LUMA as shown by the plasma assay analysis for each active component. The methods used to analyze each active component in the human plasma were developed and validated by —. The assay methods used were high performance liquid chromatography (HPLC) and — to ensure that the lowest limit of quantitation for the active components were below endogenous levels. Validation reports for the human plasma assay is still under Quality Assurance review by — The report will be submitted to the Agency upon receipt and review by Hill Dermaceuticals, Inc..

The adrenal suppression study on 29 patients with melasma, treated for 8 weeks, showed that there was no clinically or statistically significant alteration of HPA axis function after 56 days of daily use. The Cortrosyn Stimulation Test kit was used as diagnostic tool, to assess Cortisol levels (pre- and post-stimulation levels) prior to the start of application, after 4 weeks, and at the 8-week completion time of the study.

Animal toxicology studies were conducted on rodents and non-rodent species, to address the reproductive and developmental effects of TRI-LUMA on rats and rabbits when administered dermally, and to assess dermal toxicity with chronic dermal application of TRI-LUMA on mini pigs. Pharmacokinetic studies were also performed on plasma samples from these animals. Assay methods for animal plasma analysis were developed and validated by —

Since the original submission, the new Hydroquinone, USP Drug Master File (DMF) submitted to the Agency on December 16, 1999 has been under review. A DMF number has been made available to Hill Dermaceuticals for reference purposes.

Changes in chemistry, manufacturing and controls (CMC) were effected in response to the deficiencies listed in the NA letter. Microscopic examination (Particle Size Test) of the finished product to assure that no phase separation has occurred and that the product is free of particles, has been incorporated in the Finished Product Specification form. This test will also be performed as part of stability testing.

To test for homogeneity in the packaged unit, samples for assay will be taken from the top, middle and bottom portions of the tube. Homogeneity test will also be performed for the entire manufactured batch where samples for assay testing will be taken from the beginning, middle and end of the packaging run. This test has been incorporated in the In Process and Finished Product Specification forms.

Assay methods and validation reports have been submitted to the Agency on December 16,1999. Data from assay tests have verified that the known degradants from each active component did not have any effect on the assay results. No new degradant were found.

Twenty-four months room temperature stability data has been collected. Stability results are included in the CMC section.

The internal coating ——— and end sealant ———) components of the aluminum tube used for packaging TRI-LUMA Cream has been found to be suitable for this purpose based on the results of the ——— .ests performed.

Other requirements for the CMC section, description, drawings and specifications for the closure system (cap), and DMF reference for the tube sealant ——— , is included in this submission.

APPEARS THIS WAY
ON ORIGINAL

A new trade name, TRI-LUMA, is proposed for the combination drug product containing 0.01% fluocinolone acetonide, 4.0% hydroquinone and 0.05% tretinoin, in a cream base. The provisional names TRADENAME and/o: [redacted] although still referred to in some reports, shall be superseded by the new proposed trade name.

A claim for exclusivity has been previously submitted in the original NDA, file date March 19, 1999.

To the best of our abilities, all issues concerning the deficiencies outlined in the NA letter have been addressed and presented in this submission.

Thank you for your continued assistance and support. We are looking forward to a quick and favorable review.

Sincerely,

Jerry S. Roth
President

Rosario G. Ramirez, MD
Director, Medical/Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Hill Dermaceuticals, Inc.	JULY 24, 2001
TELEPHONE NO. *(Include Area Code)* 407-323-1887	**FACSIMILE (FAX) Number** *(Include Area Code)* 407-649-9213
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 2650 South Mellonville Avenue Sanford, Florida 32773	**AUTHORIZED U.S. AGENT NAME & ADDRES... ZIP Code, telephone & FAX number) IF APP...**

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 25 2001
MEGA DOC RM

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA...

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Please See Attachment	TRI-LUMA Cream
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* Please See Attachment	**CODE NAME** *(If any)* N/A
DOSAGE FORM: Cream	**STRENGTHS:** Please See Attachment
ROUTE OF ADMINISTRATION: Topical	

(PROPOSED) INDICATION(S) FOR USE:
Melasma

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Full response to Non-Approvable Letter (to NDA)

PROPOSED MARKETING STATUS *(check one)* ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: _____ THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Please See Attachment

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

ORIGINAL

This application contains the following items: *(Check all that apply)*	
X	1. Index
X	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
X	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
X	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
X	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
X	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
X	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
X	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
X	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
X	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
X	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
X	17. Field copy certification (21 CFR 314.50 (l)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. Financial Information (21 CFR Part 54)
	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Rosario G Ramirez	Rosario G. Ramirez Director, Medical/Regulatory Affairs	JULY 24, 2001

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2650 So. Mellonville Ave., Sanford, FL 32773	(407) 323-1887

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

ATTACHMENT to 356h

CHEMICAL NAME

Fluocinolone acetonide: **pregna-1,-4-diene-3,20-dione, 6,9-difluoro-11,21 dihydroxy- 16,17-[(1-methylethylidene)bis(oxy)]-, (6α,11β,16α)-.**

Hydroquinone: **1,4-benzenediol**

Tretinoin: **(*all-E*)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid**

STRENGTHS

Fluocinolone acetonide 0.01% .....0.01% FA
Hydroquinone 4.00%.....4.00% HQ
Tretinoin 0.05%.....0.05% RA

ESTABLISHMENT INFORMATION

Locations of manufacturing, packaging and control sites for drug substances and drug product:

Drug Product: TRI-LUMA Cream
Location: HILL DERMACEUTICALS, INC.
(Establishment Registration Number: 1036365/ORL)
2650 South Mellonville Avenue
Sanford, Florida 32773
Contact: Jerry Roth
Telephone: (407) 323-1887

Drug Substance: Fluocinolone acetonide USP Drug Master File Number: —
Location:
Contact:
Telephone:

Drug Substance: Hydroquinone USP Drug Master File Number: —
Location:
Contact:
Telephone:

Drug Substance: Tretinoin USP Drug Master File Number: —
Location:
Contact:

Parsippany, New Jersey

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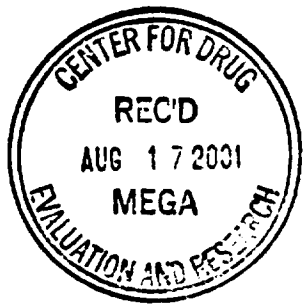
Dermaceuticals, Inc.

Specialty Dermatologicals for Children & Adults

NDA 21-112
TRI-LUMA Cream



August 16, 2001

Jonathan K. Wilkin, M.D. / Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850
ATTN: Vickey Lutwak / Project Manager

RE: Amendment to a Pending Application / Request for Mock-up Color Label

Dear Dr. Wilkin:

In reference to NDA 21-112, TRI-LUMA (Fluocinolone acetonide 0.01% + Hydroquinone 4.0% + Tretinoin 0.05%) Cream, enclosed please find mock-up, color copies of label for TRI-LUMA carton and container as requested. We now have a color diskette in Mac format and will forward a WORD diskette to you once the conversion is final.

Please do not hesitate to contact us should additional information be required. Thank you again for your continued support and consideration.

Sincerely,

Criss Molasso

Criss Molasso
Assistant Regulatory Affairs

cc: Rosario G. Ramirez, MD
Director, Medical/Regulatory Affairs

encls.

ORIGINAL

DERMA-SMOOTHE/FS®
SCALP OIL

DERMA-SMOOTHE/FS®
ATOPIC PAK

Dermaceuticals, Inc.

Specialty Dermatologicals for Children & Adults

NC

NEW CORRESP

NDA 21-112
TRI-LUMA Cream

August 21, 2001

Jonathan Wilkin, MD
Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd. , HFD-540
Rockville, MD 20850
Attn: Ms. Vickey Lutwak
Project Manager

RE: NDA 21-112 TRI-LUMA Cream
Review Copy of volume 46

Dear Ms. Lutwak,

Hill Dermaceuticals. Inc. is formally submitting the review copy of volume 46 of the amendment to the pending application to NDA 21-112.

Volume 46 of the Amendment to NDA 21-112 pending application is the last part of the full amendment submission consisting of a total of 46 volumes. Volume 46 of the NDA submission contains copies of Case Report Forms of patients that died or were dropped / terminated due to adverse events.

Thank you for your continued assistance and support.

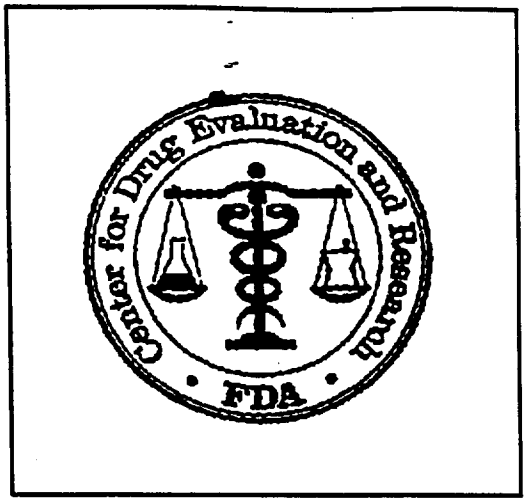
Sincerely,

Rosario G. Ramirez
Director
Medical / Regulatory Affairs

ORIGINAL

2650 South Mellonville Avenue • Sanford, FL 32773-9311 • Phone 1.800.344.5707 • Fax 1.407.649.9213

FACSIMILE TRANSMISSION
RECORD



From: Vickey Lutwak, Project Manager

Division of Dermatologic and
Dental Drug Products, HFD-540
Center for Drug Evaluation & Research
Food & Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Phone 301-827-2020 / 827-2058
Fax 301-827-2075

Date: _____

To:

Name Nini Ramirez
Company _____
City _____ State ____
Phone # 407 323-1787

FAX # (407) 649-9213

Number of Pages (INCLUDING COVER PAGE) (2)

Please telephone (301) 827-2020 IMMEDIATELY if re-transmission is necessary.

NOTE: We are providing the attached information via telephone facsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Additional message:

NDA 21,112

Nini,

Please provide the following for the medical & statistical review for NDA 21,112 - Give me an idea when this will be provided. Thanks.

/S/

Let me know if you have any questions -

NDA 21-112

Please provide the following for the medical review:

The medical officer would like to see the following photographs. Only baseline photos are needed. The following shows which patients with CRF submitted in this NDA had baseline photos shown in the CRFs (we only have CRFs of those dropouts due to AEs):

Study East

Study West

+

Additional CRFs (all in Study West)

2) Please provide samples of the test drugs used in the clinical trial 024 (the triad and three dyads - total of 4 drugs).

AND
For the statistical Review

Additional information requested from the sponsor:

1. Protocol 24 and statistical report (pages 80006-80027 in volume 1.7), ISS (integrated summary of safety), and ISE (integrated summary of efficacy) in electronic format (Microsoft Word).

Hill Laboratories

TEL No. 1-407-323-1270

FAX No. 1-407-323-1871

PAGES SENT 4 (INCLUDING THIS COVER SHEET)

TO: Ms. Vickey Lutwak

FAX #: 301-827-2091

FROM: Nini Ramirez

DATE: 8/18/99

SUBJECT:

NDA 21-112

&%&

MESSAGE:

IF YOU HAVE ANY TROUBLE WITH THIS TRANSMISSION PLEASE CALL 407-323-1270

2650 S. Mellonville Avenue
Sanford, Florida 32773

Telephone: 407-323-1887
Fax: 407-649-9213

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Division of Dermatologic and Dental Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: October 26, 1999. Number of Pages (including cover sheet) 1

TO: Rosario Ramirez, M.D., Regulatory Affairs
COMPANY: Hill Laboratories
NUMBER: 407-323-1871
MESSAGE: **RE: NDA 21-112 _____ Cream**

Medical officer's request for information follow:

Please provide the date of starting, date of completion, and date of data unblinding for each of the following studies:

24 East
24 West
0056
0059
Phototoxicity test
Photoallergenicity test

Please fax followed by a formal submission to the NDA.

NOTE: We are providing the attached information via telefacsimile for your convenience. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph. for /S/
TITLE: Project Manager
TELEPHONE: 301- 827-2020 _____ FAX NUMBER: 301-827-2075

cc: NDA 21-112
HFD-540 /DIV FILES
HFD-540/KO

PROTOCOL No 24 -
Double-blind Comparative Study of **a New Formulation.**
for the Treatment of Cutaneous Melanosis

HILL DERMACEUTICALS, INC.
Case Report Form

Date: 7/20/98 **ADMISSION Visit**

Study Site:
Investigator Name:
Patient Initials: _____ **Patient No.** 100

DEMOGRAPHICS and BACKGROUND INFORMATION

Informed Written Consent ☒ Yes ☐ No Date: 7/20/98

Date of Birth: ___ ___ ___ (Mo Day Year)
Patients must be 18 years of age or older

Gender: ☐ Male ☒ Female

Race: (Skin type II or III)
- ☐ Caucasian
- ☐ Black
- ☒ Hispanic
- ☐ Oriental
- ☐ Other, specify ___

Allergies:
- ☒ None
- ☐ Ingestants
- ☐ Contactants
- ☐ Inhalants
- ☐ Drugs

If drugs, specify _____

Drugs used in the past 2 weeks, OTC and prescription:
☒ None
☐ Yes, describe below.

Drug Name or Class	Reason for Use	Start Date	Stop Date
		__/__/__	__/__/__
		__/__/__	__/__/__
		__/__/__	__/__/__
		__/__/__	__/__/__
		__/__/__	__/__/__
		__/__/__	__/__/__

Use of bleaching agents in the past. ☐ Yes ☒ No
If YES, give name of bleaching agent _____
duration of application _____
frequency of application _____

Did pigmented lesions get lighter ___, stayed the same ___, got worse ___.

If complete clearing occurred, did the hyperpigmentation return when the bleaching agent was discontinued? ☐ Yes ☒ No
If YES, how long before darkening recurred? _____

Pregnancy Test			Date	Method of Contraception
Neg.	Pos.	N/A	7/20/98 (Mo Day Year)	(Specify) condom
☒	☐	☐		

PROTOCOL No 24

HILL DERMACEUTICALS, INC.
Case Report Form
Page 2

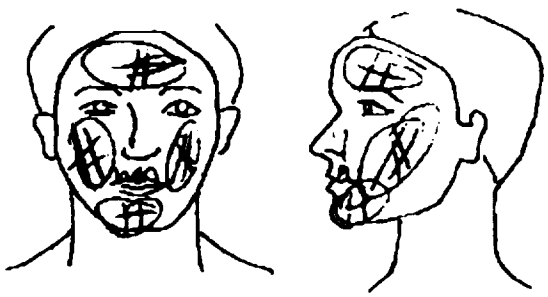
Investigator's Initials	Patient #	Patient's Initials
APK	102	—

Dispense Medication Packet. Check

Duration of hyperpigmentation: 11yrs. (Persistent, unchanged, for more than 3 months) Stable: ☑ Yes ☐ No

Photograph: ☑ Yes ☐ No

Location of pigmented lesions:



Initial Evaluation of Hyperpigmentation:
minimum score of 2

0 None	1 Mild	2 Moderate	3 Severe
		✓	

Concomitant Medication:

Drug Name or Class	Reason for Use	Start Date	Stop Date
		___/___/___	___/___/___
		___/___/___	___/___/___
		___/___/___	___/___/___
		___/___/___	___/___/___
		___/___/___	___/___/___

Signature of Investigator/sub-Investigator: [signature]

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FACSIMILE TRANSMISSION RECORD

DATE: 17 September 2001 **Pages (including cover): 1**

TO: Ms. Vickey Lutwak, Project Manager

COMPANY: FDA CDER / DDDDP

FAX PHONE #: **301-827-2075** **Hill Fax # (407) 323-1871**

Tel. no. # (407) 323-1887

RE: **Final Report on Animal Study: 26 Week Chronic Dermal Application Toxicity Study in Mini Pigs**

Dear Ms Lutwak,

The final report for the mini pig study has been signed off as of this morning and will be sent FED EX overnight to HILL. Due to last week's catastrophic events, the responsible person to sign off on the final report has been held out of town until today, 17 September.

The report will be forwarded to you forthright. You should receive the full report no later than Wednesday, September 19. We apologize for this delay.

Sincerely,

Rosario G. Ramirez
Director
Medical / Regulatory Affairs

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FACSIMILE TRANSMISSION RECORD

DATE: 20 September 2001 **Pages (including cover): 1**

TO: Ms. Vickey Lutwak, Project Manager

COMPANY: FDA CDER / DDDDP

FAX PHONE #: **301-827-2075** **Hill Fax # (407) 323-1871**

RE: **NDA 21-112**
Validation Reports for Human Plasma Assay

Dear Ms Lutwak,

Previously, we have committed to submitting the validation reports for the human plasma assays on or before September 27, 2001. Due to the repercussions of last week's disaster, the CRO ———) informed Hill yesterday, Sept 19, that there will be some delay in finishing these reports. The new date given to Hill is For October 19, 2001. In light of this unforeseen circumstance, Hill Dermaceuticals is respectfully requesting a change of timeline for the submission of human plasma validations reports to October 26, 2001, from the previously commitment date of September 27.

Your kind consideration and understanding would be greatly appreciated. Thank you.

Sincerely,

Rosario G. Ramirez
Director
Medical / Regulatory Affairs

NDE - Checked & Reviewed. This is agreeable
Change the Revised deadline to 12/1/01

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FACSIMILE TRANSMISSION RECORD

DATE: 16 November 2001 **Pages (including cover): 2**

TO: Ms. Vickey Lutwak, Project Manager

COMPANY: FDA / CDER / DDDDP

FAX PHONE #: **301-827-2075** **Hill Fax # (407) 323-1871**

RE: **NDA 21-112, Tri-Luma Cream**

Dear Vickey,

Enclosed is the letter of request for the extension of the submission date for the 12-month report on Study 29, long-term clinical safety study. I have also included an estimated response date for the other information requests.

Sincerely,

Nini

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NDA 21-112
TRI-LUMA Cream

November 16, 2001

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., HFD-540
Rockville, MD 20850
Attn: Ms. Vickey Lutwak
Project Manager

RE: Clinical Study 12-month Report for Study 29 (Long-term Safety Study)

Dear Ms. Lutwak,

There has been some delay in the data entry and transfer of data to the statistician, for the long-term safety study on Tri-Luma Cream (Study 29). Hill Dermaceuticals respectfully request change of timeline for the Clinical Study 29 Report submission, from November 23 to December 6, 2001. We will, however, submit prior to December 6 upon earlier completion of the 12-month report.

Response to the information request from the statistician, FDA facsimile correspondence dated Nov 16, 2001, should be available by December 7, 2001. Response to the information request on the mini pig study (PharmTox) should be available by November 21, 2001.

Thank you for your kind consideration and understanding.

Sincerely,

Rosario G. Ramirez

Rosario G. Ramirez
Director
Medical / Regulatory Affairs

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Dermaceuticals, Inc.

Specialty Dermatologicals for Children & Adults

November 21, 2001

VIA FACSIMILE AND FEDERAL EXPRESS

Jonathan Wilkins, M.D.
Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA 21-112 TRI-LUMA Cream

Dear Dr. Wilkin:

I am very concerned about our telephone conversation on Tuesday, November 20, 2001. We have communicated for many months regarding the submission timeframe of November 23, 2001, for the long term safety study. Not once did Division staff agency raise issues with respect to completing the review of the NDA by the user fee deadline of January 25, 2002, until your call yesterday. As you know, we have met the timelines for additional information set forth in the Agency's September 10, 2001, letter. As I emphasized during our conversation, if the Division is unable to meet its commitment for completing its NDA review by January 25, 2002, especially in view of Hill's meeting all of its commitments for submission of information as set forth in the September 10, 2001, letter, would result in severe financial hardship to the company.

We committed to submit by November 23, 2001, all outstanding data, including the 12-month safety study report, which has an adequate number of patients (314) with cumulative exposure time of greater than 6 months. This study will satisfy Dr. Ko's requirements as stated in his November 8, 2001 correspondence.

Regarding the mini-pigs, all statistical data will be included in the November 23, 2001, submission, as well as the statistician's request of November 16, 2001, for additional tables. This final submission will be hand delivered by me to the Document Room on November 23, 2001. With the November 23, 2001 submission, Hill will have met its commitment for submitting the remaining information to satisfy all of the Division's requirements. We trust that the Division will live up to its commitment to complete the review of this additional information and will meet the January 25, 2002, action date.

We look forward to the completion of the Division's review.

Sincerely yours,

Jerry Roth

cc: Mary Jean Kozma-Fornaro

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: 12/17/01

To: Nini Rameriz	**From:** Victoria Lutwak VL
Company: Hill Dermaceuticals	Division of Dermatological and Dental Drug Products
Fax number: 407-323-1871	**Fax number:** 301-827-2075/ 827-2091
Phone number: 1-800 344-5705	**Phone number:** 301-827-2073

Subject: Requests for the review of NDA 21-112

Total no. of pages including cover : 3

Comments: Please see following page(s). **This information is critical for continuing the review; would you please provide it to us by the end of Thursday (12-20-01). If this cannot be accomplished, please let me know immediately. Thank you.**

VL

Document to be mailed: ☐ YES x NO

NDA 21-112
December 17, 2001

Please provide the following
For the Medical Officer:
Deficiencies of November 22 and December 10, 2001 submissions:

1. The submission of 12/10/01 should have an **Index** (Table of Contents) to comply with 21 CFR 314.50(b).

2. The submission of 12/10/01 should have Case Report Tabulations (line listings) to comply with 21 CFR 314.50(f)(1). As the NDA is a **paper copy** NDA, listings should also be submitted in paper. Since the material in the CD is stated to be " ***12 month draft 1***", Hill should provide documentation that the paper submission is no longer draft and has been audited for accuracy.

1. Hill's letter dated 8/21/01 promised to submit a " ***Final*** Report for Study 29 ***and*** **ISS report**" by November 23, 2001. Hill has **NOT** presented an ISS to integrate the safety data from earlier studies (24 and 28), Study 29, and ongoing Study 30. For data on Study 30, all adverse events and discontinuations including pregnancies must be presented.

4. It is unclear from the material presented whether the safety data of ***patients previously treated with TRI-LUMA*** in Study 28 have been included as part of the report for Study 29. Since Study 29 is continuation of Study 28, excluding **the safety data for the first 56 days** of treatment with TRI-LUMA in this group of patients could bias the ultimate safety profile, and impact on labeling. On the other hand, safety data from ***patients who did not use TRI-LUMA*** in Study 28 should begin upon entry into Study 29. This would be consistent with the definition of study duration and completion provided by Amendment 6 of Protocol 29.

5. To be informative, the listing on adverse events (Listing 9) should incorporate data on exposure to TRI-LUMA (Listing 5.2) so that development of the **adverse events can be correlated with usage time and dose**.

6. The report for Study 29 should contain the **1572s** and **IRB approval letters** for all Investigators. Such information for Study 30 should also be provided, as only one Investigator's information has been on record in ——— ALL of their information should ALSO be submitted to the IND.

7. Questions on safety data in Study 29.
   a. Previous drug use in Study 28. What is the effect, if any, of prior treatment with a dyad on the (a) incidence of adverse events or lab abnormalities seen in Study 29, and (b) the type of adverse events in Study 29?
   b. Duration of use. What is the effect, if any, of the duration of treatment on the (a) incidence of adverse events or lab abnormalities seen in Study 29, and (b) the type of adverse events in Study 29? We can divide events by their occurrence time in relation to treatment duration [note: real treatment duration, i.e., on drug, NOT just days in the study] (0-91 days, 92-182 days, 183-273 days, 274-365 days).

8. Questions on efficacy data in Study 29.
   a. How many patients received how many courses of treatment (e.g., 1, 2, 3, 4 ..... courses)?

Tables with the following information should be provided:

Treatment duration per course	Courses of Treatment						
	1	2	3	4	5	6	etc
<4 wks	N (%)						
4 - <8 wks							
8 - <12 wks							
12 - <16 wks							
16 - <20 wks							
20 - <24 wks							
24 - <28 wks							
etc							
Total							

N = number of patients; (%) = percent of total

A Table should be provided for patients in Study 29 who came **from each of the four arms of Study 28** (4 Tables in all). An additional Table should also be provided for **ALL** patients in Study 29. The dataset on which these Tables are constructed should be provided to the Biometrics Reviewer with proper dictionary.

b. Are there differences between 1st, 2nd, 3rd, 4th ..... courses in patient responses?
c. Between treatment courses, what is the time to relapse/duration of remission, and are there differences after the 1st, 2nd, 3rd, 4th ..... course for these parameters?
d. Does efficacy relate to adverse effect, i.e., is there difference between success and failure groups in relation to adverse events or specific adverse events? The unit of analysis here should be treatment courses rather than patients. The TRI-LUMA data, but not the dyad data, from Study 28 should be part of this analysis.

9. Additional informational needs may become evident upon review of the submitted material.

****

Please provide the following
For the statisitician for Study 28:

Randomization: The issue of any selection bias in the efficacy results due to the way of assigning study sites to studies 28A and 28B as well as deviation from pre-planned randomization during the course of the trials is not addressed based on the Sponsor's submission. The Sponsor's assignment of site numbers in each study was not sequential (i.e. odd number sites as one study and even number sites as another study). It is not clear whether such assignment was a post-hoc and if so, the implication on the efficacy results. The Sponsor should provide clarification/justification to address this issue.

If you have questions, please call.
VL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

DATE: 12/26/01

To: Nini Rameriz	**From:** Victoria Lutwak
Company: Hill Dermaceuticals	Division of Dermatological and Dental Drug Products
Fax number: 407-323-1871	**Fax number:** 301-827-2075/ 827-2091
Phone number: 1-800 344-5705	**Phone number:** 301-827-2073

Subject: Requests for the review of NDA 21-112

Total no. of pages including cover: 2

Comments: Please see following page(s).

Document to be mailed: ☐ YES x NO

NDA 21-112
December 26, 2001

Please provide the following
For the Medical Officer:

1. In the ISS submitted last week, Section 25 is for Tables, and the ISS Table of Contents gives pp 100-455 for these Tables. Instead, the report ends on page 115, with the statement: "Please see Section IX for all Tables". This refers to Section IX of the submission of 12/20/01, which is not part of the ISS document. The ISS should be a stand-alone document, and if cross-reference is made to Section IX of another document, the pertinent Table numbers should be specified for the cross-reference, e.g., Table 1 of ISS refers to which Table of Section IX of that submission, etc. All Tables of the ISS should be accounted for.

2. Please specify the cleanser and the sunscreen provided to patients in Study 28 for mandatory use, or where this can be found in the protocol or study report. Please specify the instructions on the daily use of the sunscreen.