Because of the above concerns, we request that you submit a plan that outlines your course of action or additional procedures to ensure that the above noted deficiencies will not recur in any future studies that you might conduct.

We wish to remind you that we will continue to monitor your research activities to ensure that you have appropriately modified your practices and that the corrective measures implemented by you are indeed in compliance with good clinical practices and FDA regulation,

We appreciate the cooperation shown Investigator Lochner during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301)594-1032.

Sincerely,

/S/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Jan 21 2000

Isaac Willis, M.D.
3280 Howell Mill Road, N.W.
Atlanta, Georgia 30327

Dear Dr. Willis:

Between November 16 and 19, 1999, Ms. Barbara Carmichael, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #24) of the investigational drug ———— , performed for Hill Dermaceutical, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Mr. Lochner presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. The discussion included:

1. Your failure to conduct the study in accordance with the approved protocol in that: a) you enrolled subjects # 29 and #53 despite not meeting the criteria of having a minimum of three months of stable melanosis; b) you enrolled subjects # 6, #14 and #23 without documenting the duration of the hyperpigmentation; and c) subjects #10 and #73 were enrolled in the wrong extended phase of the study.

2. Your failure to report all protocol revisions to IRB for approval.

3. Your failure to keep adequate drug accountability records.

4. The consent form used in this study did not include: a) a specific statement of the approximate number of subjects involved in the study; and b) a statement of how the subject will be compensated, preferably stating that payments to subjects for participation in the study will be prorated and not contingent on completion of the study.

Because of the departures from FDA regulations, we request that you inform us in writing of the steps you have taken or plan to take to ensure that the above noted deficiencies will not recur in any future studies that you might be involved.

We appreciate the cooperation shown Investigator Carmichael during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301) 594-1032.

Sincerely,

/S/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER
FOR DRUG EVALUATION AND RESEARCH

FINAL EVALUATION OF CLINICAL INVESTIGATOR INSPECTIONS.

DATE: March 7 , 2000

NDA 21-112
HFD-540
SPONSOR: Hill Dermaceuticals
Product
Chemical Type: 4
Potential: S
Indications : Treatment of Individuals with Cutaneous Melanosis
Project Manager: Vicky Lutwak
Medical Officer: Hon Sum Ko

I. Background:

These routine inspections were part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which NDA 21-112 approval may be based and to assure that the rights and welfare of the human subjects of those studies were protected. These inspections were conducted in accordance with CP 7348.811, Clinical Investigators, in addition to concentrate in comparing source documents, CRFs , and data listings in regard to primary endpoints, adverse drug events reporting and discontinued subjects in these protocols. Sites selected in corroboration between division medical officer, Dr. Hon Sum Ko and DSI reviewer, Dr. Jose Carreras.

NAME	TY	CITY	ST	ASSIGNED	INSPECTED	RECEIVED	LETTER	CLASS
TOROK	DA	MEDINA	OH	15-OCT-99	05-NOV-99	14-DEC-99		OAI
WILLIS	DA	ATLANTA	GA	15-OCT-99	16-NOV-99	08-FEB-00		VAI
KELLY	DA	LOS ANGEL	CA	15-OCT-99	06-DEC-99	08-FEB-00		VAI

Key to Classifications
NAI = No deviation from regulations
VAI = Minor Deviation(s) from regulations
OAI = Data not acceptable

Site #1
Helen M. Torok, M.D.
Medina, Ohio
protocol #24

This investigator failed to conduct the study in accordance with the relevant protocol in that:
a) randomization of study subjects was not allocated in sequential order evidenced by 17 subjects not allocated in chronological order and 5 subjects re-enrolled purposely in the test medication arm. b) enrolling subjects # 35, #80, #85, #89, #83 #98 and #17 despite not meeting the inclusion or exclusion criteria; c) enrolling subjects #4 and #96 in the long term phase of the study despite not meeting the criteria of reaching an efficacy score of 1 at the end of the initial eight week of treatment. d) photographs were taken for subjects #1, #8 # 11,# 14, #15, #16 and #44. e) adequate accountability records were not maintained for the receipt, distribution and return of study medication.

There was no documentation of the IRB approval for recruiting ads.

The consent forms lacks;
a) a statement of the approximate number of subjects involved in the study;
b) If available, a statement of how the subject will be compensated preferably stating that payments to subjects for participation in the study will be prorated and not contingent on completion of the study.

We also noted that approximately 20 subjects were treated prior to the start of the study.

This EIR was discussed Dr. Hon Sum Ko the Medical Officer. In addition to the above violation, the bias induced by not maintaining adequate randomization, having coded color crimps in test medication tubes, having an inadequately designed randomization master key this study is practically an open label study. We agreed that the data should not be considered as generated by a adequate and well controlled study. and thus should not be used to support NDA #21-112.

Site #2

A. Paul Kelly, M.D.
Los Angeles, California 90059
protocol #24

This investigator failed to conduct the study in accordance with the approved protocol in that nine subjects were enrolled in the study despite not meeting the inclusion criteria of a moderate to severe hyperpigmentation and also ˈiled to maintain adequate records in that adverse events reported were not documented for start, durations and ˌnding for subjects # 5 #14 #31 #32 #83 and 114.
Site #3

ıssac Willis, M.D.
Atlanta, Georgia 30327
protocol #24

This investigator failed to conduct the study in accordance with the approved protocol in that he:

a) enrolled subjects # 29 and #53 despite not meeting the criteria of having a three months of stable melanosis as required by the protocol b) enrolled subjects # 6, #14 and 23 without documenting the duration of the hyperpigmentation in the case report form, c) there was no documented reason why subjects #1, #4, #6, and #35 were not enrolled in the long term follow up regimen despite qualifying and d) subjects # 10 and #73 were enrolled in long term follow ups regimen which they were not qualify to received. He also failed to report all protocol revisions to IRB for approval and failed to keep adequate drug accountability records.

APPEARS THIS WAY
ON ORIGINAL

OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS :

Objectionable conditions were found in Dr Torok site which would preclude the use of their data submitted in support of nding NDA.

Jose A. Carreras, M.D.

cc:
NDA 21-112
Division File
HFD-47/Currier
HFD-47/GPC2/ Elhage

APPEARS THIS WAY
ON ORIGINAL

Number of Pages Redacted 2

❖❖❖

Confidential,
Commercial Information

Application: NDA 21112/000
Stamp: 22-MAR-1999
Regulatory Due: 22-JAN-2000
Applicant: HILL DERMAC
2650 SOUTH MELLONVILLE AVE
SANFORD, FL 32773
Priority: 4S
Org Code: 540

Action Goal:
District Goal: 23-NOV-1999
Brand Name: [redacted] FLUOCINOLONE ACETONIDE/HYDROQ
Estab. Name:
Generic Name: FLUOCINOLONE ACETONIDE/HYDROQUINONE/TRET

Dosage Form: (CREAM)
Strength: 0.01%,4.0%,0.05%

Application Comment: THIS CREAM CONTAINS THREE (3) ACTIVE COMPONENTS. THE STRENGTH OF THE CREAM IS LISTED AS 0.01% (FLUOCINOLONE ACETATE), 4.0% (HYDROQUINONE) AND 0.05% (TRETINOIN). (on 18-MAY-1999 by E. PAPPAS (HFD-540) 301-827-2066)

FDA Contacts: M. KOZMA-FORNARO (HFD-540) 301-827-2023 , Project Manager
E. PAPPAS (HFD-540) 301-827-2066 , Review Chemist
W. DECAMP II (HFD-540) 301-827-2041 , Team Leader

Overall Recommendation:
Establishment: [redacted]

DMF No:
AADA:
Responsibilities:
Profile: CTL
OAI Status: NONE
Estab. Comment: ALSO, USP REQUIREMENTS TESTING, PER EMAIL MESSAGE FROM E. PAPPAS. (on 30-SEP-1999 by S. FERGUSON (HFD-324) 301-827-0062)
THIS FACILITY PERFORMS THE MICROBILOGY TESTING ON THE FINISHED PRODUCT. (on 30-SEP-1999 by E. PAPPAS (HFD-540) 301-827-2066)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	30-SEP-1999				PAPPAS
SUBMITTED TO DO	30-SEP-1999	GMP			FERGUSONS
DO RECOMMENDATION	18-OCT-1999			ACCEPTABLE	KRODEN

BASED ON FILE REVIEW
THE PROFILE CLASS FOR THIS FIRM IS NOT OIN. THEY ARE A CONTROL TESTING LABORATORY ONLY (CTL). A GMP PRE-APPROVAL INSPECTION WAS CONDUCTED AT [redacted] ON 6/15-7/19/99 AND NO FDA 483 WAS ISSUED. CHEMICAL AND MICROBIOLOGICAL TESTING OPERATIONS WERE EVALUATED DURING THAT INSPECTION. BASED ON THE INSPECTION FINDINGS, KAN-DO RECOMMENDS APPROVAL OF THIS APPLICATION.

OC RECOMMENDATION	19-OCT-1999			ACCEPTABLE	FERGUSONS

DISTRICT RECOMMENDATION

Establishment: 1036365
HILL DERMACEUTICALS INC
2650 SOUTH MELLONVILLE AVE
SANFORD, FL 32773

DMF No:
AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: OIN
OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	18-MAY-1999				PAPPAS
SUBMITTED TO DO	20-MAY-1999	GMP			EGASM
ASSIGNED INSPECTION	23-JUN-1999	PS			PFIGAROL

Establishment:

DMF No: AADA:
Responsibilities:
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	18-MAY-1999				PAPPAS
OC RECOMMENDATION	19-MAY-1999			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment:

DMF No: AADA:
Responsibilities:
Profile: CTL OAI Status: NONE
Estab. Comment:

E.

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	22-OCT-1999				PAPPAS
OC RECOMMENDATION	22-OCT-1999			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment:

DMF No: AADA:
Responsibilities:
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	18-MAY-1999				PAPPAS
OC RECOMMENDATION	19-MAY-1999			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment:

DMF No: AADA:
Responsibilities:
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	18-MAY-1999				PAPPAS

SUBMITTED TO DO	20-MAY-1999 GMP			EGASM
ASSIGNED INSPECTION	30-SEP-1999 PS			KNORTON
INSPECTION SCHEDULED	05-OCT-1999	15-NOV-1999		KNORTON
INSPECTION PERFORMED	14-JAN-2000	16-DEC-1999		KNORTON
DO RECOMMENDATION	14-JAN-2000		ACCEPTABLE	KNORTON

INSPECTION

12/13-16/99 INSPECTION REVEALED 5 DEVIATIONS, WHICH THE FIRM ADEQATELY ADDRESSED DURING THE INSPECTION. DISTRICT RECOMMENDS APPROVAL.

OC RECOMMENDATION	14-JAN-2000		ACCEPTABLE	FERGUSONS

DISTRICT RECOMMENDATION

APPEARS THIS WAY ON ORIGINAL

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS JAN 20 200(
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-112 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 12/15/99

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	3/19/99	3/23/99	3/26/99
AMENDMENT/BC	4/29/99	5/3/99	5/13/99
AMENDMENT/NC	4/29/99	5/10/99	5/19/99
AMENDMENT/NC	5/07/99	5/10/99	5/11/99
AMENDMENT/NC	6/04/99	9/24/99	10/06/99
AMENDMENT/BC	6/23/99	6/25/99	7/07/99
AMENDMENT/NC	8/19/99	9/24/99	10/06/99
AMENDMENT/NC	9/24/99	9/27/99	10/06/99
AMENDMENT/NC	11/08/99	11/09/99	11/18/99

NAME & ADDRESS OF APPLICANT: Hill Dermaceuticals, Inc.
2650 South Mellonville Ave.
Sanford, Florida 32773

DRUG PRODUCT NAME
Proprietary: —
Nonproprietary/USAN: Fluocinolone acetonide; Hydroquinone; Tretinoin
Code Names/#'s: none
Chem.Type/Ther.Class: **4 S**

ANDA Suitability Petition/DESI/Patent Status:
N/A [if applicable]

PHARMACOL.CATEGORY/INDICATION: —

DOSAGE FORM: Cream

STRENGTHS: 0.1%; 4.0%; 0.05%

ROUTE OF ADMINISTRATION: Topical

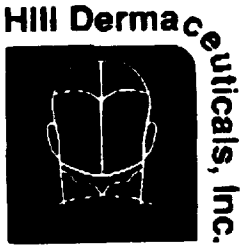
DISPENSED: X_ **Rx** _____ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

(1) Tretinoin USP:

Chemical Name: Retinoic Acid
all-trans-Retinoic Acid
Vitamin A Acid

Also known as:



"The Scalp Company"

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

August 9, 1999

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Bldg II, 2nd floor, Room N 249
Rockville, MD 20850
AttN: Ms. Vickey Lutwak
Project Manager

RE: Tradename for " — Cream"

The name proposed for the combination drug product 0.01% Fluocinolone acetonide, 4% Hydroquinone, 0.05% Tretinoin is:

—

To date, this is the only tradename I am able to send you.

Please advise on further actions. Also, if there are other items concerning this product that need to be addressed, pressing or otherwise, please let us know immediately so we can work on them as soon as possible.

Thank you very much.

Sincerely,

Nini Ramirez
Medical/Regulatory Affairs

Hill Dermaceuticals, Inc.

"The Scalp Company"

FACSIMILE TRANSMISSION RECORD

DATE: 9 AUGUST 1999 **Pages (including cover)** 2

TO: Ms VICKEY LUTWAK, PROJECT MANAGER

COMPANY: FDA / CDER

FAX PHONE #: (301) 827-2091 **My Fax # (407) 323-1871**

Tel. no. # (407) 323-1887

MESSAGE: RE: TRADENAME PROPOSED

Thank you

FROM: NINI RAMIREZ

8/10/99

CC: Ernie Pappas

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

FILE COPY

WD
8/16/99

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Mr Dan Boring, Chair, (HFD-530)

From: Division of Dermatologic and Dental Drug Products (HFD-540)
Attention Ernie Pappas Phone: 827-2066

Date: 9/24/96

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: ~~~ NDA# 21-112

Company Name: Hill Dermaceuticals, Inc.

Established name, including dosage form: 0.1 % fluocinolone acetonide, 4% hydroquinone, and 0.05% tretinoin cream

Other trademarks by the same firm for companion products: N.A.

Indications for Use (may be a summary if proposed statement is lengthly): Treatment of cutaneous melanosis

Initial comments from the submitter (concerns, observations, etc.):

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Sept.95

CSO/HFD-540
cc Vickey Lucasek

Hill Dermaceuticals, Inc.

"The Scalp Company"

2650 South Mellonville Avenue • Sanford, Florida 327[illegible] • 407-323-1887 • Fax: 407-649-9213

August 9, 1999

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Bldg II, 2nd floor, Room N 249
Rockville, MD 20850
AttN: Ms. Vickey Lutwak
Project Manager

RE: Tradename for [redacted] Cream

The name proposed for the combination drug product 0.01% Fluocinolone acetonide, 4% Hydroquinone, 0.05% Tretinoin is:

To date, this is the only tradename I am able to send you.

Please advise on further actions. Also, if there are other items concerning this product that need to be addressed, pressing or otherwise, please let us know immediately so we can work on them as soon as possible.

Thank you very much.

Sincerely,

Nini Ramirez
Medical/Regulatory Affairs

Number of Pages Redacted 13

❖❖❖

Draft Labeling
(not releasable,

Electronic Mail Message

Date: 12/21/99 4:07:44 PM
From: Sammie Beam (BEAMS)
Subject: Proprietary name consult #99-108

Hello,

This is to acknowledge receipt of consult for NDA 21-112.

Sammie Beam
Project Manager
Med Errors/OPDRA
HFD 400 15B03
301-827-3161
FAX 301-480-8173

TPademic

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
Carol Holquist, Safety Evaluator
(OPDRA; HFD-400)

DATE RECEIVED:	**DUE DATE:**	**OPDRA CONSULT #:** 99-108
December 14, 2000	January 22, 2000	

TO:

Johnathan Wilken, MD
Director, Division of Dermatologic and Dental Drug Products
HFD-540

PRODUCT NAME:	**MANUFACTURER:**
Triluma (primary name) and ~~———~~ (Fluocinolone acetonide 0.01%, Hydroquinone 4% and Tretinoin 0.05%) **NDA #:** 21-112	Hill Dermaceuticals, Inc.

PDRA RECOMMENDATION:

OPDRA has no objection to the use of the proprietary name Triluma, however OPDRA does not recommend the use of the proprietary name ~~———~~. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA.

/S/ 2/21/2000
Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

/S/ 1/27/00
Peter Honig, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 19, 2000

NDA# 21-112

NAME OF DRUG: Triluma (primary name) and

(Fluocinolone acetonide 0.01%, Hydroquinone 4% and Tretinoin 0.05%)

NDA HOLDER: Hill Dermaceuticals, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Dermatologic and Dental Drug Products (HFD-540) to review the proposed proprietary drug name, Triluma and the alternate name —— . regarding potential name confusion with existing proprietary/generic drug names.

In December 1999, OPDRA reviewed three other proprietary names for this product —— and —— . We refer you to OPDRA consult 99-036, in which we did not recommend the use of any of these names. In addition, the CDER's Labeling and Nomenclature Committee (LNC) reviewed the same three names on September 24 and November 10, 1999, respectively. The committee concluded that

PRODUCT INFORMATION

This product contains fluocinolone acetonide, hydroquinone and tretinoin in a hydrophilic cream base for topical dermatological use only. It is a depigmenting agent intended for the treatment of cutaneous melanosis for skin types II and III. The cream is applied to the face and/or neck, once daily before bedtime. During the day, the patient is directed to use sunblock or sunscreen, and protective clothing. Avoidance of sun exposure is ideal and patients may also utilize moisturizers during the day. The cream will be supplied in 1 oz aluminum tubes.

APPEARS THIS WAY
ON ORIGINAL

II. RISK ASSESSMENT:

In order to predict the potential for medication errors and to determine the degree of confusion associated with the proposed names, Triluma ——— with other approved and unapproved drug names, the medication error staff of OPDRA searched ALTMEDDEX Intranet Series, 1999, which includes the following published texts: DrugDex, Poisindex, Martindale, RPS Herbal Medicines, Index Nominum, and Physicians' Desk Reference (1999). Additional publications utilized to search for Potential sound-alike or look-alike names to approved drugs were the American Drug Index (43rd Edition), Drug Facts and Comparisons (Updated Monthly), the Electronic Orange Book, CDER's New Approvals, and the US Patent and Trademark Office online database. OPDRA also searched several FDA databases for potential sound-alike or look-alike names to unapproved/approved drugs (Establishment Evaluation System (EES), Drug Product Reference File (DPR), Decision Support System (DSS) and the LNC database). In addition, OPDRA conducted an internal study of written and verbal analysis of the proposed proprietary names, involving health care practitioners within FDA, to evaluate potential errors in handwriting and verbal communication of the names. This exercise was conducted to simulate an actual practice setting.

A. STUDY CONDUCTED BY OPDRA

Methodology:

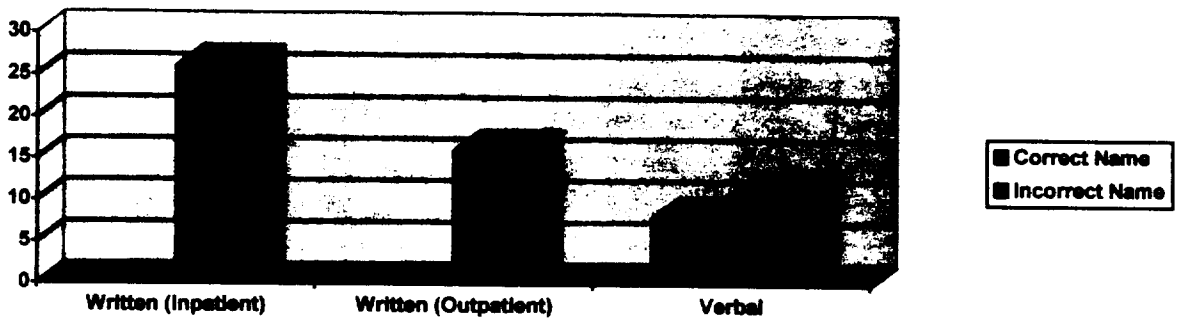
Each study involved 92 health professionals, comprised of pharmacists, physicians, and nurses within FDA, to determine the degree of confusion of Triluma ——— with other drug names due to the similarity in handwriting and verbal pronunciation of the names. OPDRA staff members wrote one inpatient order and four outpatient prescriptions, each consisting of unknown drug products in addition to a prescription for Triluma ——— (see below). These prescriptions were scanned into the computer and a random sample of the written orders, were then delivered to the participating health professionals via e-mail. In addition, one pharmacist recorded the outpatient orders on voice mail. The voice mail messages were then sent to the participating health professionals for their review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RXs: triluma Use hs UD 3 refills	Give triluma for use at bedtime as directed. Dispense one and give 3 refills.
——— UD months supply 3 refills	Give ——— Use as directed. Dispense 3 months supply and give 3 refills.
Inpatient RX: Continue on home meds: ——— UD Start triluma use hs UD	

Results:

1. Triluma Study

We received responses from sixty-one out of ninety-two participants (66%), eight of which interpreted the name correctly. Sixteen participants interpreted outpatient prescription orders, twenty-six interpreted inpatient orders, and nineteen interpreted verbal orders. The results are as follows:



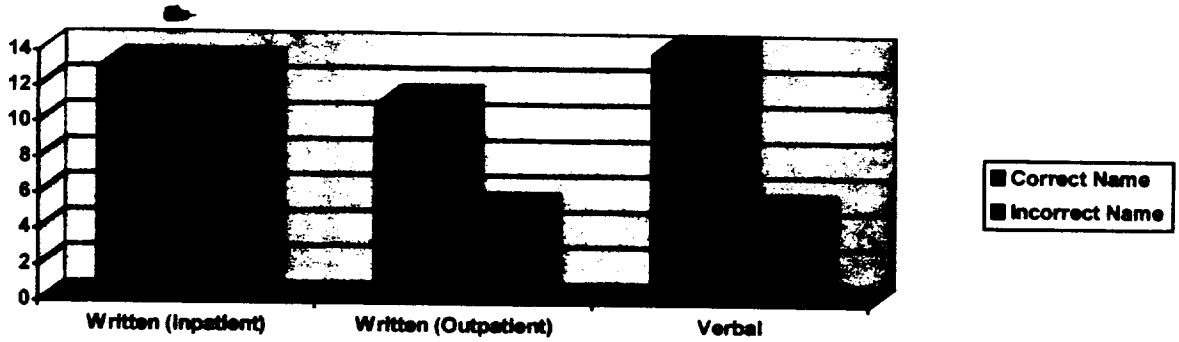
All outpatient and inpatient prescriptions were interpreted incorrectly. Two participants interpreted "trilevlen" as the name and three others thought the name sounded similar to "trilevlen". Thirteen percent of the participants interpreted the name correctly. The remaining responded with the following incorrect interpretations:

Verbal	Written
	*Trilevlen

*Currently marketed product.

2. Study

We received responses from sixty-one out of ninety-two participants (66%), thirty-eight of which interpreted the name correctly. Sixteen participants interpreted outpatient prescription orders, twenty-six interpreted inpatient orders, and nineteen interpreted verbal orders. The results are as follows:



Three participants interpreted —— as the name on verbal orders and one on a written prescription. Two others thought the name sounded similar to —— and one participant stated it "sounds like a birth control pill". In addition, one participant stated "it sounds like provera". Sixty-one percent of the participants interpreted the name correctly. The remaining responded with the following incorrect interpretations:

Verbal	Written
*Trivora ——	*Trivora

*Currently marketed product.

B. FOCUS GROUP FINDINGS

The group identified and discussed the following sound-alike/look-alike drug names (Trivora, Levora, Provera, Covera, Trilone, Trinalin and Trilevelen).

Product	Dosage form(s), Generic name	Usual dose*	Other
Trilu[redacted]	Topical Cream (Fluocinolone acetonide 0.01%, Hydroquinone 4% and Tretinoin 0.05%)	The cream is applied to the face and/or neck, once daily before bedtime.	
Trivora	Tablet, Triphasic Oral Contraceptive Levonorgestrel and Ethinyl estradiol	One daily	S/A (look-alike) per OPDRA.
Levora	Tablet, Monophasic Oral Contraceptive Ethinyl estradiol and Levonorgestrel	One daily	L/A per OPDRA
Provera	2.5 mg, 5 mg and 10 mg Tablet Medroxyprogesterone	5-10 mg daily for 12-14 days per month starting on Day 1 or Day 16.	S/A per OPDRA

Product Name	Dosage form(s), Generic name	Usual dose*	Other
Triluma®	Topical Cream (Fluocinolone acetonide 0.01%, Hydroquinone 4% and Tretinoin 0.05%)	The cream is applied to the face and/or neck, once daily before bedtime.	
Covera	180 mg, 240 mg - Extended-release Tablet Verapamil HCl	Once daily at bedtime.	L/A per OPDRA
Trilone	Injection Triamcinolone Diacetate; 40 mg/mL	2.5 to 60 mg/day	S/A per OPDRA
Trinalin	Tablet Combination of Azatadine maleate 1 mg, Pseudoephedrine sulfate 120 mg	One tablet every 12 hours	S/A (look alike) per OPDRA
Trilevelen	Tablet, Triphasic Oral Contraceptive Levonorgestrel and Ethinyl estradiol	One daily.	L/A

After discussion, the group determined the following names were too close to the proprietary name

⇒Trivora ——— is just one letter off. The letters "o" and "e" can easily be misinterpreted for each other especially when written in script.

⇒Levora, Provera and Covera look and sound too similar to ——. "T's" and "L's" are often confused when written. Provera, Covera and ——— all end in "vera".

Trilone, Trinalin and Trilevelen were considered to have a low potential for confusion with Triluma when written and spoken. The group did not believe these names would pose a significant safety risk.

C. DISCUSSION:

The results of the verbal and written analysis studies demonstrate thirty-eight out of sixty-one participants interpreted the proprietary name ——— correctly and eight out of sixty-one interpreted the proprietary name Triluma correctly. We recognize that low scores of correct interpretations would be common for all unapproved drug product names because health professionals are not familiar with the name. The majority of respondents provided misspelled variations of the drug name but these responses generally were phonetic variations of the name. The inaccurate interpretations of the proposed names did overlap with existing approved drug products. Triluma was confused with Tri-levlen, a birth control pill. OPDRA does not believe there is a significant safety risk associated with this. Trivora was confused with Trivora, a birth control pill. In this case a greater percentage of the participants (8%) either interpreted the name incorrectly or stated it sounded too similar to Trivora. poses a higher potential to be confused with several other marketed drugs on verbal orders as well as written orders due to the spelling of the name. OPDRA believes this name poses a significant safety risk

The proprietary names do not contain any USAN stems. In addition, the searches conducted within OPDRA did not uncover any additional names that were not discussed within the focus group.

III. RECOMMENDATIONS:

OPDRA has no objections to the use of the proprietary name Triluma, however we do not recommend the use of the proprietary name ——— . This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward. The firm could be asked to submit information in its periodic safety updates, in which the firm will provide the names of all FDA approved drug names from 1/19/2000 and certify that this name does not sound-alike or look-alike to those names. This information should be forwarded to OPDRA for review.

If you have further questions or need clarifications, please contact Carol Holquist at 301-827-3244.

/S/

1/19/2000

Carol Holquist, RPh
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Conc: /S/

1/21/2000

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

APPEARS THIS WAY
ON ORIGINAL

CC:

NDA 21-112
Office Files
HFD-540; DivFiles; Vickey Lutwak, Project Manager
HFD-540; Johnathan Wilken, Division Director
HFD-440; Claudia Karwoski, Safety Evaluator, DDREI, OPDRA
HFD-400; Jeffrey Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Deputy Director, OPDRA
HFD-002; Murray Lumpkin, Acting Director, OPDRA

APPEARS THIS WAY
ON ORIGINAL

Office of Post-Marketing Drug Risk Assessment

Memo

To: Jonathan Wilken, MD
Director, Division of Dermatologic and Dental Drug Products
HFD-540

From: Alina R. Mahmud, R.Ph.
Safety Evaluator, Office of Post-Marketing Drug Risk Assessment
HFD-400

Through: Jerry Phillips, R.Ph.
Associate Director, Office of Post-Marketing Drug Risk Assessment
HFD-400

CC: Vickey Lutwak
Project Manager
HFD-540

Date: September 11, 2001

Re: OPDRA Consult 01-0191; Tri-Luma (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%); NDA 21-112

This memorandum is in response to an August 31, 2001 request from your Division for a re-review of the proprietary name, Tri-Luma as well as the draft package insert, container and carton label. The sponsor has modified the name from Triluma to Tri-Luma with the addition of a hyphen.

OPDRA has not identified any additional proprietary or established names that have the potential for confusion with Tri-Luma since we conducted our initial review on January 22, 2000 (OPDRA consult 99-108). Therefore, we have no objections to the use of this proprietary name. In addition, OPDRA has no comments regarding the packaging and labeling submitted for review.

OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before

NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact Alina R. Mahmud at 301-827-0916.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Alina Mahmud
9/13/01 09:49:39 AM
PHARMACIST

Jerry Phillips
9/13/01 09:55:37 AM
DIRECTOR

APPEARS THIS WAY
ON ORIGINAL

Office of Drug Safety

Memo

To: Jonathan Wilkin, MD
Director, Division of Dermatologic and Dental Drug Products
HFD-540

From: Kevin Dermanoski, RPh
Safety Evaluator, Division of Medication Errors and Technical Support
HFD-400

Through: Carrol Holquist, RPh
Deputy Director, Division of Medication Errors and Technical Support
HFD-400

CC: Vickey Lutwak
Project Manager
HFD-540

Date: January 9, 2002

Re: OPDRA Consult 01-0191-1; Tri-Luma (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%); NDA 21-112

This memorandum is in response to the December 28, 2001 request from your Division for a re-review of the proprietary name, Tri-Luma.

The Division of Medication Errors and Technical Support (DMETS) has not identified any additional proprietary or established names that have the potential for confusion with Tri-Luma since we conducted our initial review on January 22, 2000 (OPDRA consult 99-108), and our follow-up review on September 11, 2001 (OPDRA consult 09-0191). Therefore, we have no objections to the use of this proprietary name.

DMETS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before

NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact Kevin Dermanoski at 301-827-6277.

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NDA ORIG AMENDMENT

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

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
AUG 22 2001
MEGA

RE: NDA 21-112 TRI-LUMA Cream
Requested Information

Dear Ms Lutwak,

The following items are listed in response to your request.

A. Listing of the timelines for the final report on the analytical methods validation to determine plasma concentration of Fluocinolone acetonide, Hydroquinone and Tretinoin in humans are as follows:

- Fluocinolone acetonide (HPLC)
  Human plasma.....September 24, 2001
- Fluocinolone acetonide (
  Human plasma.....September 25, 2001
- Hydroquinone (HPLC)
  Human plasma.....September 24, 2001
- Tretinoin
  Human plasma.....September 27, 2001

B. The timeline estimated for the submission of the final report on the Mini pig Study (Chronic dermal application), will be 3 weeks from the date of this letter, on September 12, 2001.

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NDA 21-112
TRI-LUMA Cream

N.000/MR
NDA ORIG AMENDMENT

August 22, 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: Request for conference with CMC department

Dear Ms. Lutwak,

Hill Dermaceuticals, Inc. is formally requesting a telephone conference with Dr. DeCamp and Mr. Pappas, with the CMC department, on the following issues. We would like to discuss the agenda presented below.

1. Proposal to use a container system (tube) without an end sealant.
   - Trade size tubes and sample size tubes will be placed on accelerated stability for 90 days, at which time the analytical test results will be submitted to the Agency.
   - Three packaging batches will be placed on stability.
   - Analytical testing to be performed will confirm the competence of the tube to maintain the claimed potency of each active component in the cream.
   - This plan of action will be initiated as soon as possible.

2. Alternate plan: to use packaging tubes with an end-sealant different from [redacted]. If this alternate plan is also chosen, Hill Dermaceuticals will provide the following:
   - DMF for the end-sealant
   - 90 days Accelerated Stability results on 3 packaging batches.

3. Questions:
   - If a different end-sealant is used, is it a requirement to conduct another leaching/migration test?

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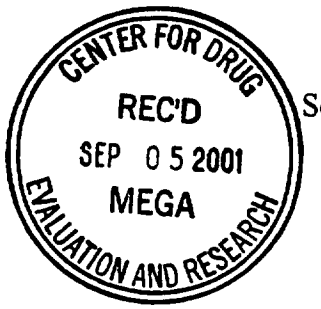
NDA 21-112
TRI-LUMA



September 4, 2001

Jonathan K. Wilkin, M.D. / Director
FDA / CDER / DDDDP
9201 Corporate Blvd., HFD-540
Rockville, MD 20850
ATTN: Ms. Vickey Lutwak / Project Manager

RE: Additional Information: Amendment to Pending NDA Application

Dear Dr. Wilkin:

Listed below please find data that were inadvertently missed for Pivotal **Study 28A,** of the Amendment to NDA 21-112, filed 07/24/01.

1. The following listings are contained:
   - *Listing 3:* *Inclusion Criteria*
   - *Listing 4:* *Exclusion Criteria*
   - *Listing 11:* *Visit Comments*
   - *Listing 12:* *Visit*

2. *Listing 9: Investigator and Patient Global Assessment Day* 56, page 18 of 18.

The following are corrections for the listings given below:

3. *Listing 7: Final Status* has duplicate pages (Statistical Section, pages 8 0631-8 0633 and 8 0634- 8 0636). Please disregard duplicate pages 8 0634-8 0636.

4. *Listing 1: Demographics* has been included twice (Statistical Section, pages 8 0645-8 0663 and 8 0664-8 0682). Please disregard duplicate pages 8 0664-8 0682.

We apologize for any inconvenience this may have caused the Agency. Should you have questions or concerns please do not hesitate to contact us. Thank you again for your continued support and understanding.

Sincerely,
Criss Molasso
Criss Molasso
Assistant Regulatory Affairs

cc: Nini Ramirez, MD / Director, Medical/Regulatory Affairs

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NDA 21-112
TRI-LUMA Cream

September 18, 2001

N-000/BP
NDA ORIG AMENDMENT

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SEP 19 2001
MEGA/CDER

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
Nonclinical Pharmacology and Toxicology Section: Final Report on the "26 Weeks Chronic Dermal Application Toxicity Study in Mini Pigs" (BSR Study # 082-002)

Dear Dr. Wilkin,

This submission contains the Final Report to the toxicity study in mini pigs, "26 Weeks Chronic Dermal Application Toxicity Study in Mini Pigs" BSR Study No. 082-002.

We apologize for the delay with this filing. Your understanding and kind consideration is much appreciated.

Respectfully,

Rosario G. Ramirez
Director
Medical / Regulatory Affairs

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NDA 21-112
TRI-LUMA Cream

September 19, 2001 N-000/BS

NDA ORIG AMENDMENT

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SEP 2 1 2001

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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: Response to Information Request: Statistical Review
Amendment to a pending application, NDA 21-112

Dear Dr. Wilkin,

In response to the information request from the Statistics division, the following information is provided to facilitate the review.

FDA: "Electronic SAS data sets (in transport file format) are needed for the review process".
Hill Dermaceuticals: The requested SAS data sets are provided on the attached CD. More detail on these data sets may be found in ***Section 1***.

FDA: "Request analyses on the primary and the secondary efficacy endpoints based on the per-protocol (PP) population originally defined in the protocol (i.e., all subjects who do not violate the protocol and complete 8-week of treatment)".
Hill Dermaceuticals: The requested analyses were performed and are presented in ***Section 2***. With the PP population definition of at least 8 weeks of treatment (allowing the subjects to report to the site up to 1 week early), a total of thirteen additional subjects were dropped from the analyses data sets, seven subjects from study 28A and six subjects from study 28B. The results, however, did not change. In other words, no significant p-value became non-significant and no non-significant p-value became significant.

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FDA: "Request subgroup analysis by disease severity at baseline".
Hill Dermaceuticals: These analyses were performed and are presented in ***Section 3*** of this document. Despite the fact that direction of the effects remained favorable, a very minimal change was observed for the individual studies due to the small sample size in two subgroups (moderate and severe) and for only two comparisons (Investigator global improvement and Static global assessment), Table 28A-19.1 and Tables 28B-20.2, 21.2. Otherwise, all other results remained the same; that is, statistically significant. However, when sufficient power is provided within each subgroup by combining the two studies, results were the same as originally submitted. That is, all p-values remained highly significant.

FDA: "Request detailed description of the randomization schedule for studies 28A and 28B".
Hill Dermaceuticals: The randomization schedule may be found in ***Section 4***.

Diskettes are also provided for the PP population analyses and subgroup analysis on baseline disease severity.

Respectfully,

Rosario G. Ramirez

Rosario G. Ramirez
Director
Medical / Regulatory Affairs

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NDA 21-112
TRI-LUMA Cream

September 26, 2001

ORIGINAL

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

Bc
CMC AMENDMENT

RE: Amendment to a pending application, NDA 21-112
Additional Information to CMC section: New manufacturer of tube end sealant.

Dear Dr. Wilkin,

The purpose of this letter is to inform the Agency, specifically the Chemistry reviewers, that Hill Dermaceuticals will be providing stability data on 30-gram tubes with an end sealant different from — sealant originally filed in the NDA amendment for TRI-LUMA Cream on July 24, 2001. The company that manufactures the new end sealant is —.

Hill Dermaceuticals, Inc. has obtained a DMF Authorization Letter from — to reference Hill NDA 21-112 for an alternate end sealant, product 7GZ216. Hill has also procured 30-gram tubes with end sealant 7GZ216 to be placed on stability studies. As previously committed, data from 60 days and 90 days accelerated stability studies will be submitted as soon as they become available.

Enclosed, please find a copy of the DMF authorization letter from —. Please advise if further information is needed. Thank you.

Respectfully,

Rosario G. Ramirez
Director
Medical / Regulatory Affairs

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HLL Dermaceuticals, Inc.

Specialty Dermatologicals for Children & Adults

NDA 21-112
TRI-LUMA Cream

October 25, 2001

N-000/BB

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: Biopharmaceutical: Validation Reports for ——— analysis in Human Plasma.
Amendment to a pending application, NDA 21-112

Dear Dr. Wilkin,

This submission contains the validation reports for ——— analysis for Tretinoin and Fluocinolone acetonide in human plasma.

After conferring with the Biopharm reviewer, Ms Abi Adebowale, the validation reports for the high-pressure liquid chromatography (HPLC) analysis of Hydroquinone and Fluocinolone acetonide in human plasma will be submitted on November 1, 2001, via overnight delivery.

We apologize for the unexpected delay of the reports on HPLC analysis. Your kind consideration is greatly appreciated.

Sincerely,

Rosario G. Ramirez
Director
Medical / Regulatory Affairs

Phone 1.800.344.5707 • Fax 1.407.649.9213

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NDA 21-112
TRI-LUMA Cream

November 1, 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: Biopharmaceutical: Validation Reports for HPLC analysis in Human Plasma.
Amendment to a pending application, NDA 21-112

Dear Dr. Wilkin,

This submission contains the validation reports for high-pressure liquid chromatography (HPLC) analysis for Fluocinolone acetonide and Hydroquinone in human plasma.

Included with the reviewer's copy are 4 diskettes containing the individual reports:

1. —— analysis for Tretinoin in human plasma.
2. —— analysis for Fluocinolone acetonide in human plasma.
3. HPLC analysis for Fluocinolone acetonide and Hydroquinone in human plasma.

Thank you for your continued support.

Sincerely,

Rosario G. Ramirez
Director
Medical / Regulatory Affairs

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NDA 21-112
TRI-LUMA

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November 22, 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:

In reference to NDA 21-112, TRI-LUMA Cream, for the indication melasma of the face, Hill Dermaceuticals, Inc. is submitting this amendment to a pending New Drug Application (NDA 21-112). This amendment is in response to FDA Information Request Letter dated September 5, 2001 (copy enclosed).

Also included in this submission are colored draft container and carton labels, as verbally requested by Ms. Lutwak, FDA Project Manager. Accompanying compact disk version of the colored labels, in Word format, are included in the Review Copy.

Incorporated in this submission, please find Hill Dermaceuticals, Inc. response to the following items:

Labeling (draft):

1. [redacted]
2.

Chemistry:

1. Weight loss testing for tubes (w/without end sealant);
2. Diagram of tube crimp;
3. 60 day accelerated stability testing for TRI-LUMA Cream.

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Non-Clinical Pharmacology and Toxicology:

(Hill response to FDA Information Request Letter dated 11/01/01);

1. Urinalysis Data;
2. Histophatology;
3. Groups means and statistical analysis for skin irritation scoring;
4. Data for weight gains and graphs of body weights and body weight gains over time;
5. Analytical determination of hydroquinone, fluocinolone acetonide, and tretinoin in mini-pig plasma, and Toxicokinetic summary. This information was previously submitted, NDA amendment filed July 24, 2001;
6. Relative gonad weight: body weight ratios separated by sex and statistical significance, if any;
7. Normal ranges for clinical pathology parameters in this strain of mini-pig.

Clinical:

1. Twelve month report for Study 29 Long Term (12 Month) Safety and Efficacy of Tri-luma in treatment of patients with melasma of the face. This report includes data on 314 patients that have cumulative time use of the drug for greater than 180 days;
2. Statistical analyses of safety and efficacy – TABLES;
3. Table with information regarding pregnancies reported during the course of the studies.

Statistical:

1. Randomization procedure information and documentation (previously submitted);
2. Tables for primary and secondary efficacy endpoints (with exclusion of only the non-nasal inhaled corticosteroid concomitant users);
3. Table for ITT analysis for the primary and the secondary efficacy endpoints based on the last observation carried forward (LOCF) scheme for handling missing data.

This final submission is being hand delivered by Jerry Roth, President / Hill Dermaceuticals, Inc., to the FDA Document Room on November 23, 2001 as we have committed. Thank you for your continued support and consideration.

Sincerely,

Rosario G. Ramirez
Director
Medical / Regulatory Affairs

Jerry S. Roth
President

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NDA 21-112
TRI-LUMA

December 10, 2001

VIA HAND DELIVERY

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

Dear Dr. Wilkin:

In follow up to our telephone discussion today, enclosed you will find line listings and case report forms for the long-term safety study (Study Protocol 29). I am also providing the case report forms for the clinical efficacy study (Study Protocol 28).

As you know, Hill has worked very hard to meet the timelines for the submissions of additional information set forth in the Agency's September 10, 2001, letter. On November 23, 2001, we submitted all outstanding data, including the 12-month safety study report in accordance with our commitments. The line listings and case report forms confirm the data presented in the safety study report submitted on November 23. All clinical studies are conducted and monitored by ———

We trust that the Division will be able to dedicate sufficient resources in order to complete its review of the NDA by January 25, 2002. As I have previously stated, a significant delay in the Agency's review of this NDA will result in severe financial hardship to the company.

We are prepared to meet with Division staff or respond immediately to requests, if any additional information or clarifications are needed to complete your review.

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

Sincerely,

Rosario G. Ramirez
Medical / Regulatory Affairs

Jerry Roth
President

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Dermaceuticals, Inc.

Specialty Dermatologicals for Children & Adults

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ORIG AMENDMENT

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December 18, 2001

Jonathan Wilkin, 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
Attn: Ms. Vickey Lutwak, Project Manager

RE: TRILUMA Cream NDA 21,112
Chemistry, Manufacturing, and Controls Section

Dear Dr. Wilkin:

We would like to give an update on the stability studies and tube weight loss studies, as requested by the Chemistry reviewer.

The 90 days accelerated stability study data is available and enclosed here for review.

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

Sincerely,

Rosario G. Ramirez

Rosario G. Ramirez
Director
Medical / Regulatory Affairs

ORIGINAL

Phone 1.800.[illegible].5707 Fax 1.407.649.9213

NDA [illegible]NT. BM

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Dermaceuticals, Inc.

Specialty Dermatologicals for Children & Adults

NDA 21-112
TRI-LUMA Cream

December 20, 2001

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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 Information Request (dated December 17, 2001) from the Medical Officer for NDA 21-112 review.

Dear Dr. Wilkin,

This submission contains information requested by the Medical Officer outlined in the correspondence faxed to Hill Dermaceuticals, Inc. on December 17, 2001. A copy of the FDA correspondence is enclosed.

All items listed in the FDA letter have been addressed. The following information is provided to facilitate the review.

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

HILL RESPONSE to item 1: The Index (Table of Contents) for the December 10, 2001 submission containing all Case Report Forms is provided in **Section I** of this submission.

FDA Comments: *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 to 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.*

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NDA DRUG AMENDMENT

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JAN 11 2002
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NDA 21-112
TRI-LUMA

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JAN 11 2002
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January 10, 2002

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: Method Validation Package / Chemistry, Manufacturing and Controls

Dear Dr. Wilkin:

Reference is made to the CMC section of NDA 21-112, TRI-LUMA Cream (0.01% fluocinolone acetonide, 4.0% hydroquinone, 0.05% tretinoin). This submission contains the Method Validation Package according to the Contents and Processing Section of the Draft Guidance, Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation, as requested by Mr. Ernest Pappas, Chemistry Reviewer, during the teleconference between FDA and Hill Dermaceuticals, Inc. on January 4, 2002.

Enclosed you will find the original, chemistry reviewer copy, and the desk copy. Please advise if further information is needed. Thank you for your continued support and cooperation.

Sincerely,

Criss Molasso

Criss Molasso
Assistant Regulatory Affairs

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

Nancy Puglia
Analytical Laboratory Manager

encls.

ORIGINAL

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

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Dermaceuticals, Inc.

Specialty Dermatologicals for Children & Adults

NDA 21-112
TRI-LUMA Cream

January 15, 2002

N-000 (BZ)

ORIG AMENDMENT

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 Information Request for NDA 21-112.
(December 21, 2001 to January 15, 2002)

Dear Dr. Wilkin,

In reference to the New Drug Application, NDA 21-112, the following information is being submitted under this NDA. All materials contained in this package have been previously forwarded to the reviewing officers as facsimile and/or electronic mail correspondence, in response to the specific information request. Copy of all correspondences between Hill and the Agency are included.

The content of this submission is sectioned according to discipline. Each section then follows time sequence starting from the earliest date of information request.

Thank you for your continued support and consideration.

Sincerely,

Rosario G. Ramirez

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

FOOD AND DRUG ADMINISTRATION
DIVISION OF DERMATOLOGIC AND
DENTAL DRUG PRODUCTS
HFD-540
9201 CORPORATE BLVD.
ROCKVILLE, MARYLAND 20850

DATE: 5/3/99

TO:

Name Niki Ramirez

Fax No. 407 323-1871

Phone No. _____

Location Hill Dermaceuticals

FROM:

Name MARY JEAN KOZMA-FORNARO
Fax No. 301 827-2075/2091
Phone No. 301 827-2020

Comments: NDA 21112

Clarification of statistical + clinical needs for NDA + reference areas for your guidance.

/S/

cc: NDA 21112
HFD 540/ KO
HFD 540/ Friedel

NDA 21112

Additional information needed from Hill Dermaceuticals STATISTICAL

1.We only need the pages that are nor legible, namely pages 80062-80066 in Volume 1.7.

2. Subgroup analysis is required both for safety and efficacy. In his email, Hon-Sum has explained requirements for the safety subgroup analysis. For details on the efficacy subgroup analysis, the sponsor should read ICH E9 Document, Section 5.7, and Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications (page 32). We request subgroup analysis (by age, sex, and race) relative to the primary efficacy parameter.

3. We also need statistical analysis of the baseline comparability of the treatment groups relative to baseline severity of disease.

CLINICAL:

21CFR314.50(d)(vi)(a) -
".....The safety data shall be presented by gender, age and racial
4. subgroups. When appropriate, safety data from other subgroups of the population of patients treated also shall be presented, such as for patients with renal failure or patients with different levels of severity of the disease. ....."

5. This is different from data listing. The data listings are simply listing the data from individual patients. The subgroup analysis refers to analyzing the data with respect to age, sex, etc. Of course the raw data will be in the listings. But to say it is analyzing the listing - it is not that. It is analyzing the "data" and not the "listing" if you want to be split-hair.

To have more info on that, they should consult ICH E3 or the Clin/stat guidelines. Both are available on the web under Guidance Documents.

Printed by Mary Jean Kozma-Fornaro

Electronic Mail Message

Date: 29-Apr-1999 03:30pm
From: Mary Jean Kozma-Fornaro
KOZMAFORNARO
Dept: HFD-540 CRP2 N252
Tel No: 301-827-2023 FAX 301-827-2075

Subject: NDA 21111

Jon and I called Jerry Roth et al of Hill Derm and gave them the basics of what was missing in our preliminary filing check of the submission.

For Biostat we told them about the illegible pages and the lack of a subgroup analysis.

1. I need the pages that are not readable or do you want a whole new volume?
2. The sponsor confused listings of safety data which Hon Sum requested as needing subgroup analysis and wants clarification. Their biostat person should know what subgroup analysis is, am I right?

I also requested a volume 1.6 for Valeria.

3. For clinical we stated: need listings for safety data, full reports of human derm safety studies, submission of ISS missing elements, and all required case report forms.

I think the sponsor told the contract biostat person that he needs to do a subgroup analysis of the listings of safety data that is why the contract person is confused.

I let you know if there are other questions. Mary Jean

APPEARS THIS WAY
ON ORIGINAL

1 800-
344-5707.
1030pm 6/24

Hill Laboratories

TEL No. 1-407-323-1270 FAX No. 1-407-323-1871

PAGES SENT 4 (INCLUDING THIS COVER SHEET)

TO: Ms Mary Jean Kozma-Fornaro

FAX #: 1-301-827-2091

FROM: Nancy Puglia

DATE: 6/4/99

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

Number of Pages Redacted 1

❖❖❖

Confidential,
Commercial Information

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 chemistry review for ~~—~~ (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.

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

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MESSAGE CONFIRMATION

08/24/99 12:23

D.	MODE	BOX	GROUP
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DATE	TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
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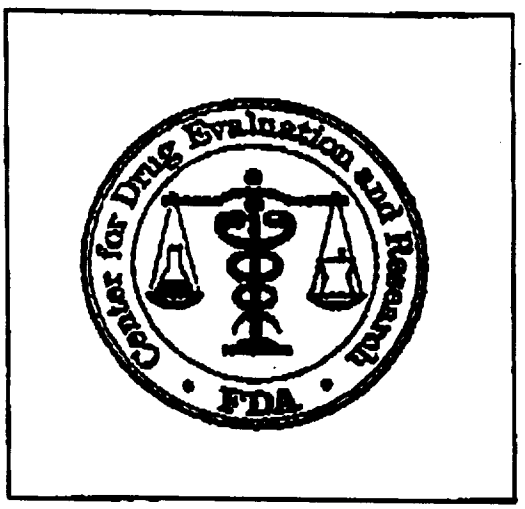
FACSIMILE TRANSMISSION RECORD



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 / 827-2053
Fax 301-827-2075

Date: _____

To: Name Nimi Dahlberg
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.

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

/s/

Kevin Dermanoski
1/10/02 09:57:54 AM
CSO

Carol Holquist
1/10/02 10:50:17 AM
PHARMACIST

Application: NDA 21112/000
Stamp: 22-MAR-1999
Regulatory Due: 22-JAN-2000
Applicant: HILL DERMAC
2650 SOUTH MELLONVILLE AVE
SANFORD, FL 32773
Priority: 4S
Org Code: 540

Action Goal:
District Goal: 23-NOV-1999
Brand Name: (FLUOCINOLONE ACETONIDE/HYDROQ
Estab. Name:
Generic Name: FLUOCINOLONE ACETONIDE/HYDROQUINONE/TRET
Dosage Form: (CREAM)
Strength: 0.01%,4.0%,0.05%

Application Comment: THIS CREAM CONTAINS THREE (3) ACTIVE COMPONENTS. THE STRENGTH OF THE CREAM IS LISTED AS 0.01% (FLUOCINOLONE ACETATE), 4.0% (HYDROQUINONE) AND 0.05% (TRETINOIN). (on 18-MAY-1999 by E. PAPPAS (HFD-540) 301-827-2066)

FDA Contacts: M. KOZMA-FORNARO (HFD-540) 301-827-2023 , Project Manager
E. PAPPAS (HFD-540) 301-827-2066 , Review Chemist
W. DECAMP II (HFD-540) 301-827-2041 , Team Leader

Overall Recommendation:
Establishment: ——
—
—
—

DMF No:
AADA:
Responsibilities: —
Profile: CTL
OAI Status: NONE
Estab. Comment: ALSO, USP REQUIREMENTS TESTING, PER EMAIL MESSAGE FROM E. PAPPAS. (on 30-SEP-1999 by S. FERGUSON (HFD-324) 301-827-0062)
THIS FACILITY PERFORMS ' ——
—— (on 30-SEP-1999 by E. PAPPAS (HFD-540) 301-827-2066)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	30-SEP-1999				PAPPAS
SUBMITTED TO DO	30-SEP-1999	GMP			FERGUSONS
DO RECOMMENDATION	18-OCT-1999			ACCEPTABLE	KRODEN

BASED ON FILE REVIEW

THE PROFILE CLASS FOR THIS FIRM IS NOT OIN. THEY ARE A CONTROL TESTING LABORATORY ONLY (CTL). A GMP PRE-APPROVAL INSPECTION WAS CONDUCTED AT —— ON 6/15-7/19/99 AND NO FDA 483 WAS ISSUED. CHEMICAL AND MICROBIOLOGICAL TESTING OPERATIONS WERE EVALUATED DURING THAT INSPECTION. BASED ON THE INSPECTION FINDINGS, —— RECOMMENDS APPROVAL OF THIS APPLICATION.

OC RECOMMENDATION	19-OCT-1999			ACCEPTABLE	FERGUSONS

DISTRICT RECOMMENDATION

Establishment: 1036365
HILL DERMACEUTICALS INC
2650 SOUTH MELLONVILLE AVE
SANFORD, FL 32773

DMF No:
AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: OIN
OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	18-MAY-1999				PAPPAS
SUBMITTED TO DO	20-MAY-1999	GMP			EGASM
ASSIGNED INSPECTION	23-JUN-1999	PS			PFIGAROL

Establishment: [redacted]

DMF No: 7734 AADA:
Responsibilities:
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	18-MAY-1999				PAPPAS
OC RECOMMENDATION	19-MAY-1999			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment: [redacted]

DMF No: AADA:
Responsibilities:
Profile: CTL OAI Status: NONE
Estab. Comment:

PAPPAS (HFD-540) 301-827-2066) (on 22-OCT-1999 by E.

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	22-OCT-1999				PAPPAS
OC RECOMMENDATION	22-OCT-1999			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment: [redacted]

DMF No: AADA:
Responsibilities:
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	18-MAY-1999				PAPPAS
OC RECOMMENDATION	19-MAY-1999			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment: [redacted]

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	18-MAY-1999				PAPPAS

SUBMITTED TO DO	20-MAY-1999 GMP			EGASM
ASSIGNED INSPECTION	30-SEP-1999 PS			KNORTON
INSPECTION SCHEDULED	05-OCT-1999	15-NOV-1999		KNORTON
INSPECTION PERFORMED	14-JAN-2000	16-DEC-1999		KNORTON
DO RECOMMENDATION	14-JAN-2000		ACCEPTABLE INSPECTION	KNORTON

12/13-16/99 INSPECTION REVEALED 5 DEVIATIONS, WHICH THE FIRM ADEQATELY ADDRESSED DURING THE INSPECTION. DISTRICT RECOMMENDS APPROVAL.

OC RECOMMENDATION	14-JAN-2000		ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS

APPEARS THIS WAY
ON ORIGINAL

Application: NDA 21112/000
Stamp: 22-MAR-1999
Regulatory Due: 22-JAN-2000
Applicant: HILL DERMAC
2650 SOUTH MELLONVILLE AVE
SANFORD, FL 32773
Priority: 4S
Org Code: 540

Action Goal:
District Goal: 23-NOV-1999
Brand Name: [redacted] (FLUOCINOLONE ACETONIDE/HYDROQ
Estab. Name:
Generic Name: FLUOCINOLONE ACETONIDE/HYDROQUINONE/TRET

Dosage Form: (CREAM)
Strength: 0.01%,4.0%,0.05%

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FDA Contacts: M. KOZMA-FORNARO (HFD-540) 301-827-2023 , Project Manager
E. PAPPAS (HFD-540) 301-827-2066 , Review Chemist
W. DECAMP II (HFD-540) 301-827-2041 , Team Leader

Overall Recommendation:
Establishment: [redacted]

DMF No: [redacted] AADA:
Responsibilities:
Profile: CTL OAI Status: NONE
Estab. Comment: ALSO, USP REQUIREMENTS TESTING, PER EMAIL MESSAGE FROM E. PAPPAS. (on 30-SEP-1999 by S. FERGUSON (HFD-324) 301-827-0062)
THIS FACILITY PERFORMS THE
(on 30-SEP-1999 by E. PAPPAS (HFD-540) 301-827-2066)

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	30-SEP-1999				PAPPAS
SUBMITTED TO DO	30-SEP-1999	GMP			FERGUSONS
DO RECOMMENDATION	18-OCT-1999			ACCEPTABLE	KRODEN

BASED ON FILE REVIEW
THE PROFILE CLASS FOR THIS FIRM IS NOT OIN. THEY ARE A CONTROL TESTING LABORATORY ONLY (CTL). A GMP PRE-APPROVAL INSPECTION WAS CONDUCTED AT [redacted] ON 6/15-7/19/99 AND NO FDA 483 WAS ISSUED. CHEMICAL AND MICROBIOLOGICAL TESTING OPERATIONS WERE EVALUATED DURING THAT INSPECTION. BASED ON THE INSPECTION FINDINGS, KAN-DO RECOMMENDS APPROVAL OF THIS APPLICATION.

OC RECOMMENDATION	19-OCT-1999			ACCEPTABLE	FERGUSONS

DISTRICT RECOMMENDATION

Establishment: 1036365
HILL DERMACEUTICALS INC
2650 SOUTH MELLONVILLE AVE
SANFORD, FL 32773

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: OIN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	18-MAY-1999				PAPPAS
SUBMITTED TO DO	20-MAY-1999	GMP			EGASM
ASSIGNED INSPECTION	23-JUN-1999	PS			PFIGAROL

C. **INVESTIGATIONAL FORMULATIONS:** Acceptable

The applicant reported the investigational formula used in the clinical trials for —— cream as Lot #97K065. This formulation is listed in Vol. 1.6, pg.7 0250.

D. **ENVIRONMENTAL ASSESSMENT**

The applicant requested a categorical exemption per 25.31 (b). In this regard, the applicant provided the calculations of the estimated concentration of the substances at the point of entry into the aquatic environment. They indicated that the estimated amount will be below the 1 ppb limit thereby complying with paragraph 25.31(b). See Vol. 1.3, pg. 4 0845

E. **METHODS VALIDATION: Pending; not an approvable issue.**

A methods validation package was submitted in the NDA. Since there are deficiencies in the analytical methods, the methods validation will be put on hold until these deficiencies are corrected.

F. **LABELING**

The following labeling information was reviewed for compliance with the provisions of 21 CFR 201 from a technical standpoint:

Trade Name:

The trade names, —— was originally proposed in the NDA. However, this name was not accepted by the CDER Labeling Committee (see Memo 9/24/99 from the L&NC committee).

Since —— was found acceptable as a trade name, the applicant proposed the following trade names on 9/24/99:

- ——
- ——

The L&NC committee found —— acceptable as a trade name (see Memo 9/24/99 from the L&NC committee).