

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number 21-112**

**ADMINISTRATIVE DOCUMENTS**  
**CORRESPONDENCE**



DEPARTMENT OF HEALTH & HUMAN SERVICES

AT 200 20 / NUTRITION

Public Health Service

Food and Drug Administration  
Rockville MD 2085

NDA 21-112

Hill Dermaceuticals, Inc.  
Attention: Jerry S. Roth,  
President  
2650 South Mellonville Ave.  
Sanford, Florida 32773

1-21-2000

Dear Mr. Roth:

Please refer to your new drug application (NDA) dated March 19, 1999, received March 22, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (fluocinolone acetonide, 0.01% / hydroquinone, 4% / tretinoin, 0.05%) Cream.

We acknowledge receipt of your submissions dated April 21, 29 (four), May 7, 10, 11, and 19, June 4, and 23, August 19, and 27, September 9 (two), 13, 24, and 27, October 12, 25 (two), and 28, November 4 and 8, December 16, 1999; and January 5, 2000.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

Clinical/Statistical:

There is insufficient information to support the safety, efficacy, and contribution of each of the three drug components of TRADENAME cream.

1. Because melasma is often a chronic condition, and because melasma may regress upon discontinuation of therapy with TRADENAME cream, the safety for long-term use should be assessed (refer to the TCH E1A Guidance Document for additional information).
2. A study with adequate sample size should be performed to determine the contact sensitization potential of the TRADENAME cream.
3. Studies on systemic absorption and HPA axis function (adrenal suppression) should be provided to support the systemic safety of the TRADENAME cream.

4. The contribution of each of the three drug components was assessed by comparing the TRADENAME cream with each of three creams that each omitted a different active drug (the three dyads). Superiority of TRADENAME cream over each of the three dyads has not been established. Also, the TRADENAME cream appears to offer no compelling advantage over the three dyads in local adverse events.

Biopharmaceutics:

Data should be provided from *in vivo* studies to determine the systemic absorption and HPA axis (adrenal) suppression for the proposed formulation.

Pharmacology/Toxicology:

The nonclinical information supplied was inadequate to support both the safety of the combination product and the proposed labeling. Mixtures may have emergent properties, properties not shared by the individual components. Although some effects of the individual components are known, the long-term effects of the product on the skin and the effects of the product on reproductive and developmental function are unknown. When assays appropriate for testing for degradants are developed and applied, any new degradants arising from the interaction of the components and present at  $> 0.1\%$  of the concentration of the relevant active component(s) will need to be qualified. To support approval of this product, the following should be conducted.

1. A chronic dermal application toxicology study in a nonrodent, preferably a minipig.
2. Reproductive and developmental toxicology studies of the combination product in the most appropriate species.
3. Any new degradants present at  $> 0.1\%$  of the concentration of the relevant active component(s) will need to be qualified.

Chemistry:

1. The drug substance information for hydroquinone does not contain information on the manufacture, controls, packaging, and stability of this raw material. We acknowledge receipt of this information as a Drug Master File on December 23, 1999. The information is currently under review.

2. The finished product specifications should include a microscopic examination. The appearance test is too subjective to assure that no phase separation has occurred and the product is free of particles.
3. The finished product specifications should include a test for homogeneity (assay of the product sampled from the top, middle and bottom of the tube).
4. a. The assay methods have not been shown to be stability indicating for the combination drug product. The fluocinolone acetonide, hydroquinone and tretinoin and their degradation products should be shown to not interfere in the assay methods. Without such validation, we can not evaluate the results of your assay, the stability studies, and your proposed expiration dating.  
b. In addition, the \_\_\_\_\_ term stability data are insufficient to support the proposed \_\_\_\_\_ expiration date. Additional data are required for the batches (Lot #s 98J067; 98K073; 98K075) placed on stability.
5. Please refer to the Guidance for Industry regarding the Container Closure Systems for Packaging Human Drugs and Biologics. The description of the container/closure system should include the following information:
  - a. A demonstration of the compatibility of the \_\_\_\_\_ with the finished product. To do this, we recommend that you conduct \_\_\_\_\_ on the \_\_\_\_\_ it in contact with the finished product.
  - b. The description of the cap, including the cap resin material, and drawings and specifications for the cap should be submitted.
  - c. The composition of the tube \_\_\_\_\_ should be described. A DMF reference may be appropriate.

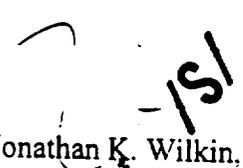
Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Victoria Lutwak, Project Manager, at (301) 827-2020.

Sincerely,



Jonathan K. Wilkin, M.D.

Director  
Division of Dermatologic and  
Dental Drug Products  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

**APPEARS THIS WAY  
ON ORIGINAL**

NDA 21-112

Page 5

cc:

Archival NDA 21-112

HFD-540/Div. Files

HFD-540/Lutwak

HFD-540/Ko

HFD-540/Papas

HFD-540/Nostrandt

HFD-860/Lee

HFD-735/Freidlin

HFD-106/Riley

HFD-002/ORM

HFD-105/ADRA

HFD-830/DNDC Division Director

DISTRICT OFFICE

Concurrence:

HFD-540/Clinical TL/Walker

HFD-540/CHEM TL/DeCamp

HFD-540 PHARM TL/Jacobs

HFD-106/MICRO TL/Cooney

HFD-880/BIOPHARM TL/Bashaw

HFD-725 BIOSTAT TL/Al-Osh

HFD-540/SUPV PROJ MGR/Kozma-Fornaro

Drafted by: vl/January 3, 2000

filename: NA letter-1-20-2000

NOT APPROVABLE (NA)

**APPEARS THIS WAY  
ON ORIGINAL**



- ◆ Status of advertising (if AP action)  Reviewed (for Subpart H – attach review)  Materials requested in AP letter
- ◆ Post-marketing Commitments
  - Agency request for Phase 4 Commitments.....
  - Copy of Applicant's commitments .....
- ◆ Was Press Office notified of action (for approval action only)?.....  Yes  No  
 Copy of Press Release or Talk Paper.....
- ◆ Patent
  - Information [505(b)(1)] ..... x
  - Patent Certification [505(b)(2)].....
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....
- ◆ Exclusivity Summary ..... x
- ◆ Debarment Statement ..... x
- ◆ Financial Disclosure
  - No disclosable information ..... x,
  - Disclosable information – indicate where review is located .....
- ◆ Correspondence/Memoranda/Faxes ..... X Vol 2
- ◆ Minutes of Meetings ..... X Vol 2
  - Date of EOP2 Meeting No meeting
  - Date of pre NDA Meeting No meeting
  - Date of pre-AP Safety Conference \_\_\_\_\_
- ◆ Advisory Committee Meeting ..... none
  - Date of Meeting .....
  - Questions considered by the committee .....
  - Minutes or 48-hour alert or pertinent section of transcript .....
- ◆ Federal Register Notices, DESI documents .....

**CLINICAL INFORMATION:**

**Indicate N/A (not applicable), X (completed), or add a comment.**

- ◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) ..... N/A
- ◆ Clinical review(s) and memoranda ..... X 1- -02

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA <u>21-112</u> <input checked="" type="checkbox"/> SE _____ - _____	
Drug <u>TRI-LUMA</u>	Applicant <u>Hill Dermaceuticals</u>
RPM <u>Victoria Lutwak</u>	Phone <u>310/827-2073</u>
x505(b)(1) <input type="checkbox"/> 505(b)(2) Reference listed drug _____	
<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rolling Review
Review priority: <input checked="" type="checkbox"/> S <input type="checkbox"/> P	
Pivotal IND(s) _____	
Application classifications:	
Chem Class	Commbination corticosteroid/depig. Agen/keratolytic
Other (e.g., orphan, OTC)	_____
PDUFA Goal Dates:	
Primary <u>January 25, 2002</u>	
Secondary _____	

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

### GENERAL INFORMATION:

- ◆ User Fee Information:  User Fee Paid  
 User Fee Waiver (attach waiver notification letter)  
 User Fee Exemption
  
- ◆ Action Letter..... x AP  AE  NA
  
- ◆ Labeling & Labels
 

FDA revised labeling and reviews.....	X
Original proposed labeling (package insert, patient package insert) .....	X <u>July 2001</u>
Other labeling in class (most recent 3) or class labeling.....	N/A
Has DDMAC reviewed the labeling? .....	x <input type="checkbox"/> Yes (include review) <input type="checkbox"/> No
Immediate container and carton labels .....	X
Nomenclature review .....	X
  
- ◆ Application Integrity Policy (AIP)  Applicant is on the AIP. This application  is x is not on the AIP.  
 Exception for review (Center Director's memo)..... \_\_\_\_\_  
 OC Clearance for approval..... \_\_\_\_\_

Continued ⇨

3

- ◆ Safety Update review(s) ..... X 1- -02
- ◆ Pediatric Information
  - Waiver/partial waiver (Indicate location of rationale for waiver)  Deferred
  - Pediatric Page..... x
  - Pediatric Exclusivity requested?  Denied  Granted  Not Applicable
- ◆ Statistical review(s) and memoranda ..... X 12-19-01 & Addendum 1- -02
- ◆ Biopharmaceutical review(s) and memoranda..... X 12-19-01 & Addendum 1- -02
- ◆ Abuse Liability review(s) ..... NA
  - Recommendation for scheduling .....
- ◆ Microbiology (efficacy) review(s) and memoranda ..... NA
- ◆ DSI Audits ..... NA 1-10-02
  - Clinical studies  bioequivalence studies ..... No issues

**CMC INFORMATION:**

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ CMC review(s) and memoranda ..... X 1-9-02
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability ..... NA
- ◆ DMF review(s) ..... X In Review
- ◆ Environmental Assessment review/FONSI/Categorical exemption ..... X In Review
- ◆ Micro (validation of sterilization) review(s) and memoranda ..... NA
- ◆ Facilities Inspection (include EES report)
  - Date completed— current .....  Acceptable  Not Acceptable
- ◆ Methods Validation .....  Completed x Not Completed

**PRECLINICAL PHARM/TOX INFORMATION:**

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ Pharm/Tox review(s) and memoranda ..... X 12-18-01
- ◆ Memo from DSI regarding GLP inspection (if any) ..... NA

- ◆ Statistical review(s) of carcinogenicity studies ..... NA  
Phase 4
- ◆ CAC/ECAC report ..... NA  
Phase 4

**APPEARS THIS WAY  
ON ORIGINAL**



# USER FEE COVER SHEET

*See Instructions on Reverse Side Before Completing This Form*

APPLICANT'S NAME AND ADDRESS

...ll Dermaceuticals, Inc.  
2650 South Mellonville Avenue  
Sanford, FL 32773

3. PRODUCT NAME

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?  
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE  
AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY  
REFERENCE TO \_\_\_\_\_  
(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

(407) 323-1867

5. USER FEE I.D. NUMBER

3673

6. LICENSE NUMBER / NDA NUMBER

N021112

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT  
APPROVED UNDER SECTION 505 OF THE FEDERAL  
FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92  
(Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE  
(See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN  
EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,  
Drug, and Cosmetic Act  
(See item 7, reverse side before checking box.)

THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT  
QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F)  
of the Federal Food, Drug, and Cosmetic Act  
(See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL  
GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED  
COMMERCIALY  
(Self Explanatory)

FOR BIOLOGICAL PRODUCTS ONLY

WHOLE BLOOD OR BLOOD COMPONENT FOR  
TRANSFUSION

A CRUDE ALLERGENIC EXTRACT PRODUCT

AN APPLICATION FOR A BIOLOGICAL PRODUCT  
FOR FURTHER MANUFACTURING USE ONLY

AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT  
LICENSED UNDER SECTION 351 OF THE PHS ACT

BOVINE BLOOD PRODUCT FOR TOPICAL  
APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES  NO

(See reverse side if answered YES)

**A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.**

Public reporting burden for this collection of information is estimated to average 30 minutes 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:

DHHS, Reports Clearance Officer  
Paperwork Reduction Project (0910-0297)  
Hubert H. Humphrey Building, Room 531-H  
200 Independence Avenue, S.W.  
Washington, DC 20201

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.

Please DO NOT RETURN this form to this address.

TITLE OF AUTHORIZED COMPANY REPRESENTATIVE

TITLE

DATE

*J. B. S.*

*President*

*3/19/99*

NDA # 21-112 DOCUMENT ID/LETTER DATE N-DOC / March 19, 1999  
 APPLICANT NAME Hill Dermaceuticals, Inc.  
 PRODUCT NAME (Fluocinolone acetonide, Hydroquinone, Tretinoin) Cream

**FORM MUST BE COMPLETED ASAP**

1.  YES User Fee Cover Sheet Validated?

pd. 3/15/99

**NOTE TO DOCUMENT ROOM:  
 PLEASE MAKE THE FOLLOWING CHANGES TO THE COLES DATA ELEMENTS**

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2.  YES  NO CLINICAL DATA?  
 [Check YES if contains study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials. Clinical data do not include data used to modify the labelling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).]

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION?

3.  YES  NO NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (OTHER THAN BUNDLING)? IF YES, list ALL NDA numbers, review divisions & indicate those for which application fees apply.

NDA #	DIVISION	FEE	NO FEE
N _____	_____	FEE	NO FEE

4.  YES  NO BUNDLING POLICY APPLIED CORRECTLY? NO DATA ENTRY REQUIRED FOR ELEMENT  
 [Check YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Check NO if application should be split into more than one application or submitted as an original instead of a supplement. IF NO, list resulting NDA numbers, and review divisions.]

NDA #	DIVISION	NDA #	DIVISION
N _____	_____	N _____	_____

5.  P  S PRIORITY OR STANDARD?

Cpmo 4/9/99

**[REDACTED]** **[REDACTED]**

6. CSO SIGNATURE/DATE SCSSO CONCURRENCE SIGNATURE/DATE

**DISTRIBUTION: ORIGINAL TO ARCHIVAL AFTER DATA ENTRY, ONE COPY EACH TO DIVISION FILE AND CDER, ASSOCIATE DIRECTOR FOR POLICY HFD-5**

**DEBARMENT CERTIFICATION (ITEM 16)**

Pursuant to 21 USC 335a(k)(1) the applicant, Hill Dermaceuticals, Inc., in Sanford, FL "did not and will not use in any capacity the services of any person debarred under subsections (a) or (b), in connection with [this] application."

3/19/99

Date

Jerry R. Roth

Jerry R. Roth  
President  
Hill Dermaceuticals, Inc.

**APPEARS THIS WAY  
ON ORIGINAL**

19 January 1999

Ms. Marianna Arsts  
Hill Pharmaceuticals  
2650 S. Mellonville Avenue  
Sanford, FL

Dear Ms. Arsts:

\_\_\_\_\_ provides contract \_\_\_\_\_ to your firm. This letter certifies that our firm does not and will not use any person debarred according to the Generic Drug Enforcement Act of 1992 (USFDA) which requires that all New Drug Applications contain:

"a certification that the applicant did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [section 306 (a) or (b)], in connection with such applications."

Section 305(k)(1) of the act (21 U.S.C.335a(k)(1)).

We are committed to perform all testing in compliance with GLP/GMP requirements. Although the majority of analyses we perform are of a non-routine nature, the functionality of the lab is dictated, wherever possible, by SOP's.

\_\_\_\_\_ is routinely inspected by auditors from our clients. Our last FDA inspection was in March, 1998. No 483's were issued as a result of that inspection. Our FDA Registration Number is \_\_\_\_\_

Please feel free to contact me again if you need further information.

Sincerely,



**Steps Taken to Minimize Potential Bias  
of the Clinical Study Results**

Please be advised that the following steps were taken to minimize the potential bias of the clinical study results in the clinical studies entitled: "Efficacy and Safety of TRI-LUMA, in the Treatment of Patients with Melasma (Study 28A and Study 28B).

First, thirteen different investigational sites with primary investigators and sub-investigators participated in the trials. The investigators, sub-investigators, and patients were blinded throughout the course of the study. The investigators and sub-investigators did not dispense the investigational products. A third party was assigned to the dispensing of the investigational materials. Each patient was scored at the initiation of the study as to the severity of their disease. During the course of the study, at each patient visit, the investigators and sub-investigators remained blinded as they conducted the patient evaluation. Finally, the blind was broken only after the study was fully completed.

In our view, the design and conduct of the studies were sufficient to minimize the potential bias of the clinical study results.

  
\_\_\_\_\_  
Jerry Roth  
Hill Dermaceuticals, Inc.

July 10, 2001  
Date

**APPEARS THIS WAY  
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration

Form Approved: OMB No. X000-X00X  
Expiration Date: X0/X0/X0X

### CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkboxes.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

<input type="checkbox"/>	Neil Brody, MD	Joshua Wieder, MD
<input type="checkbox"/>	A. Paul Kelly, MD	
<input type="checkbox"/>	Helen Torok, MD	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME		TITLE	
Jerry Roth		President	
FIRM/ORGANIZATION			
Hill Dermaceuticals, Inc.			
SIGNATURE		DATE	
		3/12/99	

#### Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857

Please DO NOT RETURN this form to this address.

# DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning Isaac Willis, MD, who participated as a clinical investigator in the submitted study Double-blind Comparative Study of \_\_\_\_\_, a new Formulation, for the treatment of Patients with Cutaneous melanosis, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

any significant payments of other sorts made on or after February 2, 1990 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

any proprietary interest in the product tested in the covered study held by the clinical investigator;

any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Jerry Roth		TITLE President
FIRM/ORGANIZATION Hill Dermaceuticals, Inc.		
SIGNATURE 		DATE 3/16/99

### Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services  
Food and Drug Administration  
3600 Fishers Lane, Room 14C-03  
Rockville, MD 20857

<-Please DO NOT RETURN this form to this address.

## CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	PLEASE SEE	ATTACHED

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Jerry S. Roth	President
FIRM/ORGANIZATION	
Hill Dermaceuticals, Inc.	
SIGNATURE	DATE
	July 10, 2001

### Paperwork Reduction Act Statement

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Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857

LIST OF ALL INVESTIGATORS

Helen Mary Torok, MD.....HMT Dermatology Associates, Inc.  
780 East Smith  
Medina, OH 44256-2662

Susan Taylor, MD.....St. Luke's-Roosevelt Hospital Center  
Department of Dermatology  
1090 Amsterdam Ave., Suite 11D  
New York, NY 10025

Leslie Baumann, MD.....University of Miami  
1295 Northwest 14<sup>th</sup> St., Suite K  
Miami, FL 33125

Terry Jones, MD.....J & S Studies, Inc.  
3201 University Dr. East, Suite 475  
Bryan, TX 77802

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4180 La Jolla Village Dr., Suite #255  
La Jolla, CA 92037

Howard I. Maibach, MD.....University of CA, San Francisco  
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San Francisco, CA 94143-0989

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Miamiville, Ohio 45147

Bruce Miller, MD.....Oregon Medical Research  
9495 SW Locust St., Suite G  
Portland, OR 97223-6683

**Patent Submission Suggested Format**

This form contains a format suggestion for submission of patent information for NDAs submitted under section 505 of the Federal Food, Drug, and Cosmetic Act. For more detailed information please refer to 21 C.F.R. 314.53.

Time Sensitive Patent Information  
pursuant to 21 C.F.R. 314.53  
for

NDA # 21-112

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: \_\_\_\_\_
- Active Ingredient(s): Fluocinolone Acetonide, Hydroquinone, Tretinoin
- Strength(s): Fluocinolone Acetonide (0.01%), Hydroquinone (4.0%), Tretinoin (0.05%)
- Dosage Form: topical cream preparation
- Approval Date: *not yet approved*

**A. This section should be completed for each individual patent**

The applicant, Hill Laboratories, Inc., declares that there are no patents (or patents pending) that cover the composition, formulation or method of use of T \_\_\_\_\_ NDA 21-211. \_\_\_\_\_ has been submitted for FDA approval.

Expiration Date:

Type of Patent – Indicate all that apply:

1. Drug Substance (Active Ingredient) \_\_\_Y\_\_\_N
2. Drug Product (Composition/Formulation) \_\_\_Y\_\_\_N
3. Method of Use \_\_\_Y\_\_\_N

If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent: \_\_\_\_\_

Name of Patent Owner:

U.S. Agent (if patent owner or applicant does not reside or have place of business in the U.S.):

U.S. Patent Number:

Expiration Date:

Type of Patent – Indicate all that apply:

1. Drug Substance (Active Ingredient) \_\_\_Y\_\_\_N
2. Drug Product (Composition/Formulation) \_\_\_Y\_\_\_N
3. Method of Use \_\_\_Y\_\_\_N

If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent: \_\_\_\_\_

Name of Patent Owner:

U.S. Agent (if patent owner or applicant does not reside or have place of business in the U.S.):

U.S. Patent Number:

Expiration Date:

**Type of Patent – Indicate all that apply:**

1. Drug Substance (Active Ingredient) \_\_\_\_\_ Y \_\_\_\_\_ N
2. Drug Product (Composition/Formulation) \_\_\_\_\_ Y \_\_\_\_\_ N
3. Method of Use \_\_\_\_\_ Y \_\_\_\_\_ N

If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent: \_\_\_\_\_

**Name of Patent Owner:** \_\_\_\_\_

**U.S. Agent (if patent owner or applicant does not reside or have place of business in the U.S.):** \_\_\_\_\_

**B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.**

This format repeats to allow up to three patents. If there are additional patents, please copy and attach.

The undersigned declares that the above stated United States Patent Number \_\_\_\_\_ covers the composition, formulation and/or method of use of \_\_\_\_\_ (name of drug product). This product is:

- \_\_\_\_\_ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act;
- OR
- \_\_\_\_\_ the subject of this application for which approval is being sought.

The undersigned declares that the above stated United States Patent Number \_\_\_\_\_ covers the composition, formulation and/or method of use of \_\_\_\_\_ (name of drug product). This product is:

- \_\_\_\_\_ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act;
- OR
- \_\_\_\_\_ the subject of this application for which approval is being sought.

The undersigned declares that the above stated United States Patent Number \_\_\_\_\_ covers the composition, formulation and/or method of use of \_\_\_\_\_ (name of drug product). This product is:

- \_\_\_\_\_ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act;
- OR
- \_\_\_\_\_ the subject of this application for which approval is being sought.

Signed: Rosario G. Ramirez  
Rosario G. Ramirez

Date: 16 March 1999

Title (Optional): Regulatory Affairs, Hill Laboratories, Inc.  
Telephone Number(Optional): (407) 323-1887

A copy of the above information should be submitted to the NDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within 30 days of the date of issuance of the patent.

**PATENT AND EXCLUSIVITY INFORMATION (ITEM 13)**

**Patent Information [21 CFR 314.50(h) and 314.53(c)(3)]**

1. *Active Ingredients:* Fluocinolone Acetonide, Hydroquinone, Tretinoin
2. *Strengths:* Fluocinolone Acetonide 0.01%, Hydroquinone 4.0%, Tretinoin 0.05%
3. *Trade Name:* \_\_\_\_\_
4. *Dosage Form and Route of Administration:* topical cream preparation
5. *Applicant Firm Name:*

The applicant, Hill Dermaceuticals, Inc., is a corporate entity doing business in the U.S. at 2650 S. Mellonville Avenue, Sanford, Florida 32746.

6. *Applicable Patent Number(s):*

*No relevant patents [21 CFR 315.53(c)(3)]* - The applicant, Hill Dermaceuticals, Inc., believes there are no patents which claim the drugs or the drug product or which claim a method of using the drug product and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

16 March 1999

Date

Rosario G. Ramirez

Rosario G. Ramirez  
Regulatory Affairs  
Hill Dermaceuticals, Inc.

**Claimed Exclusivity [21 CFR 314.50 (j)]**

1. The applicant, Hill Dermaceuticals, Inc., claims three (3) years marketing exclusivity upon approval of the drug product that is the subject of this new drug application submitted pursuant to Section 505(b)(1) of the FD&C Act.

2. The applicant makes reference to 21 USC 355 (c)(3)(D)(iii) in support of this claim.

**Claimed Exclusivity - 21 USC 355 (c)(3)(D)(iii)**

- i. *New clinical investigations*: The applicant certifies that to the best of its knowledge the Phase III safety and efficacy clinical investigations included in the application meet the definition of "new clinical investigation" set forth in 314.108 (a).
- ii. *Essential to approval*: The applicant is requesting 3 years of market exclusivity for the product \_\_\_\_\_, pursuant to 21 USC (c)(3)(D)(iii), based on the contained reports of new investigation, other than bioavailability studies, sponsored by the applicant, that is essential to the approval of this application.
- iii. *Conducted or sponsored by*: The applicant certifies that it was the sponsor named in the Form FDA 1571 for Investigational New Drug Application \_\_\_\_\_ under which the new clinical investigation that are essential to the approval of this application was conducted.

16 March 1999

Date

Rosario G. Ramirez

Rosario G. Ramirez  
Regulatory Affairs  
Hill Dermaceuticals, Inc.

**APPEARS THIS WAY  
ON ORIGINAL**

**PATENT AND EXCLUSIVITY INFORMATION (ITEM 13)**

**Patent Information [21 CFR 314.50(b) and 314.53(c)(3)]**

1. *Active Ingredients:* Fluocinolone Acetonide, Hydroquinone, Tretinoin
2. *Strengths:* Fluocinolone Acetonide 0.01%, Hydroquinone 4.0%, Tretinoin 0.05%
3. *Trade Name:* TRI-LUMA
4. *Dosage Form and Route of Administration:* topical cream preparation
5. *Applicant Firm Name:*

The applicant, Hill Dermaceuticals, Inc., is a corporate entity doing business in the U.S. at 2650 S. Mellonville Avenue, Sanford, Florida 32746.

6. *Applicant Patent Number(s):*

*No relevant patents* [21 CFR 315.53(c)(3)] – The applicant, Hill Dermaceuticals, Inc., believes there are no patents which claim the drugs or the drug product or which claim a method of using the drug product and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

19 July 2001

Date

Rosario G. Ramirez

Rosario G. Ramirez  
Director Regulatory Affairs  
Hill Dermaceuticals, Inc.

**Claimed Exclusivity [21 CFR 314.50(j)]**

1. The applicant, Hill Dermaceuticals, Inc., claims three (3) years marketing exclusivity upon approval of the drug product that is the subject of this new drug application submitted pursuant to Section 505(b)(1) of the FD&C Act.

2. The applicant makes reference to 21 USC 355 (c)(3)(D)(iii) in support of this claim.

**Claimed Exclusivity – 21 USC 355 (c)(3)(D)(iii)**

- i. *New clinical investigations:* The applicant certifies that to the best of its knowledge the Phase III safety and efficacy clinical investigations included in the application meet the definition of “new clinical investigation” set forth in 314.108(a).
- ii. *Essential to approval:* The applicant is requesting 3 years of market exclusivity for the product TRI-LUMA cream, pursuant to 21 USC (c)(3)(D)(iii), based on the contained reports of new investigation, other than bioavailability studies, sponsored by the applicant, that is essential to the approval of this application.
- iii. *Conducted or sponsored by:* The applicant certifies that it was the sponsor named in the Form FDA 1571 for Investigational New Drug Application \_\_\_\_\_ under which the new clinical investigation that are essential to the approval of this application was conducted.

19 July 2001

Date



Rosario G. Ramirez  
Director Regulatory Affairs  
Hill Dermaceuticals, Inc.

**APPEARS THIS WAY  
ON ORIGINAL**

EXCLUSIVITY SUMMARY for NDA # 21-112 SUPPL # \_\_\_\_\_  
Trade Name TRI-LUMA Generic Name (fluocinolone acetonide, 0.01% / hydroquinone, 4% / tretinoin, 0.05%) Cream.

Applicant Name Hill Dermaceuticals HFD-540  
Approval Date \_\_\_\_\_

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES / x / NO / \_\_\_ /

b) Is it an effectiveness supplement? YES / \_\_\_ / NO / x /

If yes, what type (SE1, SE2, etc.)? \_\_\_\_\_

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / x / NO / \_\_\_ /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

\_\_\_\_\_  
\_\_\_\_\_  
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:  
\_\_\_\_\_  
\_\_\_\_\_

d) Did the applicant request exclusivity?

YES /  / NO /  /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three years

e) Has pediatric exclusivity been granted for these Active Moieties?

YES /  / NO /  /

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /  / NO /  /

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES /  / NO /  /

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / \_\_\_ / NO / \_\_\_ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # \_\_\_\_\_

NDA # \_\_\_\_\_

NDA # \_\_\_\_\_

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / x / NO / \_\_\_ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 16921, 17340, 17522, 17579, 17955  
19049, 19963, 20400, 20404, 20457

Tretinoin

NDA # None, but it is in an OTC  
Monograph for a cream  
skin-bleaching product

Hydroquinone

NDA # 12787, 13960, 15296, 16161,  
19452, 20001

Fluocinolone Acetonide

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /  / NO /  /

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no

clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /  / NO /  /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

\_\_\_\_\_  
\_\_\_\_\_

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /  / NO /  /

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /  / NO /  /

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

(2) .If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO /\_x\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # Protocol 28A Efficacy & Safety of TRILUMA in the treatment of Patients with Melasma of the Face

Investigation #2, Study # Protocol 28B Efficacy & Safety of TRILUMA in the treatment of Patients with Melasma of the Face

Investigation #3, Study # \_\_\_\_\_

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /\_\_\_/ NO /\_x\_/

Investigation #2 YES /\_\_\_/ NO /\_x\_/

Investigation #3 YES /\_\_\_/ NO /\_\_\_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1                      YES /\_\_\_/                      NO /\_x\_/

Investigation #2                      YES /\_\_\_/                      NO /\_x\_/

Investigation #3                      YES /\_\_\_/                      NO /\_\_\_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1\_\_, Study # 28A \_\_\_\_\_  
Investigation #2\_\_, Study # 28B \_\_\_\_\_  
Investigation #\_\_, Study # \_\_\_\_\_

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided



(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /\_\_\_/          NO /x\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Victoria Lutwak

12-30-01

Signature of Preparer  
Title: Project Manager

Date

*/S/ 1/14/02*

Signature of OF or Division Director

Date

cc:  
Archival NDA  
HFD- /Division File  
HFD- /RPM  
HFD-093/Mary Ann Holovac  
HFD-104/PEDS/T.Crescenzi

EXCLUSIVITY SUMMARY for NDA # 21-112 SUPPL #  
Trade Name TRI-LUMA Generic Name (fluocinolone acetonide,  
0.01% / hydroquinone, 4% / tretinoin, 0.05%) Cream.

Applicant Name Hill Dermaceuticals HFD-540  
Approval Date \_\_\_\_\_

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES /  / NO /  /

b) Is it an effectiveness supplement? YES /  / NO /  /

If yes, what type (SE1, SE2, etc.)?

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /  / NO /  /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES //NO //

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three years

e) Has pediatric exclusivity been granted for these Active Moieties?

YES // NO //

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES // NO //

If yes, NDA # \_\_\_\_\_ Drug Name

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES // NO //

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**  
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /\_\_\_/ NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /\_x\_/ NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 16921,17340,17522,17579,17955                      Tretinoin  
19049,19963,20400,20404,20457

NDA # None, but it is in an OTC                      Hydroquinone  
Monograph for a cream  
skin-bleaching product

NDA # 12787,13960,15296,16161,                      Fluocinolone Acetonide  
19452,20001

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /  /      NO /  /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no

clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /\_x\_/      NO /\_\_\_/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /\_\_\_/      NO /\_x\_/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /\_\_\_/      NO /\_\_\_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO /\_x\_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # Protocol 28A Efficacy & Safety of TRILUMA in the treatment of Patients with Melasma of the Face

Investigation #2, Study # Protocol 28B Efficacy & Safety of TRILUMA in the treatment of Patients with Melasma of the Face

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /\_\_\_/ NO /\_x\_/

Investigation #2 YES /\_\_\_/ NO /\_x\_/

Investigation #3 YES /\_\_\_/ NO /\_\_\_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1                    YES /\_\_\_/                    NO /\_x\_/

Investigation #2                    YES /\_\_\_/                    NO /\_x\_/

Investigation #3                    YES /\_\_\_/                    NO /\_\_\_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1\_\_, Study # 28A

Investigation #2\_\_, Study # 28B

Investigation #\_\_, Study # \_\_\_\_\_

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided

substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

- (a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	:	
_____	:	NO /___/ Explain:
	:	
	:	
	:	
Investigation #2	:	
_____	:	NO /___/ Explain:
	:	
	:	
	:	

- (b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	:		
YES /___/ Explain _____	:	NO /___/ Explain _____	
_____	:	_____	
_____	:	_____	
	:		
Investigation #2	:		
YES /___/ Explain _____	:	NO /___/ Explain _____	
_____	:	_____	
_____	:	_____	

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /\_\_\_/      NO /x\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Victoria Lutwak

12-30-01

Signature of Preparer  
Title: Project Manager

Date

Signature of Office or Division Director

Date

cc:  
Archival NDA  
HFD- /Division File  
HFD- /RPM  
HFD-093/Mary Ann Holovac  
HFD-104/PEDS/T.Crescenzi

Form OGD-011347  
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

-----  
Jonathan Wilkin  
1/18/02 05:09:02 PM

**APPEARS THIS WAY  
ON ORIGINAL**

- Justification for Full Waiver of Pediatric Use Information

(1) The proposed drug product \_\_\_\_\_ is designed to treat hyperpigmentation of the chloasmic or melasmic types that occurs only in sexually mature females (viz., after use of oral contraceptives, surgical manipulation of the mature gonads, and in peri-menopausal females). In very rare instances, this condition may be seen in the adult male who has a very strong family history of this disorder. However, this form of hyperpigmentation is rare in males.

(2) It is rare to find precocious puberty in females in the population and exceedingly rare to find one whose hormonal status has been altered by the above factors. Therefore, even in rare cases of precocious puberty, one will not find the pigmentary disorders described above. Thus, an available population of pediatric and adolescent individuals with this disorder is virtually impossible to find.

(3) There are no other known hyperpigmentary disorders that can be found in the pediatric and adolescent populations for comparative study of this proposed drug product. \_\_\_\_\_

Please let us know if you need any additional information to support the full waiver of pediatric use information for \_\_\_\_\_ for the treatment of hyperpigmentation of the chloasmic or melasmic types.

**APPEARS THIS WAY  
ON ORIGINAL**

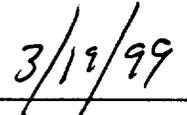
Request for Full Waiver of Pediatric Use Information

Pursuant to 21 CFR 314.55(c)(1) and (2), Hill Dermaceuticals, Inc., hereby requests a full waiver of pediatric use information requirements for the product

Hill Dermaceuticals hereby certifies that:

1. The product does not represent a meaningful therapeutic benefit for pediatric patients over existing treatments and is not likely to be used in a substantial number of pediatric patients because Cutaneous Melanosis does not affect the pediatric population; and
2. Necessary studies are impossible or highly impracticable because the number of adolescent patients (ages 12 - 16) suffering from Cutaneous Melanosis is extremely small and geographically dispersed.

  
\_\_\_\_\_  
Jerry Roth  
Hill Dermaceuticals, Inc.

  
\_\_\_\_\_  
Date

APPEARS THIS WAY  
ON ORIGINAL

# PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 21-112 Supplement # E Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 540 Trade (generic) name/dosage form: Fluocinonide acetate 0.01%, hydroquinone, 4% and tretinoin, 0.05% Action: AP AE NA

Applicant Hill Dermaceuticals, Inc Therapeutic Class Combination corticosteroid/deps agent / KORA KOLBIC

Indication(s) previously approved \_\_\_\_\_  
Pediatric labeling of approved indication(s) is adequate \_\_\_\_\_ inadequate ✓

Indication in this application Treatment of cutaneous melasma for skin types II & III.  
(For supplements, answer the following questions in relation to the proposed indication.)

NA 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

NA 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

- a. A new dosing <sup>u)</sup> formulation is needed, and applicant has agreed to provide the appropriate formulation.
- b. The applicant has committed to doing such studies as will be required.
  - (1) Studies are ongoing.
  - (2) Protocols were submitted and approved.
  - (3) Protocols were submitted and are under review.
  - (4) If no protocol has been submitted, explain the status of discussions on the back of this form.
- c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed. For sun damaged skin in adults, specifically,

    4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form. melasma does not occur often enough in pediatric patients to be studied, AND studies were only conducted in melasma products.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

/S/

Signature of Preparer and Title (PM, CSO, MO, other)

Jan. 18, 2000  
Date

cc: Orig NDA/PLA # 21-112  
HFD-540 /Div File  
NDA/PLA Action Package  
HFD-510/GTroandle (plus, for CDER APs and AEs, copy of action letter and labeling)

/S/  
1/21/00  
in melasma products.

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.



**Lutwak, Victoria L**

---

**To:** DRTL-CORP (E-mail)  
**Cc:** Victoria L Lutwak (E-mail)  
**Subject:** a change needed in comis

For NDA 21-112 and \_\_\_\_\_ (if needed), please make the following change:

COMIS Indication : Treatment of individuals with cutaneous  
**Please change from \_\_\_\_\_ to melasma.**

Thank you.  
Vickey Lutwak

**Lutwak, Victoria L**

---

**From:** Smith, Jacquelyn\*  
**Sent:** Monday, January 14, 2002 7:37 AM  
**To:** Lutwak, Victoria L; CDER-DRTL-CORP  
**Subject:** RE: a change needed in comis

Vickey,

Updates have been completed

Thank You,  
Jackie

-----Original Message-----

**From:** Lutwak, Victoria L  
**Sent:** Saturday, January 12, 2002 12:37 PM  
**To:** CDER-DRTL-CORP  
**Cc:** Lutwak, Victoria L  
**Subject:** a change needed in comis

For NDA 21-112 and \_\_\_\_\_

COMIS Indication : Treatment of individual  
**Please change from \_\_\_\_\_**

Thank you.  
Vickey Lutwak

1-24-02

### PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: NDA 21-112 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

App Date: July 25, 2001 Action Date: January 18, 2002

HFD 540 Trade and generic names/dosage form TRI-LUMA (fluocinolone acetonide, 0.01% / hydroquinone, 4% / tretinoin, 0.05%) Cream.

Applicant: Hill Dermaceuticals Therapeutic Class: combination corticosteroid/depig. Agent/keratolytic

Indication(s) previously approved: none

**Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 1

Indication #1: for the short-term treatment of moderate to severe melasma of the face, in the presence of measures for sun avoidance, including the use of sunscreens.

**Is there a full waiver for this indication (check one)?**

- Yes: Please proceed to Section A.**
- No: Please check all that apply: Partial Waiver Deferred Completed**  
**NOTE: More than one may apply**  
**Please proceed to Section B, Section C, and/or Section D and complete as necessary.**

#### Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study**
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

#### Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study

- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
 Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
 Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments: \_\_\_\_\_

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:  
**Victoria Lutwak**  
*(see appended electronic signature page)*

Regulatory Project Manager  
 DD sign off on 1-18-02 DFS 1-18-02  
 cc: NDA

NDA 21-112

Page 3

**HFD-960/ Terrie Crescenzi**  
**(revised 1-18-02)**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960**  
**301-594-7337**

**APPEARS THIS WAY**  
**ON ORIGINAL**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: \_\_\_\_\_

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: \_\_\_ Partial Waiver \_\_\_ Deferred \_\_\_ Completed  
 NOTE: More than one may apply  
 Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*udies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*(See appended electronic signature page)*

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA  
HFD-960/ Terrie Crescenzi  
(revised 1-18-02)

NDA 21-112

Page 6

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960  
1-594-7337**

**APPEARS THIS WAY  
ON ORIGINAL**

**Request for Full Waiver of Pediatric Use Information**

Pursuant to 21 CFR 314.55(c)(1) and (2), Hill Dermaceuticals, Inc., hereby requests a full waiver of pediatric use information requirements for the product TRI-LUMA.

Hill Dermaceuticals, Inc. hereby certifies that:

1. The product does not represent a meaningful therapeutic benefit for pediatric patients over existing treatments and is not likely to be used in a substantial number of pediatric patients because Melasma does not affect the pediatric population; and
2. Necessary studies are impossible or highly impracticable because the number of adolescent patients (ages 12-16) suffering from Melasma is extremely small and geographically dispersed.

  
\_\_\_\_\_  
Jerry Roth  
Hill Dermaceuticals, Inc.

July 10, 2001  
Date

**APPEARS THIS WAY  
ON ORIGINAL**

## Justification for Full Waiver of Pediatric Use Information

(1) The proposed drug product, TRI-LUMA, is designed to treat hyperpigmentation of the chloasmic or melasmic types that occurs only in sexually mature females (viz., after use of oral contraceptives, surgical manipulation of the mature gonads, and in peri-menopausal females). In very rare instances, this condition may be seen in the adult male who has a very strong family history of this disorder.

(2) It is rare to find precocious puberty in females in the population and exceedingly rare to find one whose hormonal status has been altered by the above factors. Therefore, even in rare cases of precocious puberty, one will not find the pigmentary disorders described above. Thus, an available population of pediatric and adolescent individuals with this disorder is virtually impossible to find.

(3) There are no other known hyperpigmentary disorders that can be found in the pediatric and adolescent populations for comparative study of this proposed drug product, TRI-LUMA.

Please let us know if you need additional information to support the full waiver of pediatric use information for TRI-LUMA for the treatment of hyperpigmentation of the chloasmic or melasmic types.

APPEARS THIS WAY  
ON ORIGINAL



Food and Drug Administration  
Rockville MD 20857

A. Paul Kelly, M.D.  
Martin Luther King Jr. Charles R. Drew Medical Center  
12021 South Wilmington Avenue  
Los Angeles, California 90059

MAR 29 2000

Dear Dr. Kelly:

Between December 6 and 16, 1999, Ms. Yumi J. Hiramine, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol #24) of the investigational drug ~~T~~ 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 the documents submitted with that report and your February 16, 2000, written response to the items listed on Form FDA 483, 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, Ms. Hiramine presented and discussed with you her inspectional observations. The discussion included your failure to: 1) 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 2) maintain adequate records in that adverse events were not adequately reported in the case report form for subjects # 5 #14 #31 #32 #83 and #114. We acknowledge your responses and your promise to make corrections/changes in your procedures to ensure that the findings discussed above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Hiramine 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 yours,

Antoine El-Hage, Ph.D. *151*  
Branch Chief  
Good Clinical Practices II, HFD-47  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place  
Rockville, MD 20855



DEPARTMENT OF HEALTH & HUMAN SERVICES

447D-15410  
Lettwick  
Food and Drug Administration  
Rockville MD 20857

Helen M. Torok, M.D.  
HMT Dermatology  
780 East Smith Road  
Medina, Ohio 44256

MAR 21 2000

Dear Dr. Torok:

Between November 5 and 26, 1999, Mr. Frederick M. Lochner, 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, the documents submitted with that report and your January 3, 2000, written response to the items listed on Form FDA 483, we find several departures from 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 inspectional observations. We acknowledge your response and we wish to emphasize the following:

- 1) You treated 12 subjects prior to study protocol approval and without an IND in effect.
- 2) You failed to conduct the study in accordance with the relevant protocol in that:
  - a) randomization of 17 subjects was not allocated in sequential order;
  - b) subjects #12, #13, #15, #17, #23 were purposefully allocated to the test medication;
  - c) subjects #35, #80, #85, #89, #83 #98 and #17 were enrolled despite not meeting the inclusion criteria;
  - d) subjects #4 and #96 were enrolled in the long term phase of the study despite not meeting the criteria of reaching an efficacy score of one at the end of the initial eight weeks of treatment; and
  - e) not all photographs of lesions were taken for subjects #1, #8 # 11, # 14, #15, #16 and #44.
- 3) You failed to maintain adequate drug accountability records to include the receipt, distribution and return of study medication.
- 4) You failed to obtain IRB approval for the recruitment ads.
- 5) Inadequate consent process in that the consent form used in the study did not include:
  - a) a 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, if available.