********** -COMM. JOURNAL- ********** DATE DEC-28-2001 ***** TIME 12:49 *********

MODE = MEMORY TRANSMISSION START=DEC-28 12:48 END=DEC-28 12:49

FILE NO.=534

STN NO.	COMM.	ONE-TOUCH/ ABBR NO.	STATION NAME/EMAIL ADDRESS/TELEPHONE NO.	PAGES	DURATION
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-FDA/CDER/DDDDP/HFD540 -

********** -301 827 2091 - ***** - 301 827 2091- **********

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

FACSIMILE TRANSMITTAL SHEET

DATE: 12/28/01

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

Subject: Requests for the review of NDA 21-112 BIOPHARM

Total no. of pages including cover: 2

Comments: Please see following page(s).

Document to be mailed: ☐ YES x NO

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

FACSIMILE TRANSMITTAL SHEET

DATE: 12/28/01

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

Subject: Requests for the review of NDA 21-112 BIOPHARM

Total no. of pages including cover : 2

Comments: Please see following page(s).

Document to be mailed: ☐ YES x NO

NDA 21-112
December 13, 2001

Please provide the following
For the biopharm reviewer:

Comment to be conveyed to applicant as an additional information request:
The applicant needs to recalculate the derived pharmacokinetic parameters as the values given in the summary table and the proposed draft label are not consistent with the individual plasma concentrations and, individual derived pharmacokinetic parameters provided in the submission.

APPEARS THIS WAY
ON ORIGINAL

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Dermaceuticals, Inc.

Specialty Dermatologicals for Children & Adults

NDA 21-112
TRI-LUMA
DESK COPY

December 27, 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

Copy of cover desk copy

RE: General Correspondence
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 forwarding this general correspondence regarding New Drug Application (NDA 21-112).

Enclosed you will find complete tables indicated in the response for cross-reference for tables in the ISS report, in reference to Section IX of the December 20, 2001 submission.

Electronic file copy will be submitted as soon as possible. Thank you for your continued support and consideration.

Sincerely,

Criss Molasso

Criss Molasso
Assistant Regulatory Affairs

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

Hill Laboratories

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

PAGES SENT 3 (INCLUDING THIS COVER SHEET)

TO: Ms. Vickey Lutwak

FAX #: 301-827-2075

FROM: Jerry Roth / Nini Ramirez

DATE: 1/18/02

SUBJECT: Letter of Commitment

&%&

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

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Dermaceuticals, Inc.

Specialty Dermatologicals for Children & Adults

NDA 21-112
TRI-LUMA Cream

January 18, 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: Letter of Commitment

Dear Dr. Wilkin,

In reference to NDA 21-112, TRI-LUMA Cream, Hill Dermaceuticals, Inc. has committed to comply with the following:

- Provide the complete study reports for Studies 29 as soon as each study is completed, and provide Safety Updates in those submissions.

- Collection of pregnancy outcome data arising from the use of TRI-LUMA Cream in pregnancy, and to monitor the unintended usage in pregnancy and provide measures on how this can be reduced.

  Hill Dermaceuticals will submit the methodology proposal within 3 months to date, to be discussed with the Agency.

- Conduct a dermal carcinogenicity testing of the combination drug product to support the safety of long-term use.

  The study protocol or protocols will be submitted to the Agency for review prior to the conduct of said study or studies to assure that the studies will address the concerns of the Agency with regard to the use of the product for the treatment of cutaneous melasma. The protocol(s) will be submitted within 4 months and Hill Dermaceuticals will initiate the study or studies within 6 months after the approval of the study protocols. The study or studies will be completed no later than three years after initiation, and the results submitted to the Agency within one year after completion.

- Revise the immediate container label and carton label to show: (1) light space between the ingredients listing and the "Storage" conditions line; and (2) the established name will be at least ½ the size of the tradename.

  These changes will be implemented within 6 months as of January 18, 2002.

Hill Dermaceuticals agrees to all revisions to the physician insert label, including the change in terminology from "methods" to "treatment" in line 136 of the Final Revised draft insert label.

After a brief discussion with Ms. Lutwak, Project Manager, regarding the "Patient Information" packet, corrections from the Agency's reviewing discipline will be forwarded to Hill and concurrence with the changes will be implemented with signatures from Hill representatives.

Jerry S. Roth
President

Rosario G. Ramirez
Director
Medical / Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Number of Pages Redacted 29

❖❖❖

Draft Labeling
(not releasable,

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ATOPIC PAK

Dermaceuticals, Inc.

Specialty Dermatologicals for Children & Adults

FACSIMILE TRANSMISSION RECORD

DATE: January 22, 2002 PAGES (INCLUDING COVER): 2

FOR: Ms. Vickey Lutwak / Project Manager
FDA / CDER / DDDDP

FROM: Criss Molasso
Assistant Regulatory Affairs

FAX #: (301) 827-2075 SENDER'S FAX #: (407) 323-1871
PHONE: (301) 827-2073 SENDER'S PHONE # (407) 323-1887

MESSAGE:
Vickey, following please find copy of cover letter regarding the ***Letter of Commitment*** (TRI-LUMA Cream, NDA 21-112) submission to be FedEx'd today.

Thanks,
Criss

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Dermaceuticals, Inc.

Specialty Dermatologicals for Children & Adults

NDA 21-112
TRI-LUMA Cream

January 22, 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: NDA 21-112, TRI-LUMA Cream
Letter of Commitment

Dear Dr. Wilkin,

Reference is made to NDA 21-112, TRI-LUMA Cream (0.01% fluocinolone acetonide, 4.0% hydroquinone, 0.05% tretinoin), FDA approval date January 18, 2002.

Included in this submission is Hill Dermaceuticals' Letter of Commitment, in acceptance of our Phase 4 commitments, previously sent to the Agency via facsimile on January 18, 2002. The proposed final draft labeling for the physician insert, tube label, carton label and patient information, signed by Hill representatives to acknowledge acceptance, is also included.

The requested revision to the

Sincerely,

Rosario G. Ramirez
Director
Medical / Regulatory Affairs

PRE-SUBMISSION MEETINGS

THE SPONSOR DID NOT REQUEST AN END-OF PHASE-2 MEETING

THE SPONSOR DID NOT REQUEST A PRE-NDA MEETING

HFD-540/LSTWA

MEMORANDUM OF TELEPHONE CONVERSATION

Meeting Minutes
Date: September 22, 1999
Type: T-con
NDA 21-112 ——— (fluocinolone acetonide/hydroquinone/tretinion) Cream
Sponsor: Hill Dermaceuticals, Inc.

Attendees:
FDA: W. DeCamp, E. Pappas, V. Lutwak
Hill Dermaceuticals: Nini Ramirez, Nancy Puglia, Jerry Roth, Chris Molasso, Mary Anna Arsts, Arlene McIntryre

---

Background: The sponsor never requested an End-of-Phase 2 meeting with the division before submission of the NDA. Due to the lack of guidance at this critical phase of the drug development process, combined with review oversight for ——— submissions dated from 9/15/95, outstanding CMC issues exist at this time.

The t-con is at the request of the sponsor for further clarification on the chemist's fax dated August 26, 1999, regarding the stability protocol and specifications.

Reference documents: e-mail to Yana Mille, August 26, 1999
Fax from Hill Laboratories dated, August 19, 1999
Chemist's Request to Applicant

T-con Minutes:

Item #1 in the fax 8/19/99, the division is in agreement with the sponsor that tretinoin and fluocinolone acetonide are not subjected to oxidation.

#2. A stability matrix should be used to test the compatibility of the active ingredients in the formulation. The test method for testing the compatibility of the active ingredients should be stability indicating, whereby a single method is capable to assay each of the components and potential degradation products during long term storage. If a single test method is not capable to detect the degradatants of the drug product, then a second method may be used.

#3. For establishing and validating testing methods for likely degradants in the finished product, the sponsor will use USP methods to check for interference from other products of degradation in the multiple component cream. The sponsor will adapt and validate the single method HPLC to test for each component of the cream by measuring it at the appropriate wavelengths or use of a variable wavelength detector. FDA noted that the compendial HPLC methods for fluocinolone acetonide used a detector wavelength of 254 nm, those for hydroquinone used a detector wavelength of 280nm, and those for tretinoin used a detector wavelength of 365 nm.

Noted: The sponsor was informed that the stability data for the new lot of ——— cream placed on accelerated stability is at possible risk of being submitted late in the review process.

cc:
NDA 21-112
DivFile
HFD-540/DeCamp/Pappas
HFD-540/ Lutwak

EPP VL 11/5/99

E L E C T R O N I C M A I L M E S S A G E

Date: 26-Aug-1999 12:25pm EDT
From: Wilson DeCamp
DECAMP
Dept: HFD-540 CRP2 N206
Tel No: 301-827-2041 FAX 301-827-2075

TO: Yana Mille (MILLEY)

CC: Ernest Pappas (PAPPAS)
CC: Linda Ng (NGL)
CC: Bonnie Dunn (DUNNB)

Subject: degradant specs in USP monographs

Yana:

We are in the process of reviewing an NDA for a combination cream product composed of hydroquinone, tretinoin, and fluocinolone acetonide. The applicant has indicated that the principle degradation products for each drug substance have been identified as follows:

Active Ingredient	Degradant
Hydroquinone	
Tretinoin	
Fluocinolone acetonide	

There are product monographs for creams for the first two actives, and an ointment for the third. We have the following concerns, which I hope you may be able to answer from your files:

(1) Hydroquinone is assayed

HPLC method would identify

Tony

Hill Dermaceuticals, Inc.

"The Scalp Company"

1030 South Mellonville Avenue • Sanford, Florida 32773 • 407-323-1887 • Fax: 407-649-9213

/ NDA 21-112

August 19, 1999

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

RE: Response to Chemistry request.

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

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

Sincerely,

Rosario G. Ramirez
Medical/Regulatory Affairs

Nancy Puglia
Plant Manager / Lab Supervisor

Enc.

cc.
DeCamp
Pappas

Hill Dermaceuticals, Inc.

"The Scalp Company"

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

August 19, 1999

RE: —
NDA 21-112

The following items outline the action(s) taken or planned for — Cream, in response to further information requested by the Chemistry Department (Dr. DeCamp).

FDA Comment:
The NDA did not contain compatibility studies for the use of Hydroquinone (HQ), Tretinoin (RA), and Fluocinolone acetonide (FA) in the finished product. Please note that HQ is a known oxidizing agent, and that both RA and FA are subject to oxidation. The data derived from these studies should be submitted.

HILL Response:
1. The information provided by — , states that HQ is an antioxidant that itself can be readily oxidized. It is oxidized to — which is an inhibitor. It is therefore concluded that RA and FA are not subjected to oxidation.

2. Chemical compatibility between the active ingredients can be shown by using a stability matrix. Three different formulations are used having the same active ingredients and concentrations as in — cream. The formulations are as follows:

Tretinoin + Hydroquinone cream (RED)
Tretinoin + Fluocinolone acetonide (BLUE)
Fluocinolone acetonide + Hydroquinone (BLACK)

Room temperature stability on these formulations are on-going. When additional data becomes available, these will be submitted.

FDA Comment:
3. What is the long term stability of HQ, RA and FA in the finished product on storage? The stability protocol should include tests for likely degradants of

each drug substance. Tentative specification limits for the principle degradation products of each drug substance should also be proposed.

HILL Response:

The principal degradation products for each drug substance has been identified.

Active Ingredient	Degradant
Hydroquinone	
Tretinoin	
.....	
Fluocinolone acetonide	
.....	

A new lot of ——— cream will be manufactured and placed on accelerated stability. From these stability results, a proposed specification limit for each of the principal degradation products will be included in the stability protocol.

Room temperature long term stability on ——— cream is on-going. Data will be submitted when they become available.

Nancy Puglia
Plant Manager
Laboratory Supervisor

APPEARS THIS WAY
ON ORIGINAL

9/22/99

Request to Applicant: Typ.

1. As stated in item 1 above, pleas demonstrate that the assay method is stability indicating, whereby a single method is capable to assay each of these components and potential degradation products. If the applicant is not able to provide a single assay method, they may provide a second and/or third assay method for identifying the degradation products of these active components. The validation of this assay method (s) must be provided to show its accuracy, precision, sensitivity, etc.

2. In summary, please should follow the following analytical method matrix: (Note: Please conduct studies to show that the compounds in the empty boxes below, (1) do not interfer with monograph assay, and (2) for the HPLC methods, can be detected under the monograph conditions.

Method	HQ						
#1	X						
#2			X				
#3					X		

I hope the above information provides the necessary plan to show chemical compatibility of the active ingredients the during stability studies.

Ernie

APPEARS THIS WAY
ON ORIGINAL

HFD-540/LUTWAK

MEMORANDUM OF TELEPHONE CONVERSATION

Meeting Minutes
Date: September 28, 1999
Type: T-con
NDA 21-112 —— (fluocinolone acetonide/hydroquinone/tretinion) Cream
Sponsor: Hill Dermaceuticals, Inc.
Attendees:
FDA: E Pappas, V Lutwak
Hill Dermaceuticals: N Ramirez, J Roth

T-con

A brief t-con to request from the sponsor information for the active ingredient hydroquinone by ——

The following manufacturing information is needed for the review of the NDA:

1. A flow chart of the synthesis of hydroquinone.
2. The identification and control of all impurities in the manufacturing of above.

The sponsor said they would provide the above from ——

Addendum:

The sponsor called to pass on the following: After contacting —— for the requested information, the sponsor was informed that —— has a secrecy agreement with the FDA and wishes to deal directly with the FDA on this matter. We were asked to contact —— A t-con is scheduled for October 1, 1999, at 2:00 PM.

cc:
NDA 21-112
DivFile
HFD-540/DeCamp/Pappas/ Lutwak

WD - ESP
10/8/99

MEMORANDUM OF TELEPHONE CONVERSATION

Teleconference Date: October 20, 1999 Time: 1000
Location: N225

T-Con

Sponsor: ——
Purpose of Meeting:

FDA Attendees: W. DeCamp, J. Vidra, V. Lutwak
Fujisawa: Laura Navarre, Glen Wilson, D. Baxter

Ref Doc:
NDA 18-116 S/009
NDA 18-498 S/011

Background:

The above supplements were approved, June 16, 1999, for a change in the polypropylene resin for the cap due to discontinuation by the supplier. The sponsor requested a t-con with the Division because the supplier has discontinued the approved resin and now has to change to another resin. They would like to submit this CMC change in an annual report. But before they do this, they would like concurrence from the Division.

T-con:

It was explained to the sponsor that this change cannot be submitted in an annual report and requires a prior approval supplement because the drug product can come in contact with the cap.

The sponsor should request LOAs (letters of authorization) from the DMFs holders, ——. At that time, have —— specify for the FDA the location (page number) for the information for the resin in the DMF and have —— specify the location for the information on the cap closure in their DMF.

At one point during the discussion, it was noted that the cap was polypropylene based and the standard accelerated stability conditions at 40°C/75 % RH cannot be used. They were advised to use 30°C/60% RH for 3 months beside the 25°C/60% RH for 3 months. One commercial lot should be placed on stability for one year per the stability protocol using a partial fill using caps manufactured with the old and new resins.

The sponsor was advised, that after the supplement was received, the review would be conducted in a timely manner.

It was noted by the sponsor that an ANDA product Aristicort has been approved with this new resin by OGD. A facsimile copy of the OGD approval letter was requested.

The sponsor is considering using a "gamma" seal to prevent the product from coming in contact with the cap. They were advised that they may use three months of stability with this change. In the future, by using a seal on the cap the sponsor can avoid the above approval process if the supplier changes resin. This process involves the DMF holder implementing a PIP (packaging interchange protocol). The sponsor should confirm with the DMF holder that the DMF contains a PIP.

Addendum: The sponsor stated that they were given verbal permission to submit the resin change in the annual report for five Aristocort products.

Attachments:
Emails dated: 5-OCT-99

cc:

NDA 18-116
Div File

NDA 18-498
Div File

HFD-540/ DeCamp/Vidra/Lutwak

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 05-Oct-1999 04:58pm EDT
From: Mary Jean Kozma-Fornaro
KOZMAFORNARO
Dept: HFD-540 CRP2 N252
Tel No: 301-827-2023 FAX 301-827-2075

TO: Wilson DeCamp (DECAMP)

Subject: Cyclocort NDAs 18498/S011 and 18116/S009

tony,

The sponsor for the above supplements received and approval for resin cap changes. The supplier with this approval is no longer available.

Sponsor wants to know how to submit the new supplier:

1. need a new supplement for each NDA for new supplier?

2. any other mechanism?

thanks. MJ

APPEARS THIS WAY
ON ORIGINAL

Number of Pages Redacted 6

Confidential,
Commercial Information

DEPARTMENT OF HEALTH & HUMAN SERVICES 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

JAN 2 1 2000
MT Letter

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 1[illegible], June 4, and 23, August 19, and 27, September 9 (two), 13, 24, and 27, October 12, 25 (two), [illegible] 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 ICH 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.

8 0000

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 6 month long term stability data are insufficient to support the proposed 24 month 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 internal coating and tube sealant with the finished product. To do this, we recommend that you conduct leaching and/or migration tests on the internal coating and sealant 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 sealant , 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,

/S/

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

HFD-540

Lutwak

MEMORANDUM OF MEETING

Meeting Date: March 7, 2000 Time: 2:00 PM

Meeting ID: 5491 Location: S225A

Purpose of Meeting: T-con to respond to Sponsor's response, January 24, 2000, to NA letter dated January 21, 2000.

Meeting Chair: Jonathan K.Wilkin, M.D., Director, Division of Dermatologic and Dental Drug Products

Meeting Recorder: Victoria Lutwak, Project Manager, Division of Dermatologic and Dental Drug Products, DDDDP, HFD-540

FDA Attendees:
Jonathan K.Wilkin, M.D., Director, DDDDP, HFD-540
Hon-Sum Ko, M.D., Medical Officer, DDDDP, HFD-540
Wilson DeCamp, Chemistry Team Leader, DDDDP, HFD-540
Ernest Pappas, Chemist, DDDDP, HFD-540
Abby Jacobs, Ph.D., Pharmacologist/Toxicologist Team Leader, DDDDP, HFD-540
Amy Nostrand, Ph.D., Pharmacologist/Toxicologist, DDDDP, HFD-540
Mohamed Al-Osh, Ph.D., Biostatistics Team Leader, HFD-725
Valeria Freidlin, Ph.D., Biostatistican, HFD-725
Dennis Bashaw, Pharm.D., Biopharmaceutical Team Leader, HFD-880
Victoria Lutwak, Project Management, DDDDP, HFD-540

Hill Dermaceuticals, Inc. Attendees:
Jerry Roth, President
Rosario Ramirez, M.D.
Nancy Puglia
Mary Ann Arsts
J. Rosen, Esq.

Chemistry, Manufacturing, and Controls:
The sponsor has responded to our requests for information with the following correspondences dated December 12, 1999, March 1, 2000, which have yet to be reviewed. At this time, the sponsor should be aware that there may be further review issues.

Pharmacology/Toxicology:
A chronic dermal application study would help evaluate not only local effects, but also systemic adverse effects. Since the interaction of the three active drug substances has not been evaluated, it is unknown how they might affect the systemic exposure and toxicity of each other.
Similarly, studies of reproductive/developmental toxicology of the drug product would evaluate the interactions of the three active ingredients and their combined effects in this area. These studies should be performed to support approval of the drug product and to provide information for the drug label.

Biopharmaceutics:
Dennis will revise these comments
3. Studies on systemic absorption and HPA axis function (adrenal suppression) should be provided to support the systemic safety of the TRADENAME cream.
The sponsor stated that the in vivo study for the three active ingredients has been completed
blood samples drawn and in the freezer) but the analysis of the samples has yet to be started.

While the Agency encourages the approach taken by this sponsor to assess actual in vivo absorption, the HPA axis suppression study is currently the study upon which in vivo assessment of corticosteroid bioavailabilty is based. It is for this reason that the HPA axis study cannot be deferred to phase IV without incurring very restrictive labeling regarding their products use.

While the sponsor has yet to submit their protocol for the HPA axis trial for review, the Agency will work with the sponsor to provide them a quick turn around on the review, depending upon workload constraints.

Clinical/Statistical:
Note that number three was addressed by biopharmaceutics.
2. A study with adequate sample size should be performed to determine the contact sensitization potential of the TRADENAME cream.
For the contact sensitization study a sample size of 200 is acceptable. The sample size in one study was 50 and the other study used the not-to-be marketed formulation which was not an acceptable study.
The dermal safety study is necessary for approval and cannot be a phase 4 study. The sponsor asked if they could do 150 and use the 50 from the completed study. This would be possible if there were no problems with the completed study. The sponsor was informed that the Agency is interested in knowing the effects of steroid in the to-be-marketed formulation and would be interested in a study of the to-be-marketed formulation with and without steroid. The rationale for this being that steroid can suppress sensitization. This can be a cross over study.

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 ICH E1A Guidance Document for additional information).
The sponsor was referred to the ICH E1A document, "Guidance of Industry, M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals." The patient totals for the triads equaled 100 with long-term data (6 months) for 36 patients. These were not adequate numbers for drug product indicated for chronic use i.e. recurrence of condition. The labeling (risk/benefit) will reflect the chronic use for a cosmetic type of indication. We are not asking for efficacy beyond the eight or twelve weeks. This can be open label study.

Biostatistics:

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.

Following the recommendations of the Division of Scientific Investigations (DSI), for the efficacy analysis, the Division excluded 116 patients in the East Study and 47 patients in the West Study. In this efficacy analysis, superiority of TRADENAME cream over each of the three dyads has not been established.
Dr. Roth asked what were the reasons for excluding those particular patients Dr. Freidlin told that she does not have this information available right now.

The sponsor was informed that the study had design problems and therefore, it was difficult to interpret the results.

The assignment of patients to treatments was not completely random for the following reason:

Each of the five sites had the same randomization scheme instead of having a separate scheme (as recommended in the ICH E9 Document).
As can be see from the randomization listing, the first 10 enrolled patients were to be assigned to the [redacted] arm. The next 24 patients (from #11 to #34) were to be assigned to dyads only. With this scheme, the allocation of patients to treatment arms cannot be considered random. The validity of statistical inferences is based on random allocation to treatments. With the allocation scheme used, it is difficult to draw a scientific conclusion concerning the efficacy results from these studies.

The sponsor was informed that the color coding of the tubes presented problems with the blinding of the studies.

At this time, the sponsor referred to DSI (Division of Scientific Investigation) and the 483s issued to the investigators mentioning that he informed them not to respond to the 483s. The sponsor was informed that DSI advised the division about which data they may have reservations. These reservations affected the reviewer's ability to do a proper analysis of the data.

The sponsor was informed that Dr. Willis' study was unusable because the Agency evaluates efficacy in studies where safety data are collected during the same trial. While we would accept additional safety data from other sources, we need safety information from trials for efficacy.

Regarding the randomization, the sponsor was informed that the validity of statistical conclusions is based on the assumption of random allocation of patients to treatment arms. As the randomization scheme used in the pivotal studies was not random, the validity of the statistical conclusions in the pivotal studies is questionable.

ACTION ITEM:

Provide the sponsor with the list of exclusions.
List sent via facsimile 3/8/00.

ADDENDUM:

We request that when the sponsor prepares their response to the NA letter, it be a complete response at the time of submission.

Minutes Preparer: /S/
Victoria Lutwak/Project Manager, DDDDP

Chair Concurrence: /S/
Jonathan Wilkin, M.D./Division Director, DDDDP

APPEARS THIS WAY
ON ORIGINAL

cc: NDA 21117
Div. File

cc:
HFD-540/ Wilkin
HFD-540/ DeCamp
HFD-540/ Pappas
HFD-725/ Al-Osh
HFD-725/ Freidlin
HFD-880/ Bashaw
HFD-540/ Ko
HFD-540/ Jacobs
HFD-540/ Nostrand
HFD-540/ Lutwak

MEMORANDUM OF MEETING MINUTES

Meeting Date:	June 16, 2001	Time: 1:00 p.m.
Location:	9201 Corporate	N225
Application:	NDA 21-112	Pre-Submission Guidance Meeting for NA letter Response
Meeting ID:	6966	
Sponsor:	Hill Dermaceuticals	
Meeting Chair:	Jonathan Wilkin, M.D./Division Director	
Meeting Recorder:	Victoria Lutwak/Project Manager	

FDA Attendees, Titles, and Office/Division:

Jonathan Wilkin, M.D./Division Director DDDDP, HFD-540
Hon-Sum Ko, M.D./Medical Officer, DDDDP, HFD-540
Ernest Pappas./Chemistry Reviewer DNDCIII, HFD-830
Amy Nostrandt, Ph.D./ Pharmacologist/Toxicologist DDDDP, HFD-540
Dennis Bashaw, Pharm.D./Team Leader, Pharmacokinetics DPEIII, HFD-880
Tapash Ghosh, Ph.D./ Pharmacokinetic Reviewer DPEIII, HFD-880
Shiowjen Lee, Ph.D./Acting Team Leader, Biostatistics DBIII, HFD-725
Victoria Lutwak/Regulatory Project Manager, DDDDP HFD-540

External Constituent Attendees and Titles:

[redacted] Consultant
[redacted] Consultant
Sandra Morseth, Ph.D./Toxicologist, Pharm/Tox writer
Chandra B. Louise, Ph.D./ Medical writer, Integrated Safety Summary
Fred O. Smith, MD Medical writer, Integrated Safety Summary
Xiangyi Meng, Ph.D./Biostatistician, Target Research
Cindy Davis, Ph.D./Medical writer, Integrated Efficacy Summary

Hill Dermaceuticals, Inc.

Jerry S. Roth/President and Owner
Nini Ramirez, M.D./ Medical and Regulatory
Nancy Puglia, Chemical Engineer./Plant Manager and Analytical Lab Supervisor
Marianna Arsts, B.A./Analytical Lab Chemist
Criss Molasso/Regulatory Associate
Arlene McIntyre/Secretary

Purpose:

The purpose of the meeting is to discuss and agree upon the content and format for the Sponsor's response to the Not Approvable (NA) letter of January 21, 2000. A briefing package along with questions was submitted for this meeting.

Chemistry, Manufacturing and Controls:

Hill has completely addressed all five CMC deficiencies. The data resulting from the studies described in the fax submission of June 12, 2001, should be included in your response. The adequacy of this information from a CMC standpoint is a review issue and will be addressed by an IR letter at a later date.

Pharmacology/Toxicology:

All pharmacology/toxicology issues noted in the NA letter appear to have been addressed.

Biopharmaceutics:
Note: Only item # 2 was discussed during the meeting. The remaining items are intended as guidance.

- The following comments under **HPA-axis suppression protocol** should be addressed in the final report:

1. This is a standard Cortrosyn stimulation study. Therefore, the procedure and data analysis should be consistent with the information in the Cortrosyn package insert.

2. It was agreed upon previously that an application rate of 5.5 mg/cm^2 will be used for safety assessment of the product. Therefore to be consistent with other safety protocol, the sponsor should use the same rate in the facial area to reflect possibility of HPA axis suppression under maximal usage condition. It is not clear, however, how the sponsor derived the proposed "2 $\mu g/cm^2$ rate to the entire facial area for a total maximum exposure of approximately 360 mg." [The sponsor clarified during the meeting that the 2 $\mu g/cm^2$ is incorrect and should read 2 mg/cm^2 .]

3. The protocol reads "If the pre-stimulation serum cortisol levels are between 10 and 18 $\mu g/dL$, then a post-stimulation serum cortisol level of > 18 $\mu g/dL$ will be considered a normal response." However the sponsor should consult Cortrosyn package insert carefully to interpret the results as the insert reads "The 30-minute level should show an increment of at least 7 $\mu g/dL$ above the basal level. If the 60-minute test period is used, the criterion for a normal response is an approximate doubling of the basal plasma cortisol value."

4. The protocol also reads "A pre-stimulation serum cortisol level > 18 $\mu g/dL$ will be considered indicative of normal HPA functioning." However, the sponsor should assign an upper limit for the basal plasma cortisol value as an inclusion criteria for patient's recruitment.

5. In their "Inclusion Criteria" for patients, the sponsor indicated that patients must have a normally functioning HPA axis as defined by 8 AM serum cortisol level of at least 10 $\mu g/dL$, and demonstrate a response to cosyntropin injection of at least 18 $\mu g/dL$. Therefore it is not

clear why patients with subnormal pre-stimulation serum cortisol levels of < 10 μg/dL and post-stimulation (cosyntropin) serum cortisol levels < 18 μg/dL at the end of treatment need to be recruited and re-tested 7 days after the final dose and followed until a normal level (pre- or post- stimulation) is obtained.

6. The study flow chart indicates that blood and urine sampling will be done at pretreatment and at the end of 8 weeks for measurement of actives. However details of sampling at those times need to be mentioned to make any meaningful conclusion from those levels in future.

7. Analytical procedure to be followed to analyze the actives in blood and urine samples are not mentioned in the protocol and should be provided with the results.

The comments under **Study 104479: In-vivo Study on systemic absorption after maximum exposure to the drug product are:**

- The sponsor did not submit any analytical validation report.

- The analytical method should be sensitive enough to distinguish the achieved tretinoin level from endogenous level.

- The reviewer is not aware of reviewing any protocol for this study in the past. Regulatory utility of the data with one (1) gram of cream application to 45 subjects is questionable as they will not reflect maximal usage condition.

Clinical:

1. The safety data from the original clinical studies were not reported on MedDRA system for coding. These safety data have been submitted in the original NDA. Because these data will be resubmitted along with the data report from the new clinical efficacy and safety studies in the Integrated Summary of Safety Report for this forthcoming submission, the old safety data will be presented as a listing and not decoded according to the MedDRA system. Please advise.

   - *The Agency uses MedDRA for AERS, but currently has no requirement for NDA submissions. The Sponsor may present the old safety data as a listing, but is required to analyze the safety information in the ISS. If the previous studies are not considered "pivotal" because of data quality, they may be used as supportive data and kept separate from information from the more recent studies.*

2. Regarding the assessment on safety for long-term use, the NDA submission will be adhering to the ICH guidelines, ICH E1A Guidance. The NDA will be filed containing safety data from patients treated through 6 months. Data on patients treated through 12 months will be submitted as soon as available prior to approval.

   - *The Agency will review the material presented at the time of submission of the Sponsor's response. The Agency cannot commit to completing review of late material, which may have impact on labeling, to meet the time line for the NDA action. The Sponsor is encouraged to have as much information as possible to the Agency at the time of filing.*

PRE-SUBMISSION Conference Meeting 1-16-C

3. Two study protocols (one on human volunteers, the other on monkeys) structured to provide additional supporting data on pharmacokinetics of the investigational drug were submitted under the IND. Comments were received from the Agency regarding the studies. Since these studies are optional studies undertaken by Hill, we are requesting consideration of these studies as a post-approval submission.

   - *The regulatory utility of these studies is not clear, and they are not necessary for filing purposes.*
   - *The protocol of Study Hum-01 states: "Hydroquinone, tretinoin and fluocinolone acetonide at **current approved drug concentrations**, and with one of these drugs labeled with ^{14}C-tracer, will be applied as a mixture to the ventral forearm skin of human volunteers." Currently, the Sponsor's supporting letter from [redacted] says: "The trial formulation with radioactivity will be the same as that **proposed for approval**." Thus far, no protocol amendment has been submitted to address this change.*
   - *The validation of the laboratory preparations of the radioactive drug products having the same formulation as that proposed for marketing should be described.*

Other detail for this approaching NDA submission:

1. The forthcoming submission is a paper NDA, with accompanying electronic copies in diskettes, in Word document or the appropriate program required.

   - *For electronic copies of documents for Clinical review, the Sponsor is encouraged to provide in Microsoft Word format the Clinical Study Reports of the "pivotal" studies, including protocols, the Integrated Summaries (effectiveness, safety, and benefits and risks), and draft label (annotated and clean copy).*

2. The submission will include draft labeling (Package insert, container labels, and box labels) revised from the original NDA filed, which will contain data from the recent clinical studies, non-clinical studies and animal toxicology studies. Annotated package insert will also be included.

   - *This will be a review issue.*

Overall Comments

- In its response to the Not-Approvable Letter, the Sponsor should submit the clinical section in accordance to the Guidance "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications".

- Safety Update in the Sponsor's response to Not-Approvable Letter may refer to the new Integrated Summary of Safety.

Biostatistics:

1. This submission includes only summaries of Studies 28A and 28B. This reviewer cannot comment based on the summaries of these studies. Some review issues may arise when the complete response is submitted.
2. The submission should provide the randomization list, which shows treatment allocation prior to enrollment and patient date/time of enrollment in the study. Patient

demographic/baseline characteristics and efficacy results, by center, will be needed in the subnission. Efficacy subgroup analysis (in age, race, and gender subgroups) in each study and in the two studies combined will be needed.

3. To comply with the combination policy, the test drug should be statistically significantly better than each of the three dyads. Therefore, no comparisons versus the combined dyad grouping are required. The sponsor should explain why comparisons versus the combined dyad grouping are included in the protocol.
4. Studies 28A and 28B are investigator-blinded studies. The sponsor needs to provide a rationale why the studies were not double-blinded and more details on the sinvestigator blinding.

Administrative Comments:

All comments are based upon the briefing document, which is an unofficial document submitted as information.

Pediatric Studies:
Please refer to the Federal Register Pediatric Final Rule published December 1998. The Content and Format of IND submissions must now include plans for assessing pediatric safety and effectiveness (21CFR 314.50(d)(7) & 21CFR 314.55).

A waiver can be requested in accordance with 21 CFR 314.55(c).

Financial Disclosure:

The Final Rule regarding Financial Disclosure was published on February 2, 1998, for applications submitted after February 2, 1999, the applicant is required either to certify the absence of certain financial interests and arrangements of clinical investigators or to disclose those financial interests.

Minutes Recorder: _____
Victoria Lutwak/Project Manager, DDDDP

Chair Concurrence: _____
Jonathan Wilkin, M.D./Division Director, DDDDP

cc:
NDA 21-112

Division File
HFD-540/Meeting Minutes files
HFD-540/Wilkin
HFD-540/Walker/Ko
HFD-540/Jacobs/Nostrandt
HFD-830/DeCamp/Pappas
HFD-725/Alosh/Freidlin/S.Lee
HFD-880/Bashaw/Ghosh
HFD-540/ Lutwak

Drafted by: V. Lutwak, 6-5-01
Final: 6-18-01
File: Pre-Submission Guidance Meeting for NA letter Response

MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

DERMA-SMOOTHE/FS®
SCALP OIL

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ATOPIC PAK

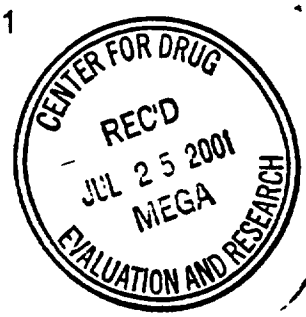
ONE AMENDMENT
A2

Dermaceuticals, Inc.

Specialty Dermatologicals for Children & Adults

NDA 21-112
TRI-LUMA Cream

July 20, 2001



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

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

Dear Dr. Wilkin :

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

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

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

ORIGINAL

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

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

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

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

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

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

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

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

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

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

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

The internal coating [redacted] and end sealant [redacted], components of the aluminum tube used for packaging TRI-LUMA Cream has been found to be suitable for this purpose based on the results of the leaching and/or migration tests performed.

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

APPEARS THIS WAY
ON ORIGINAL

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

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

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

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

Sincerely,

Jerry S. Roth
President

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

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

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

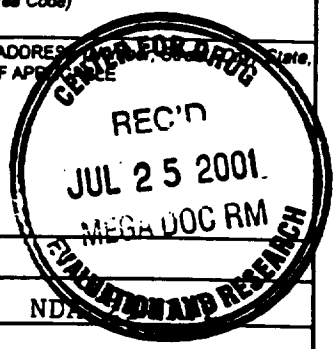
Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

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



PRODUCT DESCRIPTION

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

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

(PROPOSED) INDICATION(S) FOR USE:

Melasma

APPLICATION INFORMATION

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

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

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

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

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

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

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

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

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

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

Please See Attachment

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

FORM FDA 356h (4/00)

Created by Media Arts/USDHHS (301) 443-2454 EF

ORIGINAL

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

CERTIFICATION

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

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

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

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

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

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Rosario G Ramirez	Rosario G. Ramirez Director, Medical/Regulatory Affairs	JULY 24, 2001
ADDRESS *(Street, City, State, and ZIP Code)*		Telephone Number
2650 So. Mellonville Ave., Sanford, FL 32773		(407) 323-1887

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

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

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

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

FORM FDA 356h (4/00)

ATTACHMENT to 356h

CHEMICAL NAME

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

Hydroquinone: **1,4-benzenediol**

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

STRENGTHS

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

ESTABLISHMENT INFORMATION

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

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

Drug Substance: Fluocinolone acetonide USP Drug Master File Number:
Location:

Contact:

Telephone:

Drug Substance: Hydroquinone USP Drug Master File Number:
Location:

Contact:
Telephone. (423) 224-0260

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

Contact:

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ATOPIC PAK

Dermaceuticals, Inc.

Specialty Dermatologicals for Children & Adults

NDA 21-112
TRI-LUMA Cream

August 21, 2001

cc:
Jacobs
Nostrandt
Beshaw
Ghosh
Ko

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
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.

Response to 5042

29 & 30? for 100 pt.

C. The estimated timeline for the Long-term (12 months) Safety Study (Study Protocol 29) is as follows:

- Cut-off date for Study 29.....October 31, 2001
- Final Report for Study 29 and ISS report.....November 23, 2001

D. The number of diskettes enclosed with the review copy of the Clinical Section of the amendment to pending NDA application is 18.

- Final Report on Pivotal Study 28 A .....1 diskette
- Final Report on Pivotal Study 28 B.....1 diskette
- Tables and Listings for Pivotal Study 28 A .....1 diskette
- Tables and Listings for Pivotal Study 28 B.....1 diskette
- Final Report : Integrated Summary of Efficacy.....1 diskette
- Final Report : Integrated Summary of Safety.....1 diskette
- Tables for the Integrated Summary of Efficacy.....2 diskettes
- Tables for the Integrated Summary of Safety.....2 diskettes
- Integrated Tables for Pivotal Studies 28 A and 28 B.....2 diskettes
- Study 29 (Long-Term Safety Study) Tables.....1 diskette
- Annotated Physician Insert Label.....1 diskette
- Final Report on Study 33, Adrenal Suppression Study.....1 diskette
- Final Report, Maximum Systemic Exposure Study.....1 diskette
- Final Report, Analytical Assay test for Fluocinolone acetonide, Hydroquinone and Tretinoin, Group 1 subjects.....1 diskette
- Final Report, Analytical Assay test for Fluocinolone acetonide, Hydroquinone and Tretinoin, Group 2 subjects.....1 diskette

E. Location in the NDA amendment (page numbers) for the following items:

- Categorical Exclusion under 21 CFR 25.31(b) can be found in the original NDA submission dated March 19, 1999, volume 1.3, pages 4 0844 - 4 0846.

- Statement on animal care and use, in compliance with the Animal Welfare Act and/or the Guide for the Care and Use of Laboratory Animals, and the Office for Protection from Research Risks, for rats and rabbits, can be found in the following pages:

  Study 7169-101.....page 5 0662
  Study 7169-102.....page 5 1272
  Study 7169-103.....page 5 0503
  Study 7169-104.....page 5 1120
  Study 7169-105.....page 5 2095
  Study 7169-106.....page 5 1590

- Statement on animal housing for mini pigs.....pages 5 0120, 5 0057

- In compliance with 21 CFR part 50 and part 56, please find the Institutional Review Board approvals and approved Informed Consent Agreement for human studies, at the following pages:

  Pivotal Clinical Study 28A.....pages 7 0386 to 7 0510

  Pivotal Clinical Study 28B.....pages 7 2401 to 7 2489

  Adrenal Suppression Study 33.....pages 6 0687 to 6 0701

  Maximum Systemic Exposure Study
  (HTR 104479).....pages 6 0031 to 6 0087

Please advise if further information is needed. As always, thank you for your continued support and assistance.

Sincerely,

Rosario G. Ramirez
Director
Medical / Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

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ATOPIC PAK

Dermaceuticals, Inc.

Specialty Dermatologicals for Children & Adults

FACSIMILE TRANSMISSION RECORD

DATE: 21 August 2001 **Pages (including cover): 4**

TO: Ms. Vickey Lutwak, Project Manager

COMPANY: FDA CDER / DDDDP

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

Tel. no. # (407) 323-1887

RE: **NDA 21-112**

Dear Vickey,

This letter contains all the information you have requested. I will formally file the letter as Information Response, under the NDA.

We, here at Hill, are hoping for a very favorable and smooth filing review. Please advise if further information is needed.

Thank you for all your help and guidance.

Sincerely,

Nini

Rosario G. Ramirez
Director
Medical / Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-112

INFORMATION REQUEST LETTER

Hill Dermaceuticals, Inc.
Attention: Rosario G. Ramirez, M.D.
Director, Medical/Regulatory
2650 So. Mellonville Ave.
Sanford, FL 32773

Dear Dr. Ramirez:

Please refer to your July 20, 2001, amendment to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRI-LUMA (fluocinolone acetonide, 0.01% / hydroquinone, 4% / tretinoin, 0.05%), Cream.

We also refer to your submissions dated August 21 and 22, 2001; and facsimile dated August 29, 2001.

We are reviewing the Clinical, Statistical, Biopharmaceutical, Chemistry, Manufacturing and Controls, and Pharmacology/Toxicology sections of your submission and have the following information requests that you and Ms. Lutwak have previously discussed. During those discussions, you were requested to provide a timeline(s) for when the Agency can expect receipt of this information. May we remind you that is crucial that you adhere to your committed timeline(s) for amendments to the NDA in order for us to continue our evaluation.

Clinical:

Long-term safety study (Study Protocol 29) final report and ISS will be submitted on or before November 23, 2001.

Information on pregnancies associated with usage of study medication in clinical studies, including the number of pregnancies reported in the clinical program, and, for each pregnancy, please provide the following:

- Study
- Patient ID
- Type of treatment
- Date treatment started (or restarted, if for retreatment)
- Date of (a) LMP and (b) first positive pregnancy test
- Date of last treatment (a) visit and (b) dose
- Date pregnancy terminated (and specify how, e.g., delivery/abortion/miscarriage)
- Pregnancy Outcome
- Additional information on fetus/live-born baby
- Any post-natal follow-up data to-date

Statistical:

The following requested information will be responded to on of before September 21, 2001:

- Electronic SAS data sets (in transport file format) are needed for the review process.
- 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).
- Request subgroup analysis by disease severity at baseline.
- Request detailed description of randomization for studies 28A and 28B.

Biopharmaceutical:

The Validation Reports for the human plasma assay will be submitted on or before September 27, 2001

Chemistry, Manufacturing and Controls:

[redacted] sealant: The Agency informed you on August 22, 2001, that the DMF holder will no longer be supplying this product to Hill Dermaceuticals. A teleconference to discuss this issue was held on August 29, 2001. Minutes from this telephone conference provide the following agreements:

- The sponsor will place tubes manufactured without a sealant on accelerated stability on or about September 6, 2001, collecting data on day 30, 60, and 90. They will send in the stability information at day 60 and day 90. The last set of stability data will be submitted the 2nd or 3rd week of December for review. In addition to the assay data and the results of other release tests, selected specific tubes (probably at least 12) should be monitored for weight loss. This information will be needed for our review of the results. The stability report should include a diagram of the fold at the end of the tube.

- This stability protocol will be sufficient to be a bridge study to the previously submitted stability data. Please send in an amendment to the NDA to amend the present protocol.

- If there is a problem (failure), please notify us immediately.

Pharmacology/Toxicology:

The final report for the 6-month minipig tox study to support use of this combination product will be submitted to the NDA for review on or before September 12, 2001.

If you have any questions, please call Victoria Lutwak, Project Manager, at (301) 827-2073.

Sincerely,

{See appended electronic signature page}

Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

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/s/

Mary Jean Kozma Fornaro
9/5/01 03:59:53 PM

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELEPHONE CONVERSATION

Meeting Minutes
Date: August 21, 2001
Type: T-con
NDA 21-112 TRI-LUMA (fluocinolone acetonide/hydrocortisone/tretinoin) Cream
Sponsor: Hill Dermaceuticals, Inc.

Attendees:
FDA: W. DeCamp, E. Pappas, and V. Lutwak
Hill Dermaceuticals: Nini Ramirez, Nancy Puglia, Jerry Roth

Telephone number: 1-800-344-5707

Background:
Submission dated July, 20, 2001; rec'd July 25, 2001.
Response to NA Letter

The t-con was to inform the Applicant that we received notification from [redacted] today, the manufacturer of [redacted] sealant, that they no longer manufacturer this product, and, therefore; will not be supplying it to Hill Dermaceutical, Inc.

This information was supplied by [redacted], in response to our request for information regarding the [redacted].

We informed the sponsor that this is not a fileability issue, but we would like to know how this information impacts on their container closure system.

See attachment of telephone conversation..
cc:
NDA 21-112
DivFile
HFD-540/DeCamp/Pappas/ Lutwak

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/s/

Victoria Lutwak
12/27/01 03:09:57 PM
CSO

Ernest G. Pappas
12/27/01 03:15:40 PM
CHEMIST
I concur.

Wilson H. DeCamp
12/27/01 03:20:39 PM
CHEMIST
concur with memorandum

APPEARS THIS WAY ON ORIGINAL

IN DFS

MEMORANDUM OF TELECON

Date: August 29, 2001
Type: T-con
NDA 21-112 TRI-LUMA (fluocinolone acetonide, 0.01% / hydroquinone, 4% / tretinoin, 0.05%) Cream.

Sponsor: Hill Dermaceuticals, Inc.
Telephone number: 800-344-5707

Attendees:
FDA:
Wilson DeCamp, Ph.D./Team Leader, Chemistry DNDCIII, HFD-830
Ernest Pappas/Chemistry Reviewer DNDCIII, HFD-830
Victoria Lutwak/Regulatory Project Manager, DDDDP HFD-540

Hill Dermaceuticals

Jerry S. Roth/President and Owner
Nini Ramirez, M.D./ Medical and Regulatory
Nancy Puglia, Chemical Engineer/Plant Manager and Analytical Lab Supervisor

Background:
Submission dated July 22 , 2001. Received August 23, 2001

Hill Dermaceuticals, Inc. is formally requesting a telephone conference with Dr. DeCamp and Mr. Pappas, with the CMC department, on the following.

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.

After a brief discussion, we agreed to the following:

The sponsor will place tubes manufactured without a sealant on accelerated stability on or about September 6, 2001, collecting data on day 30, 60, and 90. They will send in the stability information at day 60 and day 90. The last set of stability data will be submitted the 2nd or 3rd week of December for review. In addition to the assay data and the results of other release tests, selected specific tubes (probably at least 12) should be monitored

for weight loss. This information will be needed for our review of the results. The stability report should include a diagram of the fold at the end of the tube.

This stability protocol will be sufficient to be a bridge study to the previously submitted stability data. Please send in an amendment to the NDA to amend the present protocol.

If there is a problem (failure), they will notify us immediately, then we will discuss plan #2.

2. Alternate plan.- to use packaging tubes with an end-sealant different from ——
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.

The sponsor is researching a replacement product for the —— in parallel with the above.

cc:
NDA 21-112
DivFile
HFD-540/DeCamp/Pappas/ Lutwak

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/s/

Victoria Lutwak
9/5/01 01:34:44 PM
CSO

Ernest G. Pappas
9/5/01 01:40:07 PM
CHEMIST

Looks OK TO ME

Wilson H. DeCamp
9/5/01 01:56:10 PM
CHEMIST
concur

APPEARS THIS WAY ON ORIGINAL

MEMORANDUM OF TELEPHONE CONVERSATION

Meeting Minutes
Date: November 20, 2001
Type: T-con
NDA 21-112 TRI-LUMA (fluocinolone acetonide/hydrocortisone/tertian) Cream
Sponsor: Hill Dermaceuticals, Inc.

Attendees:
FDA: Jonathan Wilkin, M.D., and V Lutwak
Hill Dermaceuticals: Nini Ramirez, Nancy Puglia, , Jerry Roth

Telephone number: 1-800-344-5707

Reference Fax from Hill Dermaceuticals dated November 16, 2002, requesting an extension of time for the 12-month report on study 29. This matter was discussed at pre-rounds, because the submission timelines were critical for the reviewers meeting their goals for completing their reviews. The decision was made to call the Sponsor and advise them that the reviewers are going to close out their reviews with the amendments received by Friday.

T-con:

The Division Director referred to the facsimile transmission mentioned above and informed the Sponsor the because of our projected timelines and competing timelines here in 540, we are accepting the last amendment to the NDA on this coming Friday. Anything after will not be reviewed. Dr. Wilkin stated that we recognize that it is difficult to develop a product on the review clock. Unfortunately, we have to address the practical issues of performing our duties and extending the deadline cannot be entertained at this time if we are to keep our commitments.

The Sponsor responded that they will make every effort to meet this deadline.

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF MEETING MINUTES

Date: December 21, 2001
NDA 21-112
Sponsor: Hill Dermaceuticals.
Type: teleconference
Purpose: A request for information

FDA Attendees:
Hon-Sum Ko, M.D., Clinical Reviewer, HFD-540

Victoria Lutwak, Project Manager, HFD-540

Hill Attendees:
Rosario Ramirez, M.D.

The following information or formatting information was requested from the Applicant during our conversation.

Deficiencies of November 22 and December 10, 2001 submissions:

1. The submission of 12/1 0/01 should have an **Index** (Table of Contents) to comply with 21 CFR 314.50(b).

2. The submission of 12/10/01 should have Case Report Tabulations (line listings) to comply with 21 CFR 314.50(0(1). As the NDA is a **paper copy** NDA, listings should also be submitted in paper. Since the material in the CD is stated to be ***"12 month draft l"***, Hill should provide documentation that the paper submission is no longer draft and has been audited for accuracy.

1. Please provide electronic dataset, with dictionary for the Biometries Reviewer.
2. Please provide listing in Word also. If the listings are the same as in the previously submitted CD besides Lisiting 9, then there is no need to re-submit in Word.

1. Hill's letter dated 8/21/01 promised to submit a ***"Final*** Report for Study 29 ***and*** **ISS repo** 'by November 23, 2001. Hill has **NOT** presented an [SS to integrate the safety data from earlier studies (24 and 28), Study 29, ·

Please provide the Report on Study 29 and ISS electronically.

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

This is still unclear.

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

New Listing 9 does not incorporate data in Listing 5.2 on drug exposure and dose to correlate the occurrence of an adverse event to cumulative usage time and dose. Please provide in Word a revised Listing 9.

6. The report for Study 29 should contain the **1572s** and **IRB approval letter@** for all Investigators. Such information for 's

7. Questions on safety data in Study 29.

a. Previous drug use in Study 28. What is the effect, if any, of prior treatment with a dyad on the (a) incidence of adverse events or lab abnormalities seen in Study 29, and (b) the type of adverse events in Study 29?

1. Tables 6. 1 c and 6. 1 d are unclear. Study 29 report is supposed to contain safety data of TRI-LUMA patients in Study 28, but not the dyad safety data in Study 28. Please explain what is meant by "Study 29 data only" for Table 6.1 c and "Studies 28 and 29" for Table 6.1 d. 2. Similarly Tables 8. 1.1 c and 8. 1.1 d need explanation.

3. The difference between Table 6.1.c and 6.ld in TRI-LUMA patient number is 133-115=18, but event number is 747-377=370. Please explain. Similarly the differences between Tables **8.l.lc and 8. 1.1 d need be explained.**

L4. Please locate the analysis for laboratory abnormalities.

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

1. Tables 14 and l 5 are unclear in the same way as Tables 6.1 c/d and 8. 1.1 cld. Study 29 report is supposed to contain safety data of TRI-LUMA patients in Study 28, but not the dyad safety data in Study 28. Please explain what is meant by "Study 29 data only" for those Tables.

2. Please locate the analysis for laboratory abnormalities.

8. Questions on efficacy data in Study 29.

a. How many patients received how many courses of treatment (e.g., 1, 2, 3, 4 ..... courses)?

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ON ORIGINAL

Tables with the following information should be provided:

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

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

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

1. Under the row 'Total", please provide the real number of patients having had 1, 2, 3, 4. ..... courses. The total should not be the sum of the figures in the rows, because each patient ran be counted more than once with different durations.
2. Please provide the information on patients still enrolled in the ongoing study (which course of treatment they were on when you locked the database, and how many treatment days they had in that course when the database was locked). Explain whether the shorter durations of progressive courses are accounted for by this censoring.

b. Are there differences between I st, 2nd, 3rd, 4th ..... courses in patient responses?

Please locate the answer to this question.

c. Between treatment courses, what is the time to relapse/duration of remission, and are there differences after the I st, 2nd, 3rd, 4th ..... course for these parameters?

d. Does efficacy relate to adverse effect, i.e., is there difference between success and failure groups in relation to adverse events or specific adverse events? The unit of analysis here should be treatment courses rather than patients. The TRI-LUMA data, but not the dyad data, from Study 28 should be part of this analysis.

Please locate the answer to this question.

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

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/s/

Victoria Lutwak
12/31/01 10:32:05 AM
CSO

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ON ORIGINAL

MEMORANDUM OF TELEPHONE CONVERSATION

Meeting Minutes
Date: December 18, 2001
Type: T-con
NDA 21-112 TRI-LUMA (fluocinolone acetonide/hydrocortisone/tertian) Cream
Sponsor: Hill Dermaceuticals, Inc.

Attendees:
FDA:
Jonca Bull, M.D. Acting Director ODEV,
Hon-Sum Ko, M.D. Medical Reviewer HFD-540,
Victoria Lutwak, Project Manager
Hill Dermaceuticals:
Nini Ramirez M.D., Regulatory
Jerry Roth, President, Hill Dermaceutical
David Rosen, Counsel for Hill Dermaceutical

The call was requested by the sponsor for clarification on the fax, requesting a response by COB Thursday this week, sent on Monday, December 17, 2001. The list or requested information was used as the agenda; we went over each item by number and provided clarification.

The conversation ended with the objectives met.

Our one **action item** was to check the hours of the loading dock to confirm it would be open at 4:00 pm for the sponsor's scheduled submission to the NDA. **Task completed** 12-19-01- The loading dock is open [redacted] The project manager provided to the sponsor the telephone number for the mail room/loading dock to ensure delivery.

vl 12-19-01

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/s/

Victoria Lutwak
12/19/01 10:57:17 AM
CSO

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MEMORANDUM OF TELEPHONE CONVERSATION

Meeting Minutes
Date: December 28, 2001
Type: T-con
NDA 21-112 TRI-LUMA (fluocinolone acetonide/hydrocortisone/tretinoin) Cream
Sponsor: Hill Dermaceuticals, Inc.

Attendees:
FDA: W. DeCamp, E. Pappas, and V. Lutwak
Hill Dermaceuticals: Nini Ramirez, Nancy Puglia, and Jerry Roth

Telephone number: 1-800-344-5707

Background:
Submission dated July, 20, 2001.
Response to NA Letter

The purpose to the t-con was to identify for the sponsor information in the submission on July 20, 2001, that required further clarification.

On page 4001 #2 in the NA letter referred to microscopic examination for release and long-term stability of the TRI-LUMA cream. The sponsor did not provide in the specification for the finished product a microscopic examination for release and long-term stability of the TRI-LUMA cream. The particle size attribute is unacceptable because this test does not show phase separation and the absence of particles in the cream formulation.

The sponsor responded that there was a microscopic examination performed and there were particles in the final formulation.

This new information led to a discussion about the source of these particle in the formulation (wherein every component dissolves in the oily phase of production). One source that was a possible candidate for this particle was the V-gum, magnesium aluminum silicate.

The second request addressed the following SOPs on page 4001: THR-2, THR-3, and THR-12. Please provide the methods for the SOPs or where these methods are described in the NDA submission.

The sponsor will fax us copies of all submissions to the NDA. The sponsor plans to have the results and answers to our requests this afternoon.

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/s/

Victoria Lutwak
1/9/02 10:25:31 AM
CSO

Ernest G. Pappas
1/18/02 11:41:45 AM
CHEMIST

Wilson H. DeCamp
1/18/02 11:46:37 AM
CHEMIST
concur

APPEARS THIS WAY
ON ORIGINAL

********** -COMM. JOURNAL- ********** DATE JAN-04-2002 ***** TIME 09:36 *********

MODE = MEMORY TRANSMISSION START=JAN-04 09:24 END=JAN-04 09:36

FILE NO.=548

STN NO.	COMM.	ONE-TOUCH/ ABBR NO.	STATION NAME/EMAIL ADDRESS/TELEPHONE NO.	PAGES	DURATION
001	OK	[redacted]	914073231871	005/005	00:02:15

-FDA/CDER/DDDDP/HFD540 -

********** -301 827 2091 - ***** - 301 827 2091- **********

FACSIMILE TRANSMISSION RECORD

From: Vickey Lutwak

Division of Dermatologic and Dental Drug Products, HFD-540

Phone 301-827-2073
Fax 301-827-2075

Date: 1-04-02

To: Name Nini Ramirez
Company _____
City _____ State ____
Phone # _____

FAX # 407-323-1871

Number of Pages (INCLUDING COVER PAGE) 5

Additional message:

Nini - Bring this to the 1-2pm @ 10:00am

Vickey

When an FDA laboratory contacts the applicant for samples, the applicant should provide FDA laboratories with the samples within 10 working days. With the exception of sample delivery arrangements, all communications concerning validation at the FDA laboratories should be made through or with the knowledge of the review chemist for CDER applications, or the BLA/PLA committee chair for CBER applications.

2. Review Chemist

The review chemist will review the application to determine that the analytical procedures are adequate to ensure the identity, strength, quality, purity, and potency of the drug substance and/or drug product. Any changes in the methods resulting from the review of the application may require resubmission of the methods validation package. The review chemist, in coordination with the appropriate FDA laboratories, will decide which analytical procedures are to be validated. Comments from the FDA laboratories, if any, will be forwarded by the review chemist to the applicant on completion of the studies by the laboratories.

3. FDA Laboratory

An FDA laboratory will contact applicants with instructions on the submission of samples and the addresses to which samples should be mailed. The laboratory will test the samples according to the submitted analytical procedures to determine whether the analytical procedures are acceptable for quality control and suitable for regulatory purposes. Results and comments will be forwarded to the review chemist on completion of the studies.

4. Investigator

The investigator inspects the analytical laboratory testing sites where the release and stability testing are performed to ensure that the analytical procedures are performed in compliance with CGMP/GLP.

X. METHODS VALIDATION PACKAGE: CONTENTS AND PROCESSING

Part of the methods validation process may include FDA laboratory analysis to demonstrate that an analytical procedure is reproducible by laboratory testing. A methods validation package (see X.A) and samples (see X.B) will be needed for this process.

A. Methods Validation Package

The methods validation package will usually include information copied from pertinent sections of the application. To aid the review chemist, these copies should retain the original pagination of the application sections.

For ANDA and NDA products, the archival copy and extra copies of the methods validation packages should be submitted with the application. For ANDAs and related supplemental applications, one archival copy and two extra copies of the methods validation package should be submitted. For NDAs and related supplemental applications, one archival copy and three extra copies should be submitted. For BLAs and PLAs, a separate methods validation package need not be submitted. Information similar to that specified here should be included in the BLA or PLA submission.

The methods validation package should include:

1. Tabular List of All Samples to Be Submitted

The list should include the lot number, identity (with chemical name and structure where required for clarity), package type and size, date of manufacture, and quantity of the samples.

2. Analytical Procedures

A detailed description of each of the analytical procedures listed in the specifications should be submitted. The description should be sufficient to allow the FDA laboratory analysts to perform the analytical procedure (see section VI).

3. Validation Data

Appropriate validation data to support the analytical procedures should be submitted. Individual values as well as summary tables should be provided. Representative instrument output and raw data and information regarding stress studies should be included (see section VII).

4. Results

The results obtained by the applicant for the submitted samples should be provided. Alternatively, COAs could be submitted. The dates of analysis should be stated.

5. Composition

The components and composition of the drug product should be provided.

6. Specifications

The specifications for the drug substance and the drug product should be included.

7. Material Safety Data Sheets

The applicant should include material safety data sheets (MSDSs) for all samples, standards, and reagents (29 CFR 1910.1200(g)). As appropriate, MSDSs should be provided for other materials used in the analytical procedures listed in the methods validation package. In the case of toxic or hazardous materials, MSDSs should be posted on the outside of the package to facilitate safe handling.

B. Selection and Shipment of Samples

On request from CDER, an NDA or ANDA applicant must submit samples of drug product, drug substance, noncompendial reference standards, and blanks, so that the suitability of the applicant's drug substance and drug product analytical procedures can be evaluated by FDA laboratories (21 CFR 314.50(e) and 314.94(a)(10)). For BLAs and PLAs, representative samples of the product must be submitted, and summaries of the results of tests performed on the lots represented by the submitted sample must be provided (21 CFR 601.2(a) and 601.2(c)(1)(vi)).

For CDER products, the number of sets of samples that should be submitted for methods validation will be identified in the instructions forwarded to the applicant by the FDA laboratory. In general, the quantity of samples in each set should be double the amount needed to carry out the testing as performed by the applicant. Along with the drug substance and the drug product samples, the applicant should submit internal standards, non-USP reference standards, samples of impurities, degradation products, and unusual reagents. A set of samples will be shipped to each assigned laboratory.

For biological products, CBER should be consulted on the submission of samples and supporting materials. Unless specified differently by the reviewer, samples from any batch, preferably samples from an aged batch, may be selected for NDAs and NDA supplemental applications. The submitted drug product samples should be from a batch made with the proposed market formulation. For ANDAs and appropriate supplements, a sample of the finished product from a batch being used to support approval of the submission should be used. If a sample is selected from a batch not described in the application, an amendment containing a copy of the batch record and certificate of analysis should be provided to the ANDA. For supplements that do not require submission and review of an exhibit batch record and associated data, any commercial batch may be submitted. For biological products, samples from several consecutively manufactured batches should be submitted.

The drug product should be supplied in its original packaging. Bulk substances (e.g., drug substances, impurities, excipients) should be stored in opaque nonreactive containers. To prevent breakage during shipping, the samples should be adequately packaged in a sturdy container. Samples shipped from outside the United States should contain the appropriate customs forms to reduce delay in delivery.

If special storage precautions (e.g., freezing, use of an inert gas blanket) are required to protect sample integrity, arrangements should be made in advance with the validating laboratory for scheduled direct delivery. If a sample is toxic or potentially hazardous, the container should be prominently labeled with an appropriate warning and precautionary handling instructions.

C. Responsibilities of the Various Parties

1. Applicant

In the sections of the application on analytical procedures and controls, the applicant should provide a name, address, telephone number, and facsimile number so that samples can be requested. If this information is not provided, the contact person and address listed in the NDA, ANDA, BLA, or PLA submission will be used.

The methods validation packages should be compiled and submitted with the NDA or ANDA submission. For BLAs and PLAs, a separate methods validation package need not be submitted.

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