

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022259Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 022259

SUPPL # NA

HFD # 540

Trade Name Tolak

Generic Name fluorouracil cream, 4%

Applicant Name Hill Dermaceuticals

Approval Date, If Known September 18, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505 (b)(2)

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

YES NO

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

NA

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

NA

c) Did the applicant request exclusivity?

YES NO

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

Sponsor "claims" exclusivity and did not specify how many years.

d) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA# 020985	Carac (fluorouracil) cream,0.5%
NDA# 016831	Efudex (fluorouracil) cream, 5%
NDA# 016831	Efudex (fluorouracil) topical solution, 1%
NDA# 016831	Efudex (fluorouracil) topical solution, 2%
NDA# 016988	Fluoroplex (fluorouracil) cream, 1%

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets

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

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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

YES NO

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

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted

or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

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

Investigation #1: HD-FUP3B-048 A Randomized Evaluator Blinded, Vehicle-Controlled Multi-Center Study of the Safety and Efficacy of 4% Tradename (fluorouracil) cream Versus its Vehicle Cream Versus Efudex® Cream in the Treatment of Actinic Keratosis

Investigation #2: HP-FU3S-049 A Randomized, Double Blind, Vehicle-Controlled Multicenter Study of the Safety and Efficacy of 4% Tradename (fluorouracil) cream Versus its Vehicle Cream in the Treatment of Actinic Keratosis

Investigation #3: HD-FUP4LTS-050 An open-label, multi-center, long-term safety study of 4% Tolak cream in subjects with actinic keratosis who participated in the Phase 3 studies.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

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

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #3

YES

NO

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

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

Investigation #1 HD-FUP3B-048

YES

NO

Investigation #2 HP-FU3S-049

YES

NO

Investigation #2 HD-FUP4LTS-050

YES

NO

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

NA

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

Investigation #1: HD-FUP3B-048 A Randomized Evaluator Blinded, Vehicle-Controlled Multi-Center Study of the Safety and Efficacy of 4% Tradename (fluorouracil) cream Versus its Vehicle Cream Versus Efudex® Cream in the Treatment of Actinic Keratosis

Investigation #2: HP-FU3S-049 A Randomized, Double Blind, Vehicle-Controlled Multicenter Study of the Safety and Efficacy of 4% Tradename (fluorouracil) cream Versus its Vehicle Cream in the Treatment of Actinic Keratosis

Investigation #3: HD-FUP4LTS-050 An open-label, multi-center, long-term safety study of 4% Tolak cream in subjects with actinic keratosis who participated in the Phase 3 studies.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the

sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

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

Investigation #1 HD-FUP3B-048 !
IND # 069841 YES ! NO
! Explain:

Investigation #2 HP-FU3S-049 !
IND # 069841 YES ! NO
! Explain:

Investigation #3 HD-FUP4LTS-050 !
IND # 069841 YES ! NO
! Explain:

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

Investigation #1 !
!
YES ! NO
Explain: ! Explain:

Investigation #2 !
!
YES ! NO
Explain: ! Explain:

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

the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Strother D. Dixon
Title: Senior Regulatory Project Manager
Date: September 18, 2015

Name of Division Director signing form: Kendall A. Marcus, MD
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

STROTHER D DIXON
09/17/2015

KENDALL A MARCUS
09/17/2015

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-259 Supplement Type (e.g. SE5): _____ Supplement Number: 000

Stamp Date: August 20, 2007 PDUFA Goal Date: June 20, 2008

HFD 540 Trade and generic names/dosage form: 4% 5-Fluorouracil Cream

Applicant: Hill Dermaceuticals, Inc. Therapeutic Class: Keratolytics

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): N/A

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Actinic Keratosis

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

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

- Yes: Please proceed to Section A.
 No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

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

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

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

Reason(s) for deferral:

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

Other: _____

Date studies are due (mm/dd/yy): _____

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

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

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

Comments:

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

NDA ##-###

Page 3

This page was completed by:

{See appended electronic signature page}

**Catherine Carr, M.S.
Regulatory Project Manager**

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Markham Luke

11/2/2007 08:14:26 AM

Concur with waiver. Actinic keratoses is a rare condition
in children.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 022259 BLA # NA	NDA Supplement # NA BLA Supplement # NA	If NDA, Efficacy Supplement Type: NA <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Tolak Established/Proper Name: fluorouracil, 4% Dosage Form: cream		Applicant: Hill Dermaceuticals, Inc. Agent for Applicant (if applicable): NA
RPM: Strother D. Dixon		Division: Division of Dermatology and Dental Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check: 7/6/15 and 9/21/15</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>September 18, 2015</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> None CR June 22, 2009
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
 (confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
 Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) AP – 9/18/15 CR – 6/22/09
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included 9/16/15
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included 8/17/07 SDN 1
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included 9/16/15
• Original applicant-proposed labeling	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included 8/24/15
❖ Proprietary Name	Letter – 5/22/15 Review – 5/18/15 Review – 5/16/08 Letter(Fax) – 12/19/07 Review – 12/14/07
• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i>	
• Review(s) <i>(indicate date(s))</i>	
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input type="checkbox"/> None 2/3/15 DMEPA: <input type="checkbox"/> None 3/26/15; 5/16/08 DMPP/PLT (DRISK): <input type="checkbox"/> None 7/30/15; 5/15/08 OPDP: <input type="checkbox"/> None 8/4/15 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None MH 9/4/15 & 4/18/08
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	4/4/2008
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 7/21/15 Memo – 9/2/15
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included 9/17/15

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>7/29/15</u> If PeRC review not necessary, explain: 	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	N=26
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N=6
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 11/21/05
• Mid-cycle Communication (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A
• Late-cycle Meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	NA
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/18/15; 6/22/09
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6/2/08
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) <i>(indicate date for each review)</i>	9/1/15; 6/8/09; 6/2/08
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	9/1/15; Clinical Review p. 12
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and REMS Supporting Document <i>(indicate date(s) of submission(s))</i> • REMS Memo(s) and letter(s) <i>(indicate date(s))</i> • Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i> 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) <i>(include copies of OSI letters to investigators)</i>	<input type="checkbox"/> None requested 4/16/08; Letter – 4/16/08; Letter 4/15/08; Letter 4/15/08;
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 8/5/15; 4/4/08
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 7/16/15; 4/18/08
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/5/15; 3/25/08
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/17/15; 8/27/15; 5/21/09; 6/23/08; 6/18/08
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	p. 99 CMC Review, 3/31/08
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done See 9/2/15 Memo
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done NA (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done NA
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done NA
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/

STROTHER D DIXON
09/21/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: March 11, 2015

Application Number: NDA 022259

Product Name: fluorouracil cream, 4%

Sponsor Name: Hill Dermaceuticals, Inc.

Subject: Long Term Study

FDA Participants

Kendall A. Marcus, MD, Director, DDDP

David Kettl, MD, Acting Deputy Director, DDDP

Denise Cook, MD, Acting Team Leader, DDDP

Milena Lolic, MD, Clinical Reviewer, DDDP

Mohamed Alosch, PhD, Biostatistics Team Leader, DB III

Kathleen Fritsch, PhD, Biostatistics Reviewer, DB III

Jane Chang, PhD, Product Quality Reviewer, DNDQA II, Branch IV

Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP

Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

Sponsor Participants

Cynthia Freeman, Quality Control Manager

Nicole Motley, Microbiologist

Rosario (Nini) Ramirez, Quality Assurance Manager

Jerry Roth, President

1.0 BACKGROUND:

The sponsor attempted to submit datasets for the study report HD-FUP4LTS-050 on May 5, 2008 (SDN 18) but was unsuccessful. The sponsor was notified via fax on May 5, 2008 that the xpt and pdf files were submitted as shortcuts and are not the actual files.

2.0 DISCUSSION:

During the meeting the sponsor was informed that the Division would need the files for study report HD-FUP4LTS-050 and all supporting materials related to the study. The Division clarified the documentation that needed to be submitted as well as the type of files.

3.0 ACTION ITEMS:

The sponsor agreed to submit the files requested by the Division.

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/s/

STROTHER D DIXON
09/16/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: April 27, 2015

Application Number: NDA 022259

Product Name: fluorouracil cream, 4%

Sponsor Name: Hill Dermaceuticals, Inc.

Subject: Review Extension – Major Amendment

FDA Participants

David Kettl, MD, Acting Deputy Director, DDDP

Denise Cook, MD, Acting Team Leader, DDDP

Amy Voitach, DO, Clinical Reviewer, DDDP

Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP

Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

Sponsor Participants

Linda Payne, Regulatory Affairs

Rosario Ramirez, MD., QA Manager

Cynthia Freeman, QC Manager

Nicole Motley, Microbiologist

Jerry Roth, President

1.0 BACKGROUND:

The sponsor was sent a Review Extension – Major Amendment Letter for NDA 022259. The sponsor requested a teleconference with the Division to discuss.

2.0 DISCUSSION:

The Division clarified that the submission containing the files for study report HD-FUP4LTS-050 constituted a major amendment therefore the clock was extended three months.

3.0 ACTION ITEMS:

None.

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/s/

STROTHER D DIXON
09/16/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: June 9, 2015

Application Number: NDA 022259

Product Name: fluorouracil cream, 4%

Sponsor Name: Hill Dermaceuticals, Inc.

Subject: Microbiology Information Request – Follow-up

FDA Participants

David Kettl, MD, Clinical Team Leader, DDDP

Amy Woitach, DO, MS, Clinical Reviewer, DDDP

LCDR Jessica Cole, PhD, Acting Microbiology Quality Assessment Lead,
CDER/OPQ/OPF/DMA Branch 3

Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

Sponsor Participants

Jerry Roth, President

Rosario Ramirez, MD, Senior Quality Assurance Manager

Joy Trepanier, Quality Assurance Manager

Cynthia Freeman, Quality Control Manager

Nicole Motley, Microbiologist

Linda Payne, Regulatory Affairs

1.0 DISCUSSION:

The sponsor was informed that the current proposal to establish minimum preservative levels post-approval is unacceptable. As requested in the March 5, 2015 Information Request, the minimum preservative content must be established and supported by data prior to approval of the NDA.

The sponsor was also asked to provide an update on the status of the *Burkholderia cepacia* complex test development and confirm that the July 1, 2015 completion date is still applicable.

2.0 ACTION ITEMS:

The sponsor agreed to submit the information as requested.

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/s/

STROTHER D DIXON
09/16/2015

MEMORANDUM

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

DATE: September 2, 2015

TO: File

FROM: Strother D. Dixon

SUBJECT: 505 (b)(2) Cleared for Action

APPLICATION/DRUG: NDA 022259 Tolak (fluorouracil) cream, 4%

NDA 022259 Tolak (fluorouracil) cream, 4% was discussed at the July 20, 2015 505(b)(2) clearance meeting. The application was cleared for action from a 505(b)(2) perspective. The sponsor established a clinical bridge in the clinical efficacy/Phase III study entitled “A Randomized Evaluator Blinded, Vehicle-Controlled Multi-Center Study of the Safety and Efficacy of 4% Tradename (fluorouracil) Cream Versus its Vehicle Cream Versus Efudex[®] Cream in the Treatment of Actinic Keratosis.”

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/s/

STROTHER D DIXON
09/02/2015



NDA 022259, [REDACTED] (b) (4)

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Hill Pharmaceuticals, Inc.
Attention: Rosario G. Ramirez, MD
Director, Medical/Regulatory
2650 South Mellonville Ave.
Sanford, FL 32773

Dear Dr. Ramirez:

Please refer to your New Drug Application (NDA) and Supplemental New Drug Applications (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for

NDA 022259 Tolak (fluorouracil) Cream, 4%

[REDACTED] (b) (4)

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by [REDACTED] (b) (4). The pervasiveness and egregious nature of the violative practices by [REDACTED] (b) (4) has led FDA to have significant concerns that the bioanalytical data generated at [REDACTED] (b) (4) as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Barbara Gould, Chief, Project Staff Management, at (301) 796-4224.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BARBARA J GOULD

09/15/2011

p.p. DIVISION DIRECTOR Susan J. Walker



NDA 022259

INFORMATION REQUEST

Hill Dermaceuticals, Inc.
Attention: Linda Payne
Regulatory Affairs
2650 South Mellonville Ave.
Sanford, FL 32773

Dear Ms. Payne:

Please refer to your New Drug Application (NDA) dated December 17, 2014, received December 18, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fluorouracil cream, 4%.

We are reviewing the microbiology section of your submission and have the following comments and information requests. We request a prompt written response by July 22, 2015 in order to continue our evaluation of your NDA.

1. Submit a revised stability specification with acceptance criteria of NLT (b) (4) % methylparabens, (b) (4) % propylparabens, and (b) (4) % BHT.
2. Submit a revised release specification that includes the absence of Burkholderia cepacia complex (BCC). Alternately, it is acceptable to test all purified water used in manufacturing for the absence of BCC and include this test as part of the critical in-process manufacturing controls.

If you have any questions, please contact Strother D. Dixon, Regulatory Project Manager, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JILL A LINDSTROM

07/20/2015

Signing on behalf of Kendall Marcus, MD



NDA 022259

INFORMATION REQUEST

Hill Dermaceuticals, Inc.
Attention: Linda Payne
Regulatory Affairs
2650 South Mellonville Ave.
Sanford, FL 32773

Dear Ms. Payne:

Please refer to your New Drug Application (NDA) dated December 17, 2014, received December 18, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fluorouracil cream, 4%.

We are reviewing the Labeling section of your submission and have the following comments and information requests. We request a prompt written response by July 22, 2015 in order to continue our evaluation of your NDA.

1. The draft text in Section 5, Warnings and Precautions, states that “^{(b) (4)} [redacted] but does not describe the types of hypersensitivity reactions. Clarify the types of hypersensitivity reactions (e.g., delayed-type hypersensitivity) have been reported with topical fluorouracil drugs and propose language for the appropriate management strategies (e.g., contact physician if excessive redness or swelling occurs).
2. The draft text in Section 5, Warnings and Precautions, also states that ^{(b) (4)} [redacted].” According to the guidance for industry, *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products- Content and Format*, ambiguous and uninformative statements (e.g., use caution) should be avoided. Instead, specific treatment or management strategies should be noted. We request that you clarify the types of hypersensitivity reactions that can be anticipated from using Tolak Cream in peanut-sensitive individuals. Provide the basis for your statements. We request that you propose language for section 5 (Warnings and Precautions) and section 17 (Patient Counseling Information) of the prescribing information, and for the Patient Information section.

If you have any questions, please contact Strother D. Dixon, Senior Regulatory Project Manager, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JILL A LINDSTROM
07/16/2015



NDA 022259

INFORMATION REQUEST

Hill Dermaceuticals, Inc.
Attention: Linda Payne
Regulatory Affairs
2650 South Mellonville Avenue
Sanford, FL 32773

Dear Ms. Payne:

Please refer to your New Drug Application (NDA) dated August 20, 2007, received August 17, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fluorouracil cream, 4%.

We also refer to your April 6, 2015 submission, containing a response to the Microbiology-Information Request letter dated March 6, 2015.

We are reviewing the Product Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA by July 14, 2015.

Provide the following information or a reference to its location in the subject submission.

1. The current proposal to (b) (4) is unacceptable. As requested in the March 6, 2015 information request, (b) (4) must be established and supported by data prior to approval of the NDA. Submit a revised stability specification (b) (4) effectiveness data to support these minimum levels. We refer to Questions 5& 6 from the March 6, 2015 information request for additional information.
2. We refer to your April 7, 2015 response to Question 1 and the inclusion of a copy of laboratory notebook pages beginning on page 37/130. These data refer to (b) (4) test method verification studies conducted from December 2005 to February 2006. Justify the (b) (4).

If you have any questions, please contact Strother D. Dixon, Senior Regulatory Project Manager, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

David Kettl, MD
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DAVID L KETTL
06/09/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022259

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Linda Payne
Regulatory Affairs

Dear Ms. Payne:

Please refer to your New Drug Application (NDA) dated December 17, 2014, and received December 18, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Fluorouracil Cream, 4%.

We also refer to your February 24, 2015, correspondence, received February 25, 2015, requesting review of your proposed proprietary name, Tolak.

We have completed our review of the proposed proprietary name, Tolak and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your February 24, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact Strother Dixon, Regulatory Project Manager in the Office of New Drugs at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk
Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
05/22/2015



NDA 022259

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Hill Dermaceuticals, Inc.
Attention: Linda Payne
Regulatory Affairs
2650 South Mellonville Ave.
Sanford, FL 32773

Dear Ms. Payne:

Please refer to your New Drug Application (NDA) dated December 17, 2014, received December 18, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for fluorouracil cream, 4%.

On March 24, 2015, we received your March 23, 2015, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is September 18, 2015.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 25, 2015.

If you have any questions, call Strother D. Dixon, Senior Regulatory Project Manager, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

KENDALL A MARCUS
04/21/2015



NDA 022259

DISCIPLINE REVIEW LETTER

Hill Dermaceuticals, Inc.
Attention: Linda Payne
Regulatory Affairs
2650 South Mellonville Avenue
Sanford, FL 32773

Dear Ms. Payne:

Please refer to your New Drug Application (NDA) dated August 20, 2007, received August 17, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fluorouracil cream, 4%.

We also refer to your amendments dated May 5, 2008 and December 17, 2014.

Our review of the Clinical section of your submission is complete, and we have identified the following deficiencies:

1. You originally submitted the study report for Study HD-FUP4LTS-050 on May 5, 2008. However, to support our review of your application we need all supporting materials related to Study 050. These materials include the complete study report, protocol, and electronic datasets and any additional supportive material.

Your submission should include the following:

- a. Electronic datasets in SAS transport (.xpt) form. Submit both analysis datasets and the raw datasets (information as collected on the CRF). In the May 5, 2008 submission the .xpt and .pdf files were submitted as shortcuts rather than the actual files, and thus the needed files were not received.
 - b. An adequate electronic (pdf) copy (preferred) or two paper copies of *all* study report documentation (study report, protocol, protocol addenda (if any), statistical analysis plan, interim analysis report, annotated CRF, and any additional supportive material). The Agency does not archive multiple copies of paper submissions, and multiple copies (or a complete electronic copy) are needed for the multiple reviewers.
2. The electronic datasets should include the following information and accompanying documentation:

- a. The analysis datasets should include all variables necessary to conduct all efficacy, safety, and sensitivity analyses in the protocol.
 - b. Include sufficient documentation (define.pdf file) to adequately describe the variables in the datasets, particularly definitions of derived variables.
3. The safety report for Study HD-FUP4LTS-050 should include:
- a. Subject narratives for all deaths, all serious adverse events (AEs), and AEs resulting in discontinuation from the trials conducted with your product. Case narratives should include past medical history, concomitant medications, fluorouracil cream, 4% exposure data, detailed event description, outcome, and discussion on causality.
 - b. Case report forms (CRFs) for all serious AEs, all severe AEs, and for all subjects who discontinued from the studies for safety reason. A study's CRFs should be placed in a CRF folder with a file tag of "case-report-forms". CRFs that are not submitted should be readily available upon request.
 - c. Adverse reaction tables, adverse event tables, and line listings for all safety data.
 - d. Submit any safety updates since your May 5, 2008 submission.
 - e. Should you submit an electronic version of the complete study report, within report provide cross-reference (electronic links) for:
 - i. all deaths
 - ii. all serious AEs
 - iii. all severe AEs
 - iv. all subjects who discontinued due to safety reason

We are providing these comments to you before completing our review of your entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Strother D. Dixon, Senior Regulatory Project Manager, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Denise Cook, MD
Acting Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DENISE COOK
03/13/2015



NDA 22259

INFORMATION REQUEST

Hill Dermaceuticals, Inc.
Attention: Linda Payne
Regulatory Affairs
2650 South Mellonville Avenue
Sanford, FL 32773

Dear Ms. Payne:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fluorouracil Cream 4%.

We also refer to your December 17, 2014 submission.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response by March 12, 2015, in order to continue our evaluation of your NDA.

1. Please address the following issues and provide updated drug product release and stability specifications.
 - a) The USP monograph for fluorouracil cream has been revised. Therefore, your previously proposed drug product specification should be updated, including the following:
 - i. Change identification test by (b) (4)
 - ii. Add testing for (b) (4) with a limit of NMT (b) (4) %.
 - iii. Two HPLC procedures, i.e. (b) (4) are proposed for fluorouracil assay. Please clarify which HPLC procedure is the regulatory procedure and whether the other procedure is an alternate method.
 - b) In the 10/1/2013 Amendment, it was stated that the finished product specification (TOLAK- (b) (4), page 10 of 20) has been revised. This revised specification is inconsistent with the specification provided in the stability protocol provided in the 10/1/2013 and 12/17/2014 Amendments. For example, the specification lacks of testing for degradation products. Furthermore, a USP procedure

is used for fluorouracil assay. Please clarify whether the specification is intended for the (b) (4) stability of the drug product.

2. You stated that (b) (4)-Tolak (b) (4) was a USP compendial procedure for assay of fluorouracil. Please note that the USP 37 compendial procedure has been revised. Thus, (b) (4)-Tolak- (b) (4) provided in the 10/1/2013 Amendment is no longer identical to the current compendial procedure. If you intend to use the compendial procedure, regardless of whether it is used as a regulatory or an alternative method, the following changes should be incorporated:

(b) (4)

3. The method validation data for methylparaben assay show that there is a peak (b) (4)

(b) (4)

Please provide data to support method accuracy, minimally cover the lower limit of the acceptance criterion for methylparaben.

4. In the 10/1/2013 Amendment, it was stated that the in-process specification (b) (4)

(b) (4)

Provide the updated in-process specification.

5. Please commit to submit (b) (4)

(b) (4)

6. Regarding the labeling:

- a) Replace the term (b) (4) with "peanut oil" for both container label and carton labeling, including the statement for inactive ingredients and the statement (b) (4) located below "Topical Cream".

Section 502(e)(1)(A)(iii) of the Food, Drug and Cosmetic Act requires that the established name of each inactive ingredient be included in the labeling. Section 502(e)(3)(B) of the Act defines the term "established name" with respect to a drug or ingredient as the official title used in the United States Pharmacopeia. Therefore, the



NDA 022259

INFORMATION REQUEST

Hill Dermaceuticals, Inc.
Attention: Linda Payne
Regulatory Affairs
2650 South Mellonville Avenue
Sanford, FL 32773

Dear Ms. Payne:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fluorouracil cream, 4%.

We are reviewing the Labeling section of your submission and have the following comments and information request. We request a prompt written response by February 19, 2015 in order to continue our evaluation of your NDA.

Labeling

1. We recommend that your proposed prescribing information conform to the FDA published *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy* (b)(4) *Labeling*, referred to as the “Pregnancy (b)(4) Labeling Rule” (PLLR or final rule).
2. The HIGHLIGHTS (HL) section is greater than one-half page.
3. Add the numerical identifier that corresponds to the section or subsection being referenced at the end of the fifth bullet in the DOSAGE AND ADMINISTRATION section of the HL.
4. At the beginning of the HL, the title should be: “HIGHLIGHTS OF PRESCRIBING INFORMATION.” Remove the “THE”.
5. In the HL Limitation Statement, the name of the drug product should appear in UPPER CASE.
6. Remove the section header “RECENT MAJOR CHANGES” from the HL.
7. In the Adverse Reactions section of the HL, add a “1” to the manufacturer’s phone number and remove the underline from the FDA Medwatch website address.
8. Add “and FDA-approved patient labeling” to the Patient Counseling Information Statement section.
9. Change the revision date to MM/YYYY or 06/2015 until the application is approved.

10. In the Table of Contents (TOC):

- a. Correct the spelling in subsection 5.3 (should be "Inflamed" instead of "(b) (4)").
 - b. Change the title of subsection 6.1 to "Clinical Trials Experience" instead of "(b) (4)".
 - c. Change the title of Subsection 6.2 to "Postmarketing Experience" instead of "(b) (4)".
 - d. Change the title of Subsection 13.1 from "(b) (4)" to "Carcinogenesis, Mutagenesis, Impairment of Fertility."
 - e. Remove the title for subsection (b) (4)
11. The 17 (PATIENT COUNSELING INFORMATION) section does not reference the Patient Information labeling.
12. The patient labeling must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the prescribing information (PI) upon approval. The subsection titles should also be removed from the TOC.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by February 19, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

If you have any questions, please contact Strother D. Dixon, Regulatory Project Manager, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

David Kettl, MD
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DAVID L KETTL
02/05/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
555 Winderley Place, Ste. 200
Maitland, Florida 32751

Telephone: (407) 475-4700
FAX: (407) 475-4769

November 12, 2014

VIA EMAIL AND CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Shelton T. Bradshaw
Hunton & Williams LLP
2200 Pennsylvania Avenue, NW
Washington, DC 20037

RE: United States v. Hill Dermaceuticals, Inc., et al., Civ. No. 6:11-cv-1550 (M.D. Fla.)

Dear Mr. Bradshaw:

Although Hill Dermaceuticals, Inc. ("Hill") has not fully satisfied the requirements in Paragraph 9 of the Consent Decree of Permanent Injunction ("Consent Decree") entered in the above-referenced case, you asked that the United States Food and Drug Administration ("FDA") resume its review of new drug application # 22-259 Tolak ("Tolak"). This letter is to notify you that, based on the unique circumstances of the Tolak application and without prejudice to any of FDA's rights under the Consent Decree, FDA is exercising a conditional waiver of Paragraph 9 of the Consent Decree as it applies to Tolak and will resume substantive scientific review of that application. Please keep in mind that FDA still has concerns about the reliability and integrity of information that Hill has submitted to the Agency and FDA may again decide to defer scientific review of Tolak should it discover in the future material misrepresentations by Hill related to Tolak. See Paragraphs 9 and 11 of the Consent Decree.

If you have any questions regarding this letter, please contact Matthew Thomaston, Supervisory Investigator, Florida District, at the address on this letterhead or by telephone at (407) 475-4728.

Sincerely,

Susan Turcovski
District Director

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/s/

J P PHILLIPS

11/12/2014

This letter is being checked into DARRTS by the OND RPM for administrative purposes. The original copy of this letter was signed and sent directly to the applicant's representative by the FDA Florida District Office.



NDA 022259

ACKNOWLEDGE INCOMPLETE RESPONSE

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

Dear Dr. Ramirez:

We acknowledge receipt on June 22, 2011 of your June 21, 2011 submission to your new drug application (NDA) for Tolak (fluorouracil) Cream, 4% for the treatment of actinic keratoses of the face, scalp, and ears.

We do not consider this a complete response to our action letter. Therefore, the review clock will not start until we receive a complete response. The following deficiencies from our action letter still need to be addressed:

1. Stability data from three new primary batches of Tolak Cream should be submitted for review. The data should cover minimum time periods of 12 months for the long-term and 6 months for the accelerated conditions at the time of resubmission. The stability study should follow the drug product stability protocol provided in the March 4, 2008 amendment.
2. The hold time for the bulk drug product prior to filling operation should be determined and justified. In-process samples taken [REDACTED] (b) (4) should be tested per Tolak Cream In-process Product Specification Form (provided in the February 12, 2008 amendment) [REDACTED] (b) (4).

If you have any questions, call Paul Phillips, Regulatory Project Manager, at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

STANKA KUKICH

08/08/2011

Signing for Susan Walker, Division Director



NDA 022259

**ACKNOWLEDGE –
CLASS 2 RESUBMISSION**

Hill Dermaceuticals, Inc.
Attention: Linda Payne
Regulatory Affairs
2650 South Mellonville Avenue
Sanford, FL 32773

Dear Ms. Payne:

We acknowledge receipt on December 18, 2014, of your December 17, 2014, resubmission to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Tolak (fluorouracil) cream, 4%.

We consider this a complete, class 2 response to our June 22, 2009 action letter. Therefore, the user fee goal date is June 18, 2015.

If you have any questions, call me at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Strother D. Dixon
Senior Regulatory Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

STROTHER D DIXON
01/26/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-259

Hill Dermaceuticals
Attention: Rosario G. Ramirez, MD
Medical/Regulatory Affairs
2650 South Mellonville Avenue
Sanford, FL 32773

Dear Dr. Ramirez:

Please refer to your New Drug Application (22-259) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tolak (fluorouracil) Cream, 4%.

We also refer to your November 10, 2008, correspondence, received November 12, 2008, requesting a meeting to discuss the immediate container labeling text. We are denying your request as a meeting is premature as your application is still under review.

If you have any questions, call Catherine Carr, Regulatory Project Manager, at (301) 796-2311.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D
Director
Division of Dermatology and Dental
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Stanka Kukich
3/4/2009 12:47:26 PM
Signing for Dr. Susan Walker, Division Director



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-259

Hill Dermaceuticals, Inc.
Attention: Rosario G. Ramirez, MD
Medical / Regulatory Affairs
2650 South Mellonville Avenue
Sanford, FL 32773

Dear Dr. Ramirez:

Please refer to your New Drug Application (22-259) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tolak (fluorouracil) Cream, 4%.

We also refer to your November 10, 2008, correspondence, received November 12, 2008, requesting a meeting to discuss the immediate container labeling text. We are denying your request for a meeting because your application is still under review and labeling discussions are not appropriate at this time.

If you have any questions, call Catherine Carr, Regulatory Project Manager, at (301) 796-2311.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Susan Walker
2/13/2009 01:52:45 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-259

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 New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tolak (5-fluorouracil) Cream, 4%.

We also refer to your submissions, dated June 16, 2008 and July 21, 2008, containing letters regarding your request to withdraw your CMC major amendment, dated May 23, 2008, as clarified in your July 21, 2008 submission.

We acknowledge receipt of your submission and would like to inform you that your PDUFA goal date has been changed back to June 20, 2008.

If you have any questions, call Catherine Carr, Project Manager, at 301-796-2311.

Sincerely,

{See appended electronic signature page}

Bronwyn Collier, B.S.N.
Acting Supervisor, Project Management Staff
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Bronwyn Collier
8/1/2008 02:48:04 PM



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III**

FACSIMILE TRANSMITTAL SHEET

DATE: July 30, 2008

To: Rosario Ramirez, MD	From: Catherine Carr, Project Manager
Company: Hill Dermaceuticals, Inc.	Division of Dermatologic & Dental Products
Fax number: 407-302-7196	Fax number: (301) 796-9894 or 9895
Phone number: 1-800-344-5707	Phone number: (301) 796-2311

Subject: NDA 22-259/CMC request for information

Total no. of pages including cover: 3

Comments: Please find attached the CMC Reviewer's information request.

Thank you.

Document to be mailed: YES NO

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FDA Facsimile Memorandum

Date: July 30, 2008
To: Rosario Ramirez, MD
From: Catherine Carr, Project Manager
Subject: NDA 22-259

Dear Dr. Ramirez,

Reference is made to your NDA 22-259 for 4% 5-Fluorouracil Cream. The CMC Reviewer has the following request for information regarding your application.

Please confirm that [REDACTED] (b)(4) is the manufacturer of the [REDACTED] (b)(4) peanut oil used in Tolak. The following statement was provided in the NDA, Vol 2, Section 3.2.P.2.1.2, page 3: "The [REDACTED] (b)(4) Peanut Oil NF raw material used in 4% TRADENAME cream is manufactured [REDACTED] (b)(4)

A Certificate of Analysis (COA) of the [REDACTED] (b)(4) peanut oil NF from the manufacturer should be provided. The Technical Data for two lots of [REDACTED] (b)(4) peanut oil NF provided by [REDACTED] (b)(4)

Please confirm whether the manufacturer of [REDACTED] (b)(4) peanut oil used in Tolak [REDACTED] (b)(4)

Please let me know if you have any questions. Thank you.

Catherine Carr, MSc
Regulatory Health Project Manager
Food and Drug Administration, CDER, DDDP
White Oak, Bldg 22, Room 5175
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tele: (301) 796-2311 Fax: (301) 796-9894/9895

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/s/

Catherine Carr
7/30/2008 03:26:48 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-259

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

Dear Dr. Ramirez:

Please refer to your new drug application (NDA) dated August 17, 2007, received August 20, 2007, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for 5-Fluorouracil Cream, 4%.

We also refer to the meeting between representatives of your firm and the FDA on June 17, 2008. The purpose of the meeting was to discuss the Agency's correspondence to you, dated June 16, 2008, regarding a 3-month review clock extension on your NDA application.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Catherine Carr, Regulatory Project Manager, at (301) 796-2311.

Sincerely,

{See appended electronic signature page}

Bronwyn Collier, RN
Acting Chief, Project Management Staff
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 17, 2008
TIME: 9:30 am
LOCATION: Teleconference
APPLICATION: NDA 22-259
DRUG NAME: 5-Fluorouracil Cream, 4% (Tolak)

MEETING CHAIR: Bronwyn Collier, RN

MEETING RECORDER: Catherine Carr, M.S.

FDA ATTENDEES: (Title and Office/Division)

Bronwyn Collier, RN/Acting Chief Project Management Staff, DDDP
Maria Walsh, RN/Project Officer, Office of Drug Evaluation III
Catherine Carr, M.S./Regulatory Health Project Manger, DDDP

EXTERNAL CONSTITUENT ATTENDEES:

Jerry Roth, President, Hill Dermaceuticals
Rosario Ramirez, M.D., Director of Medical and Regulatory Affairs, Hill Dermaceuticals

BACKGROUND:

Due to the submission of a CMC major amendment, dated May 23, 2008, the Agency extended the review clock by 3 months for the NDA application. The Agency faxed a letter to the sponsor on June 16, 2008, which indicated that the user fee goal date was being extended to September 19, 2008. The original user fee goal date was June 20, 2008.

The sponsor notified the Agency via email that a correspondence was being submitted to the NDA which requested the rescission of the amendment dated May 23, 2008. The sponsor also indicated via email that they will agree to the Agency's labeling revisions for the package insert and the patient package insert, which were emailed to them on May 30, 2008.

MEETING OBJECTIVES:

The objective of this teleconference was to discuss the Agency's correspondence dated June 16, 2008, regarding a clock extension on the review of NDA 22-259 and the possibility of rescinding the May 23rd amendment.

DISCUSSION POINTS:

The Agency acknowledged the receipt of the sponsor's email correspondence, dated June 16, 2008. This email contained courtesy copies of correspondence submitted to the NDA regarding the request to rescind the amendments dated May 2, 2008 and May 23, 2008. The Agency indicated that sponsor has the right to withdraw the amendments if they chose. However, it was pointed out that the decision to extend the review clock was due to the May 23rd amendment only. The Agency clarified that the May 2nd amendment was not considered a major amendment and had no bearing on the clock extension.

The Agency reminded the sponsor that if they would like to rescind the amendments, a correspondence should be submitted to that effect. In addition, the sponsor was informed that if they would like to accept the Agency's May 30th labeling revisions, a correspondence would need to be submitted to the NDA stating their agreement.

The Agency reminded the sponsor that the original user fee goal date is June 20, 2008. However, due to the fact that some issues are still unresolved, it is unlikely that this due date will be met. The Agency indicated that they are still waiting for the Office of Compliance to provide information regarding the outcome of their review of the sponsor's responses to the Form 483s received due to the establishment inspections. The sponsor indicated that their responses were submitted to the Florida district compliance office for review. However, no information has been received by the sponsor from the compliance office to date.

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/s/

Catherine Carr
6/18/2008 09:53:12 AM
CSO

Bronwyn Collier
6/18/2008 11:54:52 AM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-259

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 August 17, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tolak (5-Fluorouracil) Cream, 4%.

On May 27, 2008, we received your May 23, 2008 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is September 19, 2008.

If you have any questions, call Catherine Carr, Project Manager, at 301-796-2110.

Sincerely,

{See appended electronic signature page}

Bronwyn Collier
Acting Chief, Project Management Staff
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Bronwyn Collier
6/16/2008 08:24:55 AM



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III**

FACSIMILE TRANSMITTAL SHEET

DATE: March 20, 2008

To: Rosario Ramirez, MD	From: Catherine Carr, Project Manager
Company: Hill Dermaceuticals, Inc.	Division of Dermatologic & Dental Products
Fax number: 407-302-7196	Fax number: (301) 796-9894 or 9895
Phone number: 1-800-344-5707	Phone number: (301) 796-2311

Subject: NDA 22-259/Statistics Information Request

Total no. of pages including cover: 3

Comments: Please find attached the Statistics Reviewer's request for information.

Thank you.

Document to be mailed: YES NO

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FDA Facsimile Memorandum

Date: March 20, 2008
To: Rosario Ramirez, MD
From: Catherine Carr, Project Manager
Subject: NDA 22-259

Dear Dr. Ramirez,

Reference is made to your NDA 22-259 for 4% 5-Fluorouracil Cream. The Statistics Reviewer would like to request the following information to aid in the review of your application.

For Study HD-FUP3B-048, please submit case report forms for Subjects 4-263, 12-98, and 15-765.

The study report notes that these subjects were 'randomized correctly but the subjects forgot to start their medication so the subjects were re-randomized at Visit 2 (which became a replacement Baseline visit and Visit 2 was re-scheduled).'

For these subjects, also provide:

- the original treatment assignment and the re-randomized treatment assignment
- what information was captured at the original baseline visit and what information was captured at the 'new' baseline visit and how this information is presented in the database (e.g. did these subjects have 7 visits rather than 6?)
- any additional information about these subjects regarding the treatment assignment and drug use

Please let me know if you have any questions regarding this request. Thank you.

Catherine Carr, MSc
Regulatory Health Project Manager
Food and Drug Administration, CDER, DDDP
White Oak, Bldg 22, Room 5175
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tele: (301) 796-2311 Fax: (301) 796-9894/9895

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/s/

Catherine Carr
3/20/2008 04:13:40 PM
CSO



NDA 22-259

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 August 17, 2007 new drug application (NDA) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for 5-Fluorouracil Cream 4%.

We also refer to our letter dated January 14, 2008, to our facsimile dated January 23, 2008, and to our January 24 and February 1, 2008 teleconferences in which we communicated to you our information requests regarding the Chemistry, Manufacturing, and Controls section of your submission.

Our information requests have not been adequately addressed in your February 12, 2008 amendment. We have repeated our information requests below and we request a full written response by March 5, 2008 in order to continue our evaluation of your NDA. This information must be provided before we can approve this application.

1. Drug product release and stability specification:

- o Acceptance criteria for homogeneity assay were not provided
- o Viscosity testing was not performed and an acceptance criterion was not established.

A. Revise the proposed drug product specification listed in Table 22P, "Hill Laboratories, Inc. Finished Product Specification Form" (Section 3.2.P.5.1), and "Hill Laboratories, Inc. Stability Specification Form" (Section 3.2.P.8.2):

- 1) Establish acceptance criteria for homogeneity assay, i.e. analysis of top, middle, and bottom of each tube for total of 3 tubes. Each assay result should be within 90.0-110.0% of the label claim and the RSD of all nine assays should be NMT (b)(4) %.
- 2) Add viscosity testing to the drug product release and stability specification and commit to the following:
 - a) Provide viscosity data from the first six batches manufactured to be submitted as soon as available. Add the viscosity test to your stability protocol and provide the viscosity stability data from the three registration batches and the three validation batches.

The viscosity data from stability study of the three registration batches and the three validation batches produced postapproval can be used to justify the proposed acceptance criterion.

- b) Establish an acceptance criterion within one year after approval

B. Provide the updated drug product release and stability specifications.

2. A (b)(4) study for the drug product was not provided.

Include the following statement on the labeling for package insert, immediate container and cartons:

“Do not freeze. Maintain at 25°C (77°F), excursion permitted to 15°C - 30°C (59°F - 86°F) during storage and transportation.”

3. Analytical procedure for the (b)(4) for the drug substance regulatory specification was not provided.

Provide analytical procedure for the (b)(4) if the method is different from that listed in Ph. Eur. monograph ((b)(4)) for 5-fluorouracil.

4. The drug substance stability specification was not provided.

A. Revise the drug substance stability specification as the following:

Test	Acceptance Criteria	Method
Description	(b)(4)	visual
Loss on drying	(b)(4)	Ph. Eur. 2.2.32
Assay	(b)(4)	Method of Ph. Eur. Monograph (# (b)(4))
Related substances (TLC) (b)(4)	(b)(4)	Method of Ph. Eur. Monograph (# (b)(4))
Related substances (HPLC) (b)(4)	(b)(4)	Method of Ph. Eur. Monograph (# (b)(4))
Each unspecified impurity	(b)(4)	
Total impurities	(b)(4)	

B. Provide the updated drug substance stability specification.

5. (b)(4) was neither listed in the original submission, Section 3.2.S.2.1, nor listed in the 10/11/2007 amendment as a testing facility for release of the drug substance. However, it was listed as one of the approved testing facilities in the Hill Laboratories Raw Material Specification Form in the 2/12/2008 amendment.

Provide a clarification as to the role of (b)(4) for the release of the drug substance. If it is not involved in the release testing of 5-fluorouracil, delete (b)(4) as an approved testing facility in the Hill Laboratories Raw Material Specification Form and provide an updated Raw Material Specification Form for 5-fluorouracil.

6. Your drug product stability data for the three registration batches do not support the proposed shelf life of (b) (4) months. The data from accelerated conditions for 6 months showed that there was a significant change in assay ((b) (4) %). Only 12 months long-term stability data were submitted for the three registration batches and there are no data from intermediate condition. Per ICH Q1E, a 15-month shelf life for the drug product can be granted.

Revise the shelf life of the drug product to 15 months.

In addition, please submit the bioanalytical report, No TNJS07023, entitled "Quantitative determination of 5-FU in human plasma (EDTA) samples by LC/MS/MS for protocol HD-FU1206SA" at your earliest convenience.

If you have any questions, call Catherine Carr, Project Manager, at 301-796-2311.

Sincerely,

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Susan Walker
2/29/2008 02:08:15 PM



NDA 22-259

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 new drug application (NDA) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for 5-Fluorouracil Cream 4%.

We also refer also to the February 25, 2008 telephone conversation between you and Catherine Carr of this division regarding submission of a safety update.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Please submit this information as soon as possible.

If you have any questions, call Catherine Carr, Project Manager, at 301-796-2311.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Susan Walker
2/29/2008 02:08:48 PM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: January 24, 2008
TIME: 3 PM
LOCATION: Teleconference
APPLICATION: NDA 22-259
DRUG NAME: Fluorouracil Cream, 4%
SPONSOR: Hill Dermaceuticals

MEETING CHAIR: Jane Chang, Ph.D., Quality Reviewer, ONDQA

MEETING RECORDER: Catherine Carr, M.S./Regulatory Health Project Manger, DDDP

FDA ATTENDEES: (Title and Office/Division)

Shulin Ding, Ph.D./Pharmaceutical Assessment Lead, ONDQA, DPA-II
Jane Chang, Ph.D./Quality Reviewer, ONDQA, DPA-II
David Kettl, M.D./Clinical Reviewer, DDDP
Catherine Carr, M.S./Regulatory Health Project Manger, DDDP

EXTERNAL CONSTITUENT ATTENDEES:

Nancy Puglia, Chemical Engineer Plant Manager, Hill Dermaceuticals
Sarah Reinartz, Laboratory Chemist, Quality Assurance/Quality Control, Hill Dermaceuticals
Rosario Ramirez, M.D., Director of Medical and Regulatory Affairs, Hill Dermaceuticals
Jerry Roth, President, Hill Dermaceuticals

MEETING OBJECTIVES:

The purpose of this meeting was to allow an opportunity for dialogue between the Agency and the applicant for the amendment dated January 9, 2008. The topics for discussion were faxed to the applicant on January 23, 2008.

DISCUSSION POINTS:

The Agency asked for a clarification regarding the number of suppliers for the starting material, (b) (4) because a new supplier was mentioned in the January 9, 2008 amendment. The applicant confirmed the addition of the second supplier and stated that the original supplier, (b) (4) remained. The applicant agreed to provide supplier information for the starting material used in the manufacture of each drug substance clinical/toxicology/stability lot.

The applicant agreed to provide analytical method numbers for the following methods used in the release of (b) (4) related substances, assay, and residual solvents.

Regarding drug substance related substances testing, the applicant stated that an in-house validated HPLC method had been routinely used. However, this method had not been demonstrated to be capable of detecting the specified impurities listed in the current Ph. Eur.

The drug substance supplier had been testing related substances using the TLC method per EP monograph effective at the time of testing.

The Agency reiterated the necessity to have a clearly stated drug substance regulatory specification in the NDA, and to include related substances in the regulatory specification. FDA recommended that the drug substance regulatory specification be revised by minimally adding related substances per Ph. Eur. to the requirements outlined in the USP monograph, but was willing to review the applicant's revised proposal for drug substance regulatory specification. The proposal must clearly indicate methods, acceptance criteria, and testing lab(s).

The applicant clarified the meaning of [REDACTED] (b) (4) [REDACTED] respectively.

The Agency noted that there were inconsistencies, e.g. retest period of the drug substance and postapproval stability protocol, in the January 9th amendment. The applicant indicated that they would resolve/clarify the inconsistencies in their response to the Agency's request for information.

The Agency requested the applicant to provide a complete response by February 13th. However, if a complete response is not achievable, the applicant should provide a partial response by Feb. 13, with a timeline for a response to the remaining outstanding items. FDA expects to receive the revised drug substance regulatory specification including related substances in the Feb. 13 amendment.

ACTION ITEMS:

The applicant will provide a response to the information requests, dated January 14, 2008 and January 23, 2008, by February 13, 2008. The response is either a complete response or a partial response with committed response timelines for remaining outstanding items.

ATTACHMENTS/HANDOUTS:

None.

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/s/

Catherine Carr
2/20/2008 11:49:18 AM
CSO

Jane Chang
2/20/2008 12:06:07 PM
CHEMIST

MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 1, 2008
TIME: 10 AM and 3 PM
LOCATION: Teleconference
APPLICATION: NDA 22-259
DRUG NAME: Fluorouracil Cream, 4%
SPONSOR: Hill Dermaceuticals

MEETING CHAIR: Jane Chang, Ph.D., Quality Reviewer, ONDQA

MEETING RECORDER: Catherine Carr, M.S./Regulatory Health Project Manger, DDDP

FDA ATTENDEES: (Title and Office/Division)

Shulin Ding, Ph.D./Pharmaceutical Assessment Lead, ONDQA, DPA-II

Jane Chang, Ph.D./Quality Reviewer, ONDQA, DPA-II

Catherine Carr, M.S./Regulatory Health Project Manger, DDDP

EXTERNAL CONSTITUENT ATTENDEES:

Nancy Puglia, Chemical Engineer Plant Manager, Hill Dermaceuticals

Sarah Reinartz, Laboratory Chemist, Quality Assurance/Quality Control, Hill Dermaceuticals

Rosario Ramirez, M.D., Director of Medical and Regulatory Affairs, Hill Dermaceuticals

Criss Molasso, Regulatory Affairs, Hill Dermaceuticals

MEETING OBJECTIVES:

The purpose of this meeting was to allow an opportunity for the Agency to provide clarification regarding related substances testing in the drug substance regulatory specification which was discussed in the January 24, 2008 teleconference. In addition, the goal was to discuss some of the CMC deficiencies identified in the CMC information requests, dated January 14, 2008.

DISCUSSION POINTS:

A document entitled "Clarification Regarding Information Request on 1/23/08 (1/24/2008 teleconference)" was sent to the applicant via email prior to the teleconference and is attached to the minutes.

The Agency indicated that it was acceptable for the applicant to contract the related substances testing to the drug substance supplier. In addition, the Agency clarified that it was acceptable to use the EP methods or an in-house method, but the in-house method must be equivalent or better than those of the EP methods and must be specified in the application. A table for the proposed specification should include related substances in addition to all testing in the USP monograph. Release testing facilities should be clearly identified.

The Agency indicated that the acceptance criterion for viscosity in the drug product specification needed to be established with justification.

The sponsor indicated that they were on track with providing responses to all information requests by February 13th.

At 3PM, the sponsor was contacted to follow-up on a few points that required further clarification from the 10AM call. The Agency requested clarification regarding whether the release testing of the drug substance might be performed by (b) (4) because the name was mentioned in the morning teleconference but it had never been indicated in the NDA as a testing facility until now. The Agency was concerned that being late in the review cycle, a new request for inspection on (b) (4) might not be completed prior to the PDUFA date. The applicant indicated that they would provide documentation stating that the API manufacturer, (b) (4) would perform the release testing.

The Agency stated that it was acceptable to use the EP titration method for assay in the drug substance postapproval stability protocol. However, the retest date for the drug substance should be revised to (b) (4) or less due to the non-specific nature of the titration method. The applicant indicated that the retest date set by Hill for the drug substance is (b) (4), and they would provide information in the amendment to reflect this (b) (4) retest date.

ACTION ITEMS:

1. The applicant will provide responses to all of the Agency's information requests by February 13th.
2. The applicant will provide clarification regarding (b) (4) role in their response to the Agency's information request by February 13th.
3. The applicant will provide clarification regarding the retest date for the drug substance in their response to the Agency's information request by February 13th.

ATTACHMENTS/HANDOUTS:

1. Attachment 1: Clarification Regarding Information Request on 1/23/08 (1/24/2008 teleconference)

ATTACHMENT 1

Clarification Regarding Information Request on 1/23/2008 (1/24/2008 teleconference)

Regulatory Specification for 5-Fluorouracil Drug Substance

Please establish a regulatory specification for 5-fluorouracil. The specification should include the tests, acceptance criteria, and methods listed in Section 3.2.S.4.1, page 5 (Hill Laboratories, Inc. specification). In addition, the specification should include related substances and their acceptance criteria listed in the Ph. Eur., i.e. [REDACTED] (b) (4) [REDACTED] single unknown impurity, and total impurities by HPLC.

The analytical method(s) for related substances should be equivalent or better than those listed in the Ph. Eur. for 5-fluorouracil. Analytical procedures and validation data should be submitted. Alternatively, the testing can be contracted and performed by the drug substance supplier. In such case, it should be clearly stated.

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/s/

Catherine Carr
2/20/2008 11:52:27 AM
CSO

Jane Chang
2/20/2008 12:05:49 PM
CHEMIST



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: February 15, 2008

To: Rosario Ramirez, MD	From: Catherine Carr, Project Manager
Company: Hill Dermaceuticals, Inc.	Division of Dermatologic & Dental Products
Fax number: 407-302-7196	Fax number: (301) 796-9894 or 9895
Phone number: 1-800-344-5707	Phone number: (301) 796-2311

Subject: NDA 22-259/Clinical Information Request

Total no. of pages including cover: 3

Comments: Please find attached the Clinical Reviewer's request for information.

Thank you.

Document to be mailed: YES NO

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FDA Facsimile Memorandum

Date: February 15, 2008
To: Rosario Ramirez, MD
From: Catherine Carr, Project Manager
Subject: NDA 22-259

Dear Dr. Ramirez,

Reference is made to your NDA 22-259 for 4% 5-Fluorouracil Cream. The Clinical Reviewer would like to request the following information to aid in the review of your application.

Please submit the full CRF for subject 18-1-162, the 66 year old male in study 048 that had the alleged "anaphylactoid reaction" to your product. He is referred to in the proposed labeling, but the event was not characterized as serious.

Please let me know if you have any questions regarding this request. Thank you.

Catherine Carr, MSc
Regulatory Health Project Manager
Food and Drug Administration, CDER, DDDP
White Oak, Bldg 22, Room 5175
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tele: (301) 796-2311 Fax: (301) 796-9894/9895

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/s/

Catherine Carr
2/15/2008 03:18:17 PM
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Center for Drug Evaluation and Research
Office of Drug Evaluation III**

FACSIMILE TRANSMITTAL SHEET

DATE: January 31, 2008

To: Rosario Ramirez, MD	From: Catherine Carr, Project Manager
Company: Hill Dermaceuticals, Inc.	Division of Dermatologic & Dental Products
Fax number: 407-302-7196	Fax number: (301) 796-9894 or 9895
Phone number: 1-800-344-5707	Phone number: (301) 796-2311
Subject: NDA 22-259/CMC Comments	

Total no. of pages including cover: 3

Comments: Please find attached the CMC Reviewer's comments regarding labeling.

Thank you.

Document to be mailed: YES NO

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FDA Facsimile Memorandum

Date: January 31, 2008
To: Rosario Ramirez, MD
From: Catherine Carr, Project Manager
Subject: NDA 22-259

Dear Dr. Ramirez,

Reference is made to your NDA 22-259 for 4% 5-Fluorouracil Cream. The CMC Reviewer has the following comments regarding the labeling submitted in your application.

1. Revise the package insert:

- a) Revise established name to “fluorouracil”. Strength is not part of the established name. For example, the trade name and established name can be provided as the following:

“TRADENAME (fluorouracil) Cream”

or

“TRADENAME Cream
(fluorouracil cream)”

Strength should be provided after the trade name and established name.

- b) In Section 11-DESCRIPTION, provide trade name, established name, route of administration, and pharmacological/therapeutic class.
c) In Section 16-HOW SUPPLIED/STORAGE AND HANDLING, provide NDC number.

2. Revise labeling for immediate container and carton:

- a) See comment from 1a).
b) Add Lot number, expiration date, “Rx only” statement, and bar code for the immediate container labeling. “Rx only” statement should be prominently displayed.
c) Add “Rx only” statement for the carton label. It should be prominently displayed on the main panel.
d) Increase the font size for established name so that it is at least one half of the trade name.

Please let me know if you have any questions. Thank you.

Catherine Carr, MSc
Regulatory Health Project Manager
Food and Drug Administration, CDER, DDDP
White Oak, Bldg 22, Room 5175
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tele: (301) 796-2311 Fax: (301) 796-9894/9895

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/s/

Catherine Carr
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Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 23, 2008

To: Rosario Ramirez, MD	From: Catherine Carr, Project Manager
Company: Hill Dermaceuticals, Inc.	Division of Dermatologic & Dental Products
Fax number: 407-302-7196	Fax number: (301) 796-9894 or 9895
Phone number: 1-800-344-5707	Phone number: (301) 796-2311

Subject: NDA 22-259/CMC Information Request

Total no. of pages including cover: 4

Comments: Please find attached the CMC Reviewer's request for information.

Thank you.

Document to be mailed: YES NO

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FDA Facsimile Memorandum

Date: January 23, 2008
To: Rosario Ramirez, MD
From: Catherine Carr, Project Manager
Subject: NDA 22-259

Dear Dr. Ramirez,

Reference is made to your NDA 22-259 for 4% 5-Fluorouracil Cream. The CMC Reviewer would like to request the following information to aid in the review of your application. Please refer to our information request, dated November 1, 2007, and your response to the information request, dated January 9, 2008.

1. Please clarify whether (b) (4) is no longer the supplier for (b) (4).
In the validation runs for (b) (4) (Section 3.2.S.2.5, page 34).
2. Please assign analytical method numbers (not "in-house") for related substances, assay, and residual solvents for (b) (4) (11/1/07 IR, Item 1e).
3. Please establish a regulatory specification for 5-fluorouracil. The specification should include the tests, acceptance criteria, and methods listed in Section 3.2.S.4.1, page 5 (Hill Laboratories, Inc. specification). In addition, the specification should include related substances and their acceptance criteria listed in the Ph. Eur., i.e. (b) (4)

Provide a statement indicating that this established specification is the regulatory specification.

4. Provide the meaning of (b) (4) in the reference standards table in the 1/9/2008 amendment.
5. Please provide the following information:
 - a. Clarify the proposed retest date for 5-fluorouracil drug substance. Retest dates of (b) (4) months were proposed in the 1/9/2008 amendment.
 - b. The stability specification presented in Section 3.2.S.7.1 and postapproval stability protocol presented in Section 3.2.S.7.2 are not consistent with the information presented in the 1/9/2008 amendment. Please revise the postapproval stability protocol to include container closure system, storage conditions, testing time points, and stability specification. The stability specification should include testing for appearance, assay, loss on drying, and related substances with the same acceptance criteria and methods as those of the release specification.

Please let me know if you have any questions. Thank you.

Catherine Carr, MSc
Regulatory Health Project Manager
Food and Drug Administration, CDER, DDDP
White Oak, Bldg 22, Room 5175
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tele: (301) 796-2311 Fax: (301) 796-9894/9895

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/s/

Catherine Carr
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CSO



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III**

FACSIMILE TRANSMITTAL SHEET

DATE: January 14, 2008

To: Rosario Ramirez, MD	From: Catherine Carr, Project Manager
Company: Hill Dermaceuticals, Inc.	Division of Dermatologic & Dental Products
Fax number: 407-302-7196	Fax number: (301) 796-9894 or 9895
Phone number: 1-800-344-5707	Phone number: (301) 796-2311

Subject: NDA 22-259/CMC Information Request

Total no. of pages including cover: 5

Comments: Please find attached the CMC Reviewer's request for information.

Thank you.

Document to be mailed: YES NO

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FDA Facsimile Memorandum

Date: January 14, 2008
To: Rosario Ramirez, MD
From: Catherine Carr, Project Manager
Subject: NDA 22-259

Dear Dr. Ramirez,

Reference is made to your NDA 22-259 for 4% 5-Fluorouracil Cream. The CMC Reviewer would like to request the following information to aid in the review of your application.

1. Provide the following information regarding the container and closure system proposed for marketing:
 - a) Clarification as to whether end sealant (b)(4). A report for an extractable study for end sealant (b)(4) was provided. If they are different, please provide data for extractable study for (b)(4), which was stated to be the end sealant for the proposed container closure system.
 - b) A justification for use of (b)(4)
 - c) Clarification for the tubes as to whether they (b)(4) should be described.
 - d) The product code and supplier of aluminum tube.
 - e) A statement certifying the (b)(4) cap being in compliance with the indirect food additive regulations (21 CFR (b)(4)).
 - f) Clarification as to where the colorant, product code (b)(4), is used. Is it used in the cap, inside the tube, or outside the tube?
2. Provide the following information regarding manufacturing of the drug product:
 - a) Impact of temperature on critical product quality attributes. Adequate temperature control for adding the ingredients was stated to be critical.
 - b) Establish acceptance criteria for viscosity, pH, and ratio (b)(4) drug (Table 21P).
 - c) Include a test and acceptance criteria for (b)(4) cream (Table 21P).
3. Provide the following information regarding excipients:
 - a) Addresses of the manufacturers for Arlachel-165 and Methyl Gluceth-10. Please clarify whether the same manufacturers supply these excipients for the manufacture of Tri-Luma Cream.
 - b) Weight ratios of (b)(4) Arlachel-165 and the degree of (b)(4)

- c) Include a test for residual solvents per USP <467> (b) (4)
 - d) COAs of Arlacel-165 and Methyl Gluceth-10 used in the manufacture of the registration batches of the drug product.
4. The proposed drug product specifications listed in Table 22P and “Hill Laboratories, Inc. Finished Product Specification Form” (Section 3.2.P.5.1) are not consistent. Please revise the drug product specification to include the following items in addition to those listed in the “Hill Laboratories, Inc. Finished Product Specification Form”.
- a) Establish acceptance criteria for pH and ratio (b) (4).
 - b) Add tests and acceptance criteria for related substances (specified, each unknown, and total impurities), butylated hydroxytoluene assay, viscosity, microscopic examination (i.e. particle size test, method (b) (4)). The acceptance criteria for related substances should comply with the ICH Q3B limits. Please be advised that the sample preparation for 5-fluorouracil assay listed in (b) (4).
 - c) Add a test and acceptance criterion for total molds and yeasts count. The acceptance criterion should be NMT (b) (4) cfu/g per USP <1111>.
 - d) Add a test and acceptance criterion for minimum fill per USP <755>.
 - e) Revise the acceptance criteria for (b) (4) % of label claim.

Revise Table 22P following above recommendations.

5. Provide the following information regarding analytical procedures and method validation for the drug product:
- a) Validation of (b) (4)
 - b) Analytical procedure and method validation for assay of butylated hydroxytoluene. See also the comments from a) for validation criteria.
 - c) Assay and total impurities under each condition of drug substance and cream product forced degradation studies (in validation of method (b) (4)).
6. Revise the drug product stability specification to add the tests for related substances (specified, each unknown, and total impurities), butylated hydroxytoluene assay, viscosity, homogeneity, and weight change.

7. Provide the following information regarding drug product stability data:
- Verify accuracy of data for pH and ratio of 5-FU to the sodium salt shown in the table below. The ratios of 5-FU to the sodium salt were calculated using the formula listed in Section 3.2.P.5.1.

Lot	Conditions	pH	Ratio 5-FU:salt provided in the NDA	Ratio 5-FU:salt calculated by the Agency
(b) (4)				

- Please provide updated stability data, including particle size test, for Batches 06L092/L060167, 06L093/L060169, and 06L098/L060174. Per ICH Q1A, long term stability testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission.
 - Provide stability data for (b) (4) study. The data should include all tests in the stability specification.
 - Perform a one-time test for (b) (4) content for Lots 06L092/L060167, 06L093/L060169, and 06L098/L060174 stored at 40°C/75% RH to address mass balance concern. Stability data showed a decrease in assay (b) (4) % in these three lots after 6 months, which does not correspond to the amount of increase (up to (b) (4) % total impurities) in the impurities.
8. Provide the following information regarding analytical method (b) (4) protein analysis for (b) (4) Peanut Oil:
- Demonstrate adequacy of the extraction procedures by:
 - Protein analysis data from each extraction of (b) (4) peanut oil NF and peanut oil which has not been heated at (b) (4) °C.
 - Perform multiple extractions on the same sample of (b) (4) peanut oil and analyze protein content of each extraction separately to establish required number of extractions for complete protein removal into the aqueous solution.
 - Provide analytical procedure and validation data for protein analysis performed by (b) (4). The validation data should include accuracy, precision (repeatability and intermediate precision), specificity, linearity, range, limit of detection, and limit of quantitation.

Please let me know if you have any questions. Thank you.

Catherine Carr, MSc
 Regulatory Health Project Manager
 Food and Drug Administration, CDER, DDDP
 White Oak, Bldg 22, Room 5175
 10903 New Hampshire Avenue
 Silver Spring, MD 20993
 Tele: (301) 796-2311 Fax: (301) 796-9894/9895

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/s/

Catherine Carr
1/14/2008 10:11:47 AM
CSO



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Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: December 19, 2007

To: Rosario Ramirez, MD	From: Catherine Carr, Project Manager
Company: Hill Dermaceuticals, Inc.	Division of Dermatologic & Dental Products
Fax number: 407-302-7196	Fax number: (301) 796-9894 or 9895
Phone number: 1-800-344-5707	Phone number: (301) 796-2311
Subject: NDA 22-259 Tradename	

Total no. of pages including cover: 3

Comments: Please find attached the comments regarding your proposed tradename for NDA 22-259 for 4% 5-Fluorouracil (5-FU) Cream.

Thank you.

Document to be mailed: YES NO

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FDA Facsimile Memorandum

Date: December 19, 2007
To: Rosario Ramirez, MD
From: Catherine Carr, Project Manager
Subject: NDA 22-259

Dear Dr. Ramirez,

Reference is made to your submission to NDA 22-259 for 4% 5-Fluorouracil Cream, dated October 15, 2007.

The Agency finds the proposed trade name "^{(b)(4)}" unacceptable because it minimizes the risks of the drug product. "^{(b)(4)}" easily invokes the word ^{(b)(4)}

Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a trade name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

It is recommended that you submit two or three alternative proprietary names for our review. If you have any questions, please feel free to give me a call.

Thank you.

Catherine Carr, MSc
Regulatory Health Project Manager
Food and Drug Administration
Division of Dermatology and Dental Products (DDDP)
White Oak, Bldg 22, Room 5175
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tele: (301) 796-2311
Fax: (301) 796-9894/9895

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/s/

Catherine Carr
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-259

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

Dear Dr. Ramirez:

Please refer to your new drug application (NDA) dated August 17, 2007, received August 20, 2007, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for 5-Fluorouracil Cream, 4%.

We also refer to the meeting between representatives of your firm and the FDA on October 18, 2007. The purpose of the meeting was to gain clarification regarding the readiness of your manufacturing site for pre-approval cGMP inspection.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Catherine Carr, Regulatory Project Manager, at (301) 796-2311.

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Deputy Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 18, 2007
TIME: 11:30 am
LOCATION: Teleconference
APPLICATION: NDA 22-259
DRUG NAME: 5-Fluorouracil Cream, 4%

MEETING CHAIR: Stanka Kukich, M.D.

MEETING RECORDER: Catherine Carr, M.S.

FDA ATTENDEES: (Title and Office/Division)

Stanka Kukich, M.D./Deputy Director, Division of Dermatology and Dental Products (DDDP)
Markham C. Luke, M.D., Ph.D./Lead Medical Officer, Dermatology, DDDP
David Kettl, M.D./Medical Officer, DDDP
Susmita Samanta, M.D./Acting Chief Project Management Staff, DDDP
Catherine Carr, M.S./Regulatory Health Project Manger, DDDP
Elaine Morefield, Ph.D./Director, Division of Pre-Marketing Assessment II (DPA-II), Office of
New Drug Quality Assessment
Shulin Ding, Ph.D./Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment II
(DPA-II), Office of New Drug Quality Assessment

EXTERNAL CONSTITUENT ATTENDEES:

Jerry Roth, President, Hill Dermaceuticals
Rosario Ramirez, M.D., Director of Medical and Regulatory Affairs, Hill Dermaceuticals
Elaine Cox, Production Manager, Hill Dermaceuticals
Nancy Puglia, Chemical Engineer Plant Manager, Hill Dermaceuticals
Gregory Wulff, Quality Assurance/Quality Control, Hill Dermaceuticals
Ingrid Warner, Quality Assurance/Quality Control, Hill Dermaceuticals

BACKGROUND:

In response to the Agency's request for clarification regarding whether the manufacturing site for 5-Fluorouracil Cream was ready for pre-approval cGMP inspection, the sponsor provided an email communication, dated October 15, 2007, indicating that Hill proposed the date for FDA site inspection for the week of May 5, 2008. The sponsor subsequently proposed this date in a fax submission, dated October 17, 2007.

Due to the fact that the PDUFA goal date for this application is June 20, 2008, the Agency requested a teleconference with the applicant to gain clarification on the timeframe in which the manufacturing site for 5-Fluorouracil Cream would be ready for pre-approval cGMP inspection.

MEETING OBJECTIVES:

The objective of this teleconference was to gain clarification on the readiness of the sponsor's manufacturing site for pre-approval cGMP inspection.

DISCUSSION POINTS:

The Agency inquired about the readiness of the manufacturing site for 5-Fluorouracil Cream for pre-approval cGMP inspection. The Agency reminded the sponsor that the expectation is that the manufacturing site is ready for inspection upon submission of the NDA. The sponsor was informed that it could be a filing issue if the site is not ready to accommodate inspectors. The sponsor was also reminded that the inspection would be a product-specific inspection.

The sponsor indicated that they are in the process of building a new manufacturing line that would be solely dedicated to the manufacturing of this product. While the new line is currently under construction, the sponsor indicated that they have another identical manufacturing line at the same site that is ready for a product-specific inspection. The sponsor mentioned that they have had some concerns about cleaning of equipment, but stated that is now no longer a concern.

The Agency requested the sponsor to submit a correspondence to the NDA stating that the existing facility is ready for a pre-approval cGMP inspection. The sponsor agreed.

ACTION ITEMS:

1. Sponsor will submit a correspondence documenting that the manufacturing site is ready for inspection.

ATTACHMENTS:

1. The facsimile transmission record, dated October 17, 2007, indicating Hill Dermaceuticals' proposed date for site inspection as the week of May 5, 2008.
2. The sponsor faxed a correspondence, dated October 18, 2007, documenting the readiness of the manufacturing site for a product-specific inspection by the FDA for NDA 22-259.

Hill Dermaceuticals, Inc.
Innovative Dermatologicals for Children and Adults

FACSIMILE TRANSMISSION RECORD

DATE: 17 October 2007 Pages 1
TO: Catherine Carr, Regulatory Health Project Manager
COMPANY: FDA / CDER
FAX PHONE #: (301) 796-9895 Hill Fax # (407) 302-7196
Hill Tel. # (407) 323-1887

RE: NDA 22-259, 4% TRADENAME Cream (5-Fluorouracil)
Requested Information

Dear Ms. Carr,

In response to the Agency's request for the date of manufacturing site inspection by FDA, Hill Dermaceuticals, Inc. (Hill) has indicated the week of May 5 to 9, 2008, which Hill has determined to be a realistic and safe estimation. In the event that Hill is able to provide an earlier date, this notification will immediately be relayed to the Agency.

Thank you for your patience and understanding.

Sincerely,


Rosario G. Ramirez, MD
Director
Medical / Regulatory Affairs

Hill Dermaceuticals, Inc.
Innovative Dermatologicals for Children and Adults

Facsimile correspondence
18 October 2007

Food and Drug Administration
Division of Dermatology and Dental Products (DDDP)
White Oak, Bldg 22, Room 5175
10903 New Hampshire Avenue
Silver Spring, MD 20993

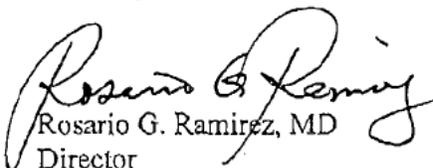
Attn: Catherine Carr, M.S.
Regulatory Health Project Manager

RE: NDA 22-259, 4% TRADENAME Cream (5-Fluorouracil)
Requested Information

Dear Ms Carr,

This letter serves to give notice that Hill Dermaceuticals, Inc. (Hill) is ready for the manufacturing site *product-specific* inspection by the FDA for the 4% TRADENAME (5-fluorouracil) Cream, NDA 22-259. This declaration supersedes all other previous correspondence pertaining to the (product-specific) site inspection for this NDA.

Sincerely,


Rosario G. Ramirez, MD
Director
Medical / Regulatory Affairs

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/s/

Catherine Carr
11/9/2007 09:19:28 AM
CSO

Stanka Kukich
11/9/2007 09:47:48 AM
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-259

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

Dear Dr. Ramirez:

Please refer to your new drug application (NDA) dated August 17, 2007, received August 20, 2007, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for 5-Fluorouracil Cream, 4%.

We also refer to your submissions dated September 10, 2007, October 11, 2007, October 15, 2007, and October 18, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is standard. Therefore, the user fee goal date is June 20, 2008.

During our filing review of your application, we identified the following potential review issues:

1. The NDA should clearly identify which sections are intended to fulfill the elements of a 505(b)(2) application and articulate how, in your opinion, the elements of a 505(b)(2) application have been fulfilled. This issue was previously communicated in the pre-NDA meeting minutes, dated April 20, 2007.
2. Submit the name of your Reference Listed Drug (RLD) formally to your NDA. There is currently no RLD listed on the Form 356h submitted with your NDA.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

1. Mock-up container and carton labels bearing the proposed trade name. These labels should be presented in the sizes and colors proposed for marketing.
2. Establishment information for drug product packaging and stability testing site(s).
3. Updated drug product stability results.

4. Representative drug product samples (6 units) [REDACTED] (b) (4)
[REDACTED] of the formulation
5. DMF references with letters of authorization for drug product contain/closure system (tubes, tube liner, caps, etc.). Alternatively, provide the following information in the NDA:
 - Description and composition for tubes, tube liner, and caps
 - Description and composition for the fabrication materials of tubes, tube liner and caps
 - Description and composition for colorants used in the container/closure system
 - Name and address of the supplier/manufacturer for each packaging component
 - Supplier's/manufacturer's certificate of analysis for each packaging component
6. In addition, a statement of Good Clinical Practice (that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures) is required.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients.

If you have any questions, call Catherine Carr, Regulatory Project Manager, at (301) 796-2311.

Sincerely,

{See appended electronic signature page}

Susan Walker, M.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Susan Walker

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NDA 22-259

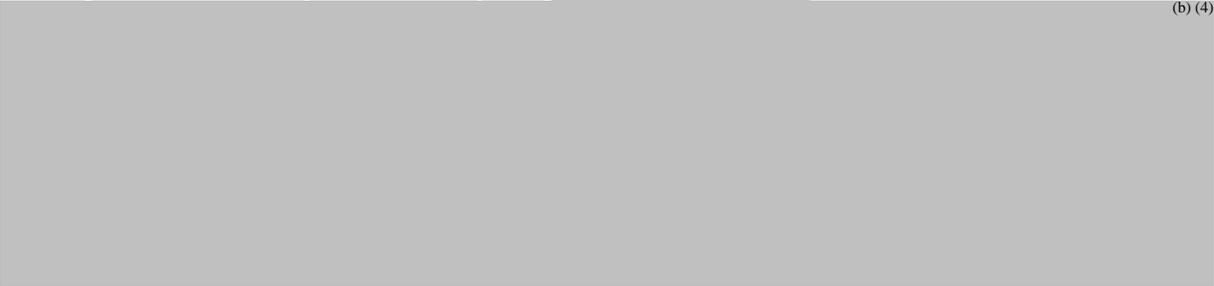
INFORMATION REQUEST LETTER

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 August 17, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for 5-Fluorouracil Cream, 4%.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

- 1) Please provide the following information regarding (b) (4):
 (b) (4)
- 2) Provide the test method (e.g. HPLC) and the identity of the impurities being monitored for the (b) (4) manufacture of the drug substance described in Section 3.2.S.2.2, page 4 (Table S1).
- 3) Provide the ranges for the amounts of raw materials for the manufacture of the drug substance at the (b) (4) scale. The ranges were stated to be critical.
- 4) Revise fluorouracil regulatory specification.
 - a) The proposed drug substance specification should include all tests for Fluorouracil USP and the following tests:
 - i) Related substances by HPLC for specified, each unknown, and total impurities. The specified impurities should include (b) (4).
 - ii) Free (b) (4) content.
 - b) Procedure and validation of the HPLC method should be provided. The validation should include evaluation of the drug substance under forced degradation conditions to demonstrate that the method is stability indicating.
 - c) The proposed acceptance criteria for specified impurities and each unknown impurity should comply with the ICH Q3A qualification and identification thresholds, respectively, unless data, e.g. toxicology lots or clinical lots, are provided to justify the proposed limits.
- 5) Clarify which drug substance release test(s) will be performed by (b) (4)

- 6) Clarify whether compendial methods are used by (b) (4) for release of the drug substance. Method number, procedure, and validation data should be provided if non-compendial methods are used.
- 7) Provide the sources of reference standards for the specified impurities for the drug substance and the drug product, including the reference standards for (b) (4). If USP reference standards are used, please indicate so. If USP reference standards are not available, please indicate the suppliers and batch numbers.
- 8) Provide a certification indicating that (b) (4) used for packaging and shipping of the drug substance comply with the U.S. Indirect Food Additive Regulations.
- 9) Revise the drug substance postapproval stability protocol to include the following tests:
 - a) Loss on drying to be continued in all future stability studies.
 - b) Related substances by HPLC, including specified impurities, each unknown, and total impurities.
- 10) Commit to placing at least one new batch of the commercial lot of the drug substance (b) (4) if available, on stability studies.
- 11) Revise the drug substance retest date to (b) (4) months. This recommendation is based on the following observations:
 - a) (b) (4)
 - b) Insufficient information on related substances. The stability data provided were based on limit tests, i.e. TLC methods.
- 12) Provide the following stability data for Lots 20126/0103B005, 20126/0103B006, and 20126/0103B007 (these tests were included in Table S33, but the data was not provided):
 - a) Clarity of solution.
 - b) Color of solution.
 - c) pH.
 - d) Related substances, including (b) (4) total unknown and total impurities.
 - e) (b) (4) content.

If you have any questions, call Linda Mullins Athey, Regulatory Health Project Manager for Quality, at 301-796-2096.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Assessment Division II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
11/1/2007 12:58:44 PM
Chief, Branch III



NDA 22-259

INFORMATION REQUEST LETTER

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

Dear Dr. Ramirez:

Please refer to your August 17, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for 5-Fluorouracil Cream, 4%.

We are reviewing the Clinical and Chemistry, Manufacturing and Controls (CMC) sections of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Please provide the following information:

1. Mock-up container and carton labels bearing the proposed trade name. These labels should be presented in the sizes and colors proposed for marketing.
2. Establishment information for drug product packaging and stability testing site(s).
3. Updated drug product stability results.
4. Representative drug product samples (6 units) [REDACTED] (b) (4)
[REDACTED] of the formulation
5. DMF references with letters of authorization for drug product contain/closure system (tubes, tube liner, caps, etc.). Alternatively, provide the following information in the NDA:
 - Description and composition for tubes, tube liner, and caps
 - Description and composition for the fabrication materials of tubes, tube liner and caps
 - Description and composition for colorants used in the container/closure system
 - Name and address of the supplier/manufacturer for each packaging component
 - Supplier's/manufacturer's certificate of analysis for each packaging component
6. In addition, a statement of Good Clinical Practice (that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures) is required.

If you have any questions, call Catherine Carr, Project Manager, at 301-796-2311.

Sincerely,

{See appended electronic signature page}

Susmita Samanta, M.D.
Acting Chief, Project Management Staff
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Susmita Samanta
10/23/2007 03:30:28 PM



IND 69,841

Hill Dermaceuticals, Inc
Attention: Jerry Roth, President/Owner
2650 South Mellonville Avenue
Sanford, FL 32773-9311

Dear Mr. Roth:

Please refer to your IND file for 4 % TRADENAME 5-fluorouracil, (5-FU) cream for the topical treatment of multiple actinic keratoses of the ears, face and scalp.

We also refer to the meeting between representatives of your firm and the FDA on November 21, 2005. The purpose of the meeting was to discuss your proposed Phase 3 drug development program.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact Frank H. Cross, Jr., M.A., MT (ASCP), CDR, Senior Regulatory Management Officer, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Acting Division Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Date: November 21, 2005 **Time:** 10:30-11:30am
Location: White Oak, building #22, room # 5201 Meeting ID: 16393
Topic: IND 69,841, 4 % TRADENAME 5-fluorouracil,
(5-FU) cream for the topical treatment of multiple
actinic keratoses of the ears, face and scalp
Subject: End-Of-Phase 2 (EOP2) meeting
Sponsor: Hill Dermaceuticals, Inc.
Meeting Chair: Stanka Kukich, M.D./ Acting Division Director, DDDP
Meeting Recorder: Shalini Jain, PA-C/Regulatory Management Officer, DDDP



FDA Attendees, titles and offices:

Stanka Kukich, M.D., Acting Division Director, DDDP
Jill Lindstrom, M.D., Acting Deputy Division Director, DDDP
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, ONDQA, DPA II
Zhengfang Ge, Ph.D., Chemistry Team Leader, ONDQA, DPA II
Barbara Hill, Ph.D., Pharmacology/Toxicology Reviewer, DDDP
E. Dennis Bashaw, Pharm.D., Clinical Pharmacology/Biopharmaceutics Team Leader, DCPBP III
Markham Luke, M.D., Ph.D., Clinical Team Leader, DDDP
Brenda Carr, M.D., Medical Officer, DDDP
Mohamed Alish, Ph.D., Biostatistics Team Leader, DBIII
Mat Soukup, Ph.D., Biostatistics Reviewer, DBIII
Shalini Jain, PA-C, Regulatory Project Manager, DDDP

Sponsor Attendees, titles and offices:

Hill Dermaceuticals, Inc.
Jerry Roth, President/Owner, Hill Dermaceuticals, Inc.
Nancy Puglia, ChmEng, Chemist, Hill Dermaceuticals, Inc.
Rosario Ramirez, M.D., Director, Medical/Regulatory Affairs, Hill Dermaceuticals, Inc.
(b)(4) Consultant

(b)(4)
(CRO)
(b)(4), President/Medical Monitor
Project Manager
Project Manager

(b)(4)
(CRO)
(b)(4) Ph.D., Consultant
(u)(4) M.D., Consultant

(b) (4)

(b) (4)

President/Biostatistician,
Project Manager/Biostatistician

Purpose:

To provide general guidance on the content and format of the proposed new Investigational New Drug Application under 21 CFR 312. The pre-meeting briefing document (submitted October 19, 2005) provides background and questions. The sponsor requests discussion of the clinical development of 4 % TRADENAME 5-fluorouracil, (5-FU) cream for the topical treatment of multiple actinic keratoses of the ears, face and scalp.

Chemistry, Manufacturing and Controls:

Question 12: “Does the Division have any comments on the current CMC submissions as noted in the IND amendments?”

Agency:

Regarding your submission on February 15, 2005, about the change of excipients for the placebo used in the clinical trials (remove (b) (4) to adjust placebo pH), please clarify whether (b) (4) has any function other than adjusting the pH in the drug product.

Additional Agency Comments:

1. We would like to reiterate the CMC comments conveyed to you in the pre-IND meeting dated August 16, 2004. The Pre-IND meeting minutes were faxed to you on September 15, 2005.
2. We want to remind you to include a proper specification on impurities and related substances in the drug product specification, and monitor impurities/degradants in the drug product stability program. A comparison of impurity profile between toxicology and clinical lots for drug product should be submitted as soon as possible.
3. Please provide a UV spectrum (200-700 nm) for each of formulation excipients.
4. Update the in-coming specification for peanut oil (b) (4) NF to include a test on allergenic compounds.
5. Update the in-coming specification for each of formulation excipients to include an identity test.

Pharmacology/Toxicology:

Question 9: “As written in the minutes of the Pre-IND Teleconference of August 16, 2004, the Division agreed that nonclinical dermal irritation and ocular irritation studies is waived for the 4% TRADENAME Cream, since it has been well established that topical treatment with 5-FU is a dermal irritant and would also be an ocular irritant.”

Agency:

The need for nonclinical dermal irritation and ocular irritation studies for the 4% fluorouracil cream are waived since it has been well established that topical treatment with 5-FU is a dermal irritant and would also be an ocular irritant. It has been established that Efudex cream has the potential to elicit a hypersensitivity reaction. Therefore, the need to conduct a nonclinical hypersensitivity test for the 4% fluorouracil cream is waived. It is recommended that appropriate warning information be included in the [REDACTED] (b) (4) for the 4% fluorouracil cream and in the label for the 4% fluorouracil cream if approved.

Question 10: “As written in the minutes of the Pre-IND Teleconference of August 16, 2004, the Division stated that a nonclinical photoirritation study is waived for the 4% TRADENAME Cream, since Hill has agreed to incorporate a warning statement in the Investigator Brochure similar to that contained in the Efudex label.”

Agency:

It is important to note that a rather large shoulder absorbance is noted in the 290 – 320 nm range according to the UV-VIS spectrum provided for the 4% 5-FU cream in the briefing package. Normally, this would trigger the need for nonclinical photoirritation and clinical phototoxicity and photoallergenicity studies. Refer to clinical comments for a discussion of the need for clinical phototoxicity and photoallergenicity studies.

The need for a nonclinical photoirritation study is waived for the 4% 5-FU cream since the sponsor is willing to incorporate a warning statement in the “[REDACTED] (b) (4)” similar to the one contained in the Efudex label; “Exposure to ultraviolet rays should be minimized during and immediately following treatment with Efudex because the intensity of the reaction may be increased.” It is recommended that a similar warning be incorporated in the label for the 4% 5-FU cream if approved.

Additional Agency Comments:

1. Treatment of actinic keratosis could be considered a chronic indication due to the recurrence rate associated with actinic keratosis. The need for a dermal carcinogenicity study to support marketing of the 4% 5-FU cream will be dependent on the actual clinical use of the 4% 5-FU cream for the treatment of actinic keratosis, which will be evaluated in the proposed long-term follow up clinical study.
2. If the sponsor is able to generate an adequate clinical bridge to Efudex cream, then the Agency’s findings of safety for the listed drug product can be used to support the 4% 5-FU cream product. However, if an adequate clinical bridge to Efudex cream is not established, then the sponsor can not rely on the Agency’s findings of safety for the listed drug product and must provide complete nonclinical toxicology information (i.e., general toxicology, genetic toxicology, reproductive and developmental toxicology and carcinogenicity) either from studies conducted by the sponsor, or for which the sponsor has the right of reference or from other publicly available information such as published studies.

Clinical Pharmacology and Biopharmaceutics:

Question 8: “Does the Division concur that the proposed pharmacokinetic study proposed in Section 4.5 provides adequate evaluation of the dosage form?”

Agency:

It is unclear from the material submitted in the meeting package whether or not the amount to be used in the trial would represent the "maximal" anticipated use in both the Phase 3 trials and in the eventual label. In addition, it is unclear whether or not the use would involve "lesional" or "area" application. We are also concerned that the number of subject per treatment arm is insufficient either to allow for the characterization of the in vivo bioavailability or to allow for the collection of meaningful clinical safety data on the proposed product. As this study will be the only anticipated in vivo pk characterization, the Agency recommends enrolling at least 30 subjects per treatment arm in this study.

These issues relating to both use and study size need to be addressed in the eventual full protocol as the outline submitted here is of insufficient detail to address these and other issues. We encourage the submission of a full protocol for review and comment prior to study initiation with sufficient lead time to permit a substantive review.

Clinical:

Question 1: Do the protocols presented for the Phase 3 pivotal studies meet the Agency's requirement for demonstration of comparative efficacy and safety with the reference listed drug (Efudex) for TRADENAME Cream, and demonstration of superiority of 4% TRADENAME Cream over its vehicle, as written in the minutes of the Pre-IND Teleconference of August 16, 2004, Item 4.c?

Question 2: Are the two proposed Phase 3 studies adequately designed to support approval of a 505(b) (2) NDA?

Agency (combined response to Questions 1 and 2):

1. Studies may provide some information regarding the comparative safety and efficacy of the sponsor's product and vehicle and Efudex. However, adequacy of blinding is in question for both studies given that:
 - a. In HD-FU-048 (bridging study) regimens are once daily for the sponsor's product and vehicle and twice daily for Efudex. Also, the appearance of the products may compromise blind (i.e. the appearance of Efudex relative to the sponsor's product and the sponsor's vehicle). For purposes of blinding, it is again recommended that an arm be added to mimic the vehicle of the reference listed drug. Please also refer to Biostatistics comments, below. Please comment regarding what measures you are taking to preserve blinding with regard to the known increased local erythema and irritation that will be seen with application of the active (e.g. separate assessor, timing of evaluation, etc.).

The sponsor proposed to add a second vehicle arm to mimic that of Efudex.

- b. In HD-FU-049 (safety and efficacy study), duration of treatment will be four weeks in two arms and two weeks in the third arm. The sponsor is requested to provide the regulatory intent of the two-week arm. If this arm is intended to support labeling for a two-week treatment duration, the sponsor should define the population who would be candidates for the two-week course and two studies that evaluated the two-week treatment duration would be needed.

The sponsor indicated that they will eliminate the two-week arm.

Additional comments regarding the proposed Phase 3 studies include:

- a. Laboratory testing (hematology and chemistries) should be conducted in the Phase 3 studies.

The sponsor agreed to obtaining labs in the Phase 3 trials. They will propose a number alternative to 500 subjects for obtaining labs.

- b. The sponsor should consider stratification by treatment areas (face/ears and scalp) since treatment effects may not be the same. The sponsor is also encouraged to evaluate use of their product on the extremities. The sponsor should also consider stratifying by baseline disease severity (i.e. number of lesions). Also, the treatment area needs additional definition, e.g., field treatment vs lesional treatment.

The sponsor indicated that treatment would be limited to the face in the Phase 3 trials. (b) (4)

- c. Post-treatment assessment at four weeks may not be sufficiently long to allow for evaluation of resolution of drug effects. The sponsor might also consider an assessment at eight weeks post-treatment.
- d. The rationale for having subjects apply the first dose of study drug under observation of study personnel is unclear. This would not be encouraged in phase 3 trials, unless there is some unique property of the study drugs which would require initial application under observation ((b) (4)
- e. If the sponsor intends to make claims that the vehicle contributes to safety and/or efficacy, such contribution must be demonstrated, and development of the product should be in compliance with 21 CFR 300.50.

Question 3: “Does the Division concur that the Clinical Development Plan offered by Hill Dermaceuticals, Inc., is complete and satisfies the Division’s requirements for evaluation of TRADENAME Cream (4% fluorouracil cream) to support approval of the 505(b) (2) NDA?”

Agency:

The sponsor should consider the comments provided regarding study design issues. Other comments may follow review of revised and/or complete protocols.

Question 4: “Does the Division accept Hill’s proposal (b) (4) of Hill’s NDA for TRADENAME 4% 5-FU Cream?”

Question 5: “Hill proposes tha (b) (4) .”

Agency:

Question 6: “Cumulative irritancy study is waived, since Hill agrees to label its product as an irritant, as written in the minutes of the Pre-IND Teleconference of August 16, 2004.”

Question 7: “Since the final to-be-marketed formulation exhibits no absorption in the UVB, UVA, or visible light spectra (280-700 nm), photoallergenicity and phototoallergenicity, and phototoxicity studies will be waived, as written in the minutes of the Pre-IND Teleconference of August 16, 2004.”

Agency:

It is agreed that the cumulative irritancy study may be waived. However, the sponsor will need to conduct contact sensitization (at least 200 evaluable subjects), photoallergenicity (at least 50 evaluable subjects) and phototoxicity (at least 30 evaluable subjects) studies.

Biostatistics:

Question 11: Does the Division have any comments on the proposed studies?

Agency:

1. When both subjects and investigators are blind to treatment, this preserves the integrity of the trial. The sponsor’s proposed method of blinding for HFD-FU-048 was to not have investigators involved in collecting or dispensing of study medication, and subjects were informed not to discuss treatment frequencies with the investigators. While such a strategy may preserve blinding, the sponsor might consider the following treatment arms which results in both subject and investigator blind to treatment.
 - Efudex twice per day
 - 4% FU once per day plus FU vehicle once per day
 - FU vehicle twice per day.
2. It is unclear the objective of including a third treatment arm with dosing duration of 2 weeks in HD-FU-049. For efficacy claims of two weeks treatment duration, replication of study findings in two separate studies is needed. Consequently, with the sponsor's proposed clinical development plans there is no replication of the comparison of 4% TRADENAME applied once daily for 2 weeks to vehicle.
3. The sponsor plans to test for overall treatment effect and if this is significant then they will test for individual treatment durations in HFD-FU-049. It should be noted that testing for overall treatment effect would not establish efficacy for any of the individual doses. Efficacy claims should be established for individual doses.
4. Imputation of missing data using LOCF is acceptable. However, the protocol should also list an alternate imputation technique as a sensitivity analysis to ensure that efficacy claims are not driven by the method of imputation.

5. In testing for treatment by center interaction, the sponsor stated that they will test for ‘poolability’ of centers. It should be noted that the goal of testing for treatment by center interaction is to determine if results of some centers might be extreme in comparison with other centers.
6. As efficacy results might vary by treatment area (face/ears and scalp) and disease severity, to ensure balance with respect to these factors, stratification is important (see clinical comments). It should be noted, however, that a design with many strata might be impractical for study enrollment and/or analysis. The sponsor should propose a stratification approach with a limited number of strata (such as pooling treatment areas and baseline severities with similar efficacy).

Regulatory Project Management:

1. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
2. All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.
3. The sponsor is encouraged to submit its revised protocols for the topical treatment actinic keratosis as Special Protocols to its original IND through the 45-day Special Protocol Assessment (SPA) mechanism for Agency review and comment, prior to study initiation.
4. The sponsor should request a pre-NDA meeting at the appropriate time.

The teleconference ended amicably.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

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/s/

Stanka Kukich
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