

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022259Orig1s000**

**CHEMISTRY REVIEW(S)**

**MEMORANDUM**

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

**DATE:** September 17, 2015

**TO:** Review #3 of NDA 22259

**FROM:** Jane Chang, Ph.D.  
Review Chemist, OPQ/OPF/DPA III/Branch IX  
For OPQ/ONDP/ Division II/Branch V

**SUBJECT:** Final CMC Recommendation  
NDA 22259  
Tolak Cream

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**SUMMARY**

In NDA 22259 CMC Review #3 dated 30-Jul-2015, it was recommended that the NDA was not ready for approval in its present form because labeling issues were not resolved and the facility evaluation was still pending.

Subsequently, the applicant provided a revised package insert labeling per the agency's recommendation. This memorandum covers the labeling review pertaining to sections 'Highlights', 'Dosage Forms and Strengths', 'Description' and 'How Supplied/Storage and Handling'.

On September 17, 2015, an overall "Acceptable" recommendation was issued from OPQ/OPF/DIA.

**RECOMMENDATION**

This NDA is now recommended for **APPROVAL** from the CMC perspective.

Review Notes

Labeling issues were identified in CMC Review #3 dated 30-Jul-2015 (see pages 39 - 43). Subsequently, the applicant provided a revised package insert labeling to Project Manager, Strother Dixon, on September 15, 2015 via a courtesy copy. The revised labeling incorporated this reviewer's recommendations for sections 'Dosage Forms and Strengths', 'Description' and 'How Supplied/Storage and Handling' (see Review #3). In addition, additional changes were made to Section 3 regarding expression of strength in metric system (i.e. the amount in mg per gram of cream) and the available packaging size per the recommendation from Labeling Development Team (LDT). The updated labeling information is presented below.

**1. Physician's Labeling Rule Prescription Drug Labeling**

Revised package insert was provided on 9/15/2015. The information pertaining to CMC is presented below.

**1) "Highlights" Section**

**TOLAK (fluorouracil) Cream, 4%, for topical use**  
**Initial US Approval: 1962**

-----DOSAGE FORMS AND STRENGTHS-----

Cream: 40 mg of fluorouracil per gram of cream (4%) (3).

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name and established name	Proprietary name and established name are described as TOLAK (fluorouracil).	Satisfactory
Dosage form and route of administration	Cream, topical	Satisfactory
Dosage forms and strengths	The strength 40 mg per gram of cream (4%) is provided.	Satisfactory

Conclusion: The "Highlights" section is satisfactory.

**2) "Full Prescribing Information" Section**

**a. Section 3 Dosage Forms and Strengths**

Cream: 40 mg of fluorouracil per gram (4%) of white cream in 40 gram tubes.

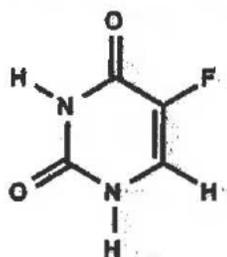
Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Dosage form and strength	Cream, 40 mg of fluorouracil per gram (4%)	Satisfactory
Identifying characteristics of the dosage forms	Identifying characteristics (i.e. white) of the cream is provided. The packaging size (i.e. 40 gram tubes) is included per the Labeling Review Tool, version August 2015.	Satisfactory

Conclusion: This section is satisfactory.

**b. Section 11 Description**

Tolak (fluorouracil) Cream, 4% contains 40 mg of fluorouracil per gram of white cream for topical application. It is a nucleoside metabolic inhibitor. Chemically, fluorouracil is 5-fluoro-2,4 (1H,3H)-pyrimidinedione. The molecular formula of 5-fluorouracil is  $C_4H_3FN_2O_2$ , and its molecular weight is 130.1. Its structural formula is:



Tolak Cream contains the following inactive ingredients: arlacel-165, butylated hydroxytoluene, cetyl alcohol, anhydrous citric acid, glycerin, isopropyl myristate, methyl gluceth-10, methylparaben, propylparaben, purified water, peanut oil, sodium hydroxide, stearic acid, and stearyl alcohol. Tolak Cream formulation has an alkaline pH at 8.3 to 9.2.

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name and established name*	Tolak (fluorouracil)	Satisfactory
Dosage form and route of administration	cream, topical	Satisfactory
Active moiety expression of strength	40 mg of fluorouracil per gram of cream (4%).	Satisfactory
Inactive ingredient information	All inactive ingredients are listed correctly.	Satisfactory
Pharmacological/ therapeutic class	nucleoside metabolic inhibitor	Satisfactory
Chemical name, structural formula, molecular weight	Chemical name, structural formula and molecular weight are correctly described in this section.	Satisfactory
Other important chemical or physical properties (such as pKa or pH)	The pH range (8.3 – 9.2) of the formulation is provided correctly.	Satisfactory

\*Per 201.10(g)(1), the established name shall accompany the proprietary name.

*Conclusion: The "Description" section is satisfactory.*

**c. Section 16 How Supplied/Storage and Handling**

**16.1 How Supplied**

Tolak (fluorouracil) Cream, 4% containing 40 mg fluorouracil per gram of white cream is available in a 40 gram tube (NDC 28105-421-40).

**16.2 Storage and Handling**

Store at 25°C (77°F), with excursion permitted from 15°C to 30°C (59°F - 86°F) [See USP Controlled Room Temperature]. Do not freeze.

*Reviewer's Assessment:*

Item	Comments on the Information Provided in NDA	Conclusions
Strength of dosage form in metric system	Strengths are correctly described as 40 mg of fluorouracil per gram of cream (4%).	Satisfactory
Units of dosage form	Available units are correctly described as 40 gram per tube	Satisfactory
Identification of dosage forms, such as shape, color, coating, scoring, imprinting, or NDC number	NDC Number is stated. The description for color of the cream, i.e. white, is provided.	Satisfactory
Special handling and Storage condition	The storage condition and special handling instruction "Do not freeze" are provided.	Satisfactory

**Conclusion:** The "How Supplied/Storage and Handling" section is satisfactory.

**d. Manufacturer's or Distributor's name per 21 CFR 201.1(h)(5)**

**Manufactured and Distributed by:**

Hill Dermaceuticals, Inc.  
Sanford, Florida 32773

**Reviewer's Assessment:** The information was provided at the end of labeling.

**Conclusion:** Satisfactory

**2. Facility Evaluation**

An overall recommendation of "Approve" was made by Facility reviewer, Donald Lech, on September 17, 2015.

BEST AVAILABLE COPY

**NDA/BLA** - 022259

**NDA 022259-Orig1-Resubmission/Class 2(41)**

Project Name: Ad-048 Project Number: 1

4 Current In Trouble Jun 18, 2015 45.9%

Project Summary Project Details Application History **Inspection View** Tasks Milestones Plans

**Inspection View**

Inspection View

Export Details Summary

Task Number	Task Name	Comments	Assignments	Plan Comp	Act Comp	Task Status	Actions	Additional Information
5	Application search/inspector criteria	If you are finished with this task, change the Task Status to Complete.		1/16/15	2/23/15	Complete	Go to Form	
43	Overall Recommendation/Inspection Summary		Donald Lech	5/28/15	5/17/15	Complete	No to Follow	Inspection/Inspection: Approve

### 3. Administrative

#### A. Reviewer's Signature

**Jane L. Chang -S**

Digitally signed by Jane L. Chang -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Jane L. Chang -S,  
0.9.2342.19200300.100.1.1=1300379266  
Date: 2015.09.17 16:14:13 -04'00'

Jane Chang, Ph.D.  
Review Chemist  
DPA III/Branch IX  
Office of Process and Facilities  
Office of Pharmaceutical Quality

#### B. Endorsement Block

**Moojhong Rhee -S**

Digitally signed by Moojhong Rhee -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Moojhong Rhee -S,  
0.9.2342.19200300.100.1.1=1300041261  
Date: 2015.09.17 16:16:01 -04'00'

Moo-Jhong Rhee, Ph.D.  
Chief, Branch V  
Office of New Drug Products  
Office of Pharmaceutical Quality



**NDA 22259**

**Tolak (Fluorouracil) Cream  
4%**

**Hill Dermaceuticals, Inc.**

**Jane L. Chang, Ph.D.**

**Review Chemist**

**Office of New Drug Products  
Division of New Drug Products II  
Branch V**

**For Division of Dermatologic and Dental Drug Products  
HFD-540**

# Table of Contents

<b>Table of Contents .....</b>	<b>2</b>
<b>Chemistry Review Data Sheet.....</b>	<b>3</b>
<b>The Executive Summary .....</b>	<b>8</b>
<b>I. Recommendations.....</b>	<b>8</b>
A. Recommendation and Conclusion on Approvability .....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
<b>II. Summary of Chemistry Assessments.....</b>	<b>8</b>
A. Description of the Drug Product and Drug Substance .....	8
B. Description of How the Drug Product Is Intended To Be Used .....	9
C. Basis for Approvability or Not-Approval Recommendation.....	10
<b>III. Administrative.....</b>	<b>10</b>
A. Reviewer's Signature .....	10
B. Endorsement Block.....	10
<b>REVIEW NOTTES.....</b>	<b>11</b>
<b>I. Introduction.....</b>	<b>11</b>
<b>II. Deficiencies Listed in the FDA 22-Jun-2009 Complete Response Letter.....</b>	<b>12</b>
<b>III. Other Revisions.....</b>	<b>35</b>
<b>IV. Labeling Amendments.....</b>	<b>38</b>



# Chemistry Review Data Sheet

1. NDA 22-259
2. REVIEW #: 3
3. REVIEW DATE: 30-Jul-2015
4. REVIEWER: Jane L. Chang
5. PREVIOUS DOCUMENTS:

Documents	Document Date
Original Submission	17-AUG-2007
Amendment (BZ)	10-SEP-2007
Amendment (BC)	11-OCT-2007
Correspondence (C)	15-OCT-2007
Amendment (BZ)	19-NOV-2007
Amendment (BC)	09-JAN-2008
Amendment (BC)	12-FEB-2008
Amendment (BC)	04-MAR-2008
CMC Review #1	31-MAR-2008
CMC Memo to File	18-JUN-2008
Amendment (BC)	02-APR-2008
Amendment (WA)	16-JUN-2008
Amendment (BC)	23-JUN-2008
Amendment (BL)	24-JUN-2008
Amendment (BC)	21-JUL-2008
Amendment (BC)	04-AUG-2008
CMC Review #2	21-May-2009
FDA Complete Response Letter	22-JUN-2009
FDA Acknowledge Incomplete Response Letter	08-AUG-2011

6. SUBMISSION(S) BEING REVIEWED:

## Chemistry Review Data Sheet

Submissions Reviewed	Document Date
Amendment (Quality) SDN-30	04-FEB-2009
Amendment (Labeling) SDN-31	31-MAR-2009
General Correspondence SDN-32	10-FEB-2010
Amendment SDN-34 (Withdrawal Request)	18-MAY-2011
Amendment SDN-35 (Duplicate of SDN-34)	18-MAY-2011
Resubmission SDN-36	21-JUN-2011
Amendment SDN-38 (Withdrawal Request)	07-SEP-2011
General Correspondence, SDN-40	01-OCT-2013
Resubmission/Class 2, SDN-41	17-Dec-2014
Amendment SDN-45	25-Feb-2015
Amendment SDN-48	26-Mar-2015
Amendment SDN-50	30-Jun-2015
Amendment SDN-53	22-Jul-2015
Amendment	28-Jul-2015

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Hill Dermaceuticals, Inc  
Address: 2650 South Mellonville Avenue  
Sanford, Florida 32773  
Representative: Linda Payne, Regulatory Affairs  
Telephone: 407-323-1887  
Fax: 407-302-7196

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: TOLAK
- b) Non-Proprietary Name: Fluorouracil Cream
- c) Code Name/# (ONDP only): N/A
- d) Chem. Type/Submission Priority (ONDP only):
  - Chem. Type: 5 (New Formulation)
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

## 10. PHARMACOL. CATEGORY: nucleoside metabolic inhibitor

## 11. DOSAGE FORM: Cream

## 12. STRENGTH/POTENCY: 4%

Chemistry Review Data Sheet

13. ROUTE OF ADMINISTRATION: Topical

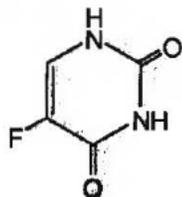
14. Rx/OTC DISPENSED:  X  Rx:   OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

X  Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



5-Fluorouracil

2,4(1*H*,3*H*)-Pyrimidinedione, 5-fluoro-

Molecular Formula: C<sub>4</sub>H<sub>3</sub>FN<sub>2</sub>O<sub>2</sub>

Molecular Weight: 130.0 <sup>(b)</sup><sub>(4)</sub>

CAS No: 51-21-8

## Chemistry Review Data Sheet

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	N/A	See CMC Review #1*
	III			1	Adequate	3/20/2008	By J. Chang
	III			4	N/A	N/A	**
	III			4	N/A	N/A	**

\*DMF (b) (4) Original Submission was submitted on June 30, 2008. A letter of authorization dated 2/6/2015 from the DMF holder was provided via an email through Project Manager, Ms. Kerri-Ann Jennings. This DMF was last reviewed on 11/13/2013 and concluded to be adequate to support an (b) (4) product.

\*\*See page 82 of CMC Review #1 under container and closure system for details.

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A. (There is enough data in the application, therefore the DMF did not need to be reviewed).

## B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	69,841	5-Fu (fluorouracil) Cream



## Chemistry Review Data Sheet

## 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
Facility	Pending*		
Pharm/Tox	N/A		
Biopharm	N/A		
Methods Validation	N/A		
DMEPA	Acceptable**	5/18/2015	C. M. Mena-Grillasca
EA	Categorical exclusion (see CMC review #1)	3/30/2008	J. Chang
Microbiology	Approval	7/22/2015	Jessica Cole

\*As of the date of this review, evaluation of the drug substance manufacturing site, (b) (4) and the drug product manufacturing site, Hill Dermaceuticals, Inc. is still pending.

\*\*The proposed proprietary name Tolak is acceptable.

# The Chemistry Review for NDA 22-259

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. However, a recommendation from the Office of Process and Facility on the site acceptability has not been made. Labeling issues are still pending as of the date of this review. Therefore, from the CMC perspective, this NDA is not ready for approval per 21 CFR 314.125(b)(6),(13) in its present form until all issues are satisfactorily resolved:

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product and Drug Substance

##### (1) Drug Product

Fluorouracil Cream, 4%, is a white cream indicated for the topical treatment of actinic keratosis. The formulation is (b) (4) butylated hydroxytoluene NF, cetyl alcohol NF, glycerin USP, isopropyl myristate NF, methyl gluceth-10, methylparaben NF, propylparaben NF, peanut oil NF, stearyl alcohol NF, and stearic acid NF (b) (4) sodium hydroxide NF (b) (4) Arlacel-165 (b) (4)

Peanut oil NF is used in the formulation. Based on the Agency's current position, the use of (b) (4) peanut oil meeting the NF standard is adequately safe for drug products and an assay to determine the level of peanut oil protein is not required as a condition of approval. (b) (4)

## Executive Summary Section

The proposed drug product specification (see page 30) includes description, pH, assay (RP-HPLC), homogeneity (RP-HPLC), identification (IR and RP-HPLC), microbial limits, methylparaben and propylparaben assays (RP-HPLC), ratio (5-FU:salt), particle size testing (microscopic examination), related substances (RP-HPLC), (b) (4) butylated hydroxytoluene assay (RP-HPLC), apparent viscosity, and minimum fill. The analytical procedures and their method validations were reviewed and found to be adequate to support their intended purpose. The microbiological quality attributes were reviewed by Microbiology Reviewer, Dr. Jessica Cole, and concluded on July 22, 2015 to be acceptable.

The drug product will be packaged into a 40 g commercial package size.

Twenty-four months long-term (25°C/60% RH and 20-25°C/ambient humidity) and six months accelerated stability data have been provided for the three primary stability batches. A significant change (decrease at up to (b) (4)%) in fluorouracil assay was observed during the accelerated stability studies. The long-term data also showed a decreasing trend for fluorouracil assay, pH, methylparaben, propylparaben, and viscosity. The stability data support a (b) (4) months expiration dating period when stored at 25°C/ (b) (4) % RH or controlled room temperature (b) (4).

## (2) Drug Substance

Fluorouracil is a well-established compendial drug substance whose structure has been fully elucidated. Fluorouracil is marketed in various formulations since 1962. The approved formulations include an injectable solution (50 mg/mL, NDA 12-209) for treatment of cancer, and topical solutions [2% and 5% (NDA 16-831)] as well as topical creams [0.5% (NDA 20-985), 1% (NDA 16-988), and 5% (NDA 16-831)] for the treatment of multiple actinic or solar keratosis.

The drug substance is manufactured (b) (4). The CMC information pertaining to synthesis and control of fluorouracil was presented in the NDA. A letter of authorization dated 06-Feb-2015 from DMF (b) (4) for fluorouracil was also provided.

## B. Description of How the Drug Product Is Intended To Be Used

Fluorouracil Cream 4% is indicated for the topical treatment of actinic keratosis lesions of the face, ears, and scalp. It is intended to be applied once daily in an amount sufficient to cover the lesions with a thin film, using the fingertips to gently massage the medication uniformly into the skin. Fluorouracil Cream should be applied for a period of four weeks as tolerated. Hands should be thoroughly washed following Fluorouracil Cream application.

## Executive Summary Section

Fluorouracil Cream, 4% is to be stored at controlled room temperature 25°C (77°F). Stability data support the proposed (b) (4) months expiration dating period.

**C. Basis for Approvability or Not-Approval Recommendation**

This NDA is not recommended for approval in its present form for the following reasons:

- 21 CFR 314.125 (b)(6)  
Labeling issues are not resolved.
- 21 CFR 314.125 (b)(13)  
An overall recommendation from the Office of Process and Facility on the site acceptability has not been made.

**III. Administrative****A. Reviewer's Signature**

Jane L.  
Chang -S

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ou=HHS, ou=FDA, ou=People,  
cn=Jane L. Chang -S,  
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Jane Chang, Ph.D.  
Review Chemist  
Office of Process and Facilities  
Office of Pharmaceutical Quality

**B. Endorsement Block**

Moojhong Rhee  
-S

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ou=FDA, ou=People, cn=Moojhong Rhee -  
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Moo-Jhong Rhee, Ph.D.  
Chief, Branch V  
Office of New Drug Products  
Office of Pharmaceutical Quality

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#### **IV. Labeling Amendments**

**1. Physician's Labeling Rule Prescription Drug Labeling**

Revised package insert was provided in the 2/19/2015 Amendment. The information is presented below.

**1) "Highlights" Section**

**Tolak (fluorouracil) Cream, 4%  
For topical use only**

**Initial U.S. Approval: 1962**

Chemistry Assessment Section

**DOSAGE FORMS AND STRENGTHS**

40 (b)(4) fluorouracil (b)(4)

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name and established name	Proprietary name and established name are correctly described as Tolak (fluorouracil)	Satisfactory
Dosage form and route of administration	Cream, topical	Satisfactory
Dosage forms and strengths	The strength (4%) is provided. (b)(4)	Unsatisfactory

Conclusion: The "Highlights" section is unsatisfactory.

The following revisions are made to the labeling in SharePoint under DOSAGE FORMS AND STRENGTHS:

(b)(4)

2) "Full Prescribing Information" Section

a. Section 3 Dosage Forms and Strengths

(b)(4) 40 (b)(4) fluorouracil (b)(4)

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Dosage form and strength	Cream, 4% fluorouracil	Satisfactory
Identifying characteristics of the dosage forms	(b)(4)	Unsatisfactory

Conclusion: This section is unsatisfactory.

## Chemistry Assessment Section

The following revisions are made to the labeling in SharePoint:

(b) (4)

**b. Section 11 Description**

Tolak (fluorouracil) Cream

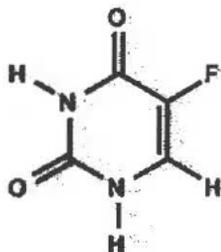
contains 4% (b) (4) fluorouracil

(b) (4)

The molecular formula of (b) (4) fluorouracil is  $C_4H_3FN_2O_2$ , and its molecular weight is 130.1. Its structural formula is (b) (4).

(b) (4)

(b) (4)



(b) (4)

Reviewer's Assessment:

Chemistry Assessment Section

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name and established name*	Tolak (fluorouracil)	Satisfactory
Dosage form and route of administration	cream, topical	Satisfactory
Active moiety expression of strength	4%	Satisfactory
Inactive ingredient information	All inactive ingredients are listed. However, the established name for anhydrous citric acid (b) (4) and peanut oil (b) (4) are not used correctly. Based on the COA of (b) (4) provided in the submission, the excipient is "anhydrous citric acid".	Unsatisfactory
Pharmacological/therapeutic class	nucleoside metabolic inhibitor	Satisfactory
Chemical name, structural formula, molecular weight	Chemical name, structural formula and molecular weight are correctly described in this section.	Satisfactory
Other important chemical or physical properties (such as pKa or pH)	The pH range (8.3 – 9.2) of the formulation is provided incorrectly.	Unsatisfactory

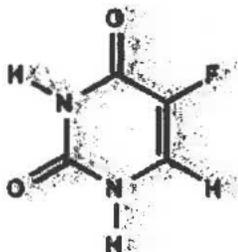
\*Per 201.10(g)(1), the established name shall accompany the proprietary name.

**Conclusion:** The "Description" section is unsatisfactory.

The following revisions are made to the labeling in SharePoint:



Chemistry Assessment Section



[Redacted]

**c. Section 16 How Supplied/Storage and Handling**

Tolak (fluorouracil) Cream, 4% [Redacted] (b) (4)

40 gram tube

NDC 28105-421-40

**Storage**

[Redacted] (b) (4) at 25°C (77°F), excursion permitted to 15°C - 30°C (59°F - 86°F) [Redacted] (b) (4)  
Do not freeze.

[Redacted] (b) (4)

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Strength of dosage form in metric system	Strengths are correctly described as 4%.	Satisfactory
Units of dosage form	Available units are correctly described as 40 gram per tube	Satisfactory
Identification of dosage forms, such as shape, color, coating, scoring, imprinting, or NDC number	NDC Number is stated. The description for color of the cream is missing.	Unsatisfactory
Special handling and Storage condition	Replace the word [Redacted] (b) (4)	Unsatisfactory

Conclusion: The "How Supplied/Storage and Handling" section is unsatisfactory.

## Chemistry Assessment Section

*The following revisions are made to the labeling in SharePoint:*

## 16.1 How Supplied

Tolak (fluorouracil) Cream, 4%

(b) (4)

40 gram tube (NDC 28105-421-40).

(b) (4) 6.2 Storage and Handling

(b) (4) Store at 25°C (77°F), with excursion permitted from (b) (4) 15°C to 30°C (59°F - 86°F) (b) (4) [See USP Controlled Room Temperature]. Do not freeze.

(b) (4)

d. *Manufacturer's or Distributor's name per 21 CFR 201.1(h)(5)*

**Manufactured and Distributed by:**

Hill Dermaceuticals, Inc.  
Sanford, Florida 32773

Reviewer's Assessment: *The information was provided at the end of labeling.*

Conclusion: *Satisfactory*

**2. Immediate Container**

Revised mock-up container label and carton labeling were provided in the 2/4/2009 Amendment. The information is presented below.

(b) (4)



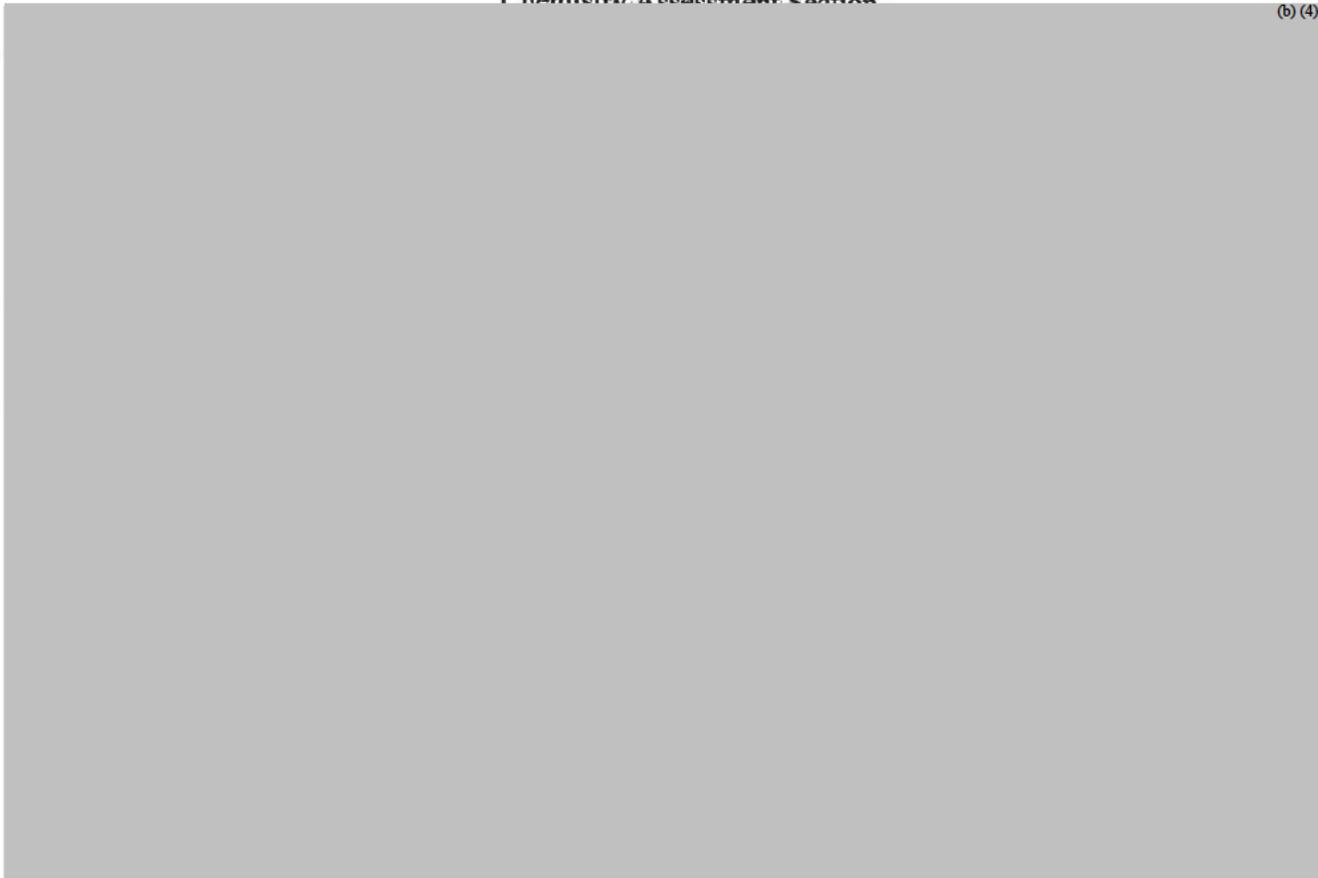
## Chemistry Assessment Section

Labeling Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The established name is presented correctly. The font size for established name is at least one half of the trade name.	Satisfactory
Strength	Strengths (4%) are correctly expressed.	Satisfactory
Net contents	The net content (40 g) is described.	Satisfactory
Lot number per 21 CFR 201.18	The information (b) (4)	Satisfactory
Expiration date per 21 CFR 201.17	The information (b) (4)	Satisfactory
"Rx only" statement per 21 CFR 201.100(b)(1)	The statement is prominently displayed	Satisfactory
Storage	Storage condition is correctly described.	Satisfactory
NDC number	NDC number is indicated.	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)	Barcode is indicated.	Satisfactory
Name of distributor/manufacturer per 21 CFR 201.1(h)(5)	The name of manufacturer is correctly described.	Satisfactory
Route of Administration	Route of administration "Topical" is provided.	Satisfactory
Others	A statement "Contains (b) (4) Peanut Oil" is included. "(b) (4)" should be replaced with "Peanut Oil". The inactive ingredient (b) (4) should be replaced with "anhydrous citric acid", which is the title of the USP monograph.	Unsatisfactory

## 3. Cartons

Chemistry Assessment Section

(b) (4)



Chemistry Assessment Section

Labeling Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The established name is presented correctly. The font size for established name is at least one half of the trade name.	Satisfactory
Strength	Strengths (4%) are correctly expressed.	Satisfactory
Net quantity	The net content (40 g) is described.	Satisfactory
Lot number per 21 CFR 201.18	There is a space allocated on the bottom flap for this information.	Satisfactory
Expiry date 21 CFR 201.17	There is a space allocated on the bottom flap for this information.	Satisfactory
"Rx only" statement per 21 CFR 201.100(b)(1)	The statement is displayed on the main panel.	Satisfactory
Name of all inactive ingredients	All excipients are provided as the following statement: (b)(4) arlacel-165, butylated hydroxytoluene, cetyl alcohol, (b)(4) glycerin, isopropyl myristate, methyl gluceth-10, methylparaben, propylparaben, purified water, (b)(4) peanut oil, sodium hydroxide, stearic acid, and stearyl alcohol". The statement (b)(4) (b)(4)	Unsatisfactory
"See package insert for dosage information"	The statement is present.	Satisfactory
"Keep out of reach of children"	The statement is present.	Satisfactory
NDC number	NDC number is indicated.	Satisfactory
Storage	Storage condition is correctly described as "Do not freeze: Maintain at 25°C (77°F); excursion permitted to 15°C - 30°C (59°F - 86°F) during storage and transportation".	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)	The location of bar code was marked.	Satisfactory
Name of distributor/manufacturer per 21 CFR 201.1(h)(5)	The name of manufacturer is correctly described.	Satisfactory
Route of Administration	Route of administration "Topical" is provided. (b)(4)	Satisfactory
Others	(b)(4)	Unsatisfactory

*Reviewer's Assessment:* Except for the use of (b)(4) (b)(4) all other labeling information as provided in the 2/4/2009 Amendment is acceptable. Instead of (b)(4) "peanut oil" should be used because "peanut oil" is the title of the NF monograph. 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

## Chemistry Assessment Section

*the term “established name” with respect to a drug or ingredient as the official title used in the United States Pharmacopeia. Per 21 CFR 201.10(b), the term “ingredient” applied to any substance in the drug. Therefore, the title of the USP or NF monograph should be used as the established name for all ingredients.*

*The following comments were conveyed to the applicant on 2/27/2015:*

- 1) Replace the term <sup>(b) (4)</sup> with “peanut oil” for both container label and carton labeling, including the statement for inactive ingredients and the statement “Contain <sup>(b) (4)</sup> Peanut Oil” 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 title of the USP or NF monograph should be used as the established name for all ingredients.*

- 2) Replace the term <sup>(b) (4)</sup> with “anhydrous citric acid”, which is the title of the USP monograph, for both container label and carton labeling.
- 3) Delete <sup>(b) (4)</sup> in the inactive ingredients statement for the carton labeling. For example, change the statement from:

<sup>(b) (4)</sup>

to

*“Inactive ingredients: arlacel-165, butylated hydroxytoluene, cetyl alcohol, anhydrous citric acid, glycerin, isopropyl myristate, methyl gluceth-10, methylparaben, propylparaben, purified water, peanut oil, sodium hydroxide, stearic acid, and stearyl alcohol.”*

In the 6/30/2015 Amendment, container label and carton labeling were provided as shown below:

## Chemistry Assessment Section

(b) (4)



*The revised container label and carton labeling show that all issues have been resolved. The information is acceptable.*

**3) Product Data Elements in Structured Product Labeling**

The applicant did not submit Structured Product Labeling (SPL).



Chemistry Assessment Section

*Reviewer's Assessment: The request for SPL was made on the 74-day letter dated November 2, 2007. However, the SPL has still yet to be submitted.*

*The following comments were conveyed to the applicant on 2/27/2015:*

*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. The SPL was requested in the FDA Filing Communication Letter dated 11/2/2007.*

*In the 3/26/2015 Amendment, Hill stated that they were working in SPL and will provide it through the required gateway. The response is acceptable.*



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 Microbiology section of your submission and have the following comments and information requests. We request a prompt written response by April 6, 2015, in order to continue our evaluation of your NDA.

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

1. We note the inclusion of a copy of methods MB-60:00 and MB-14:03 in Volume 2. Please provide the method verification studies that demonstrate the proposed methods are appropriate for use with this drug product.
2. We refer to Method MB-14:03. Please define the medium “(b) (4)” and provide a justification for using this non-compendial medium in the microbial enumeration and absence of specified organism studies.
3. We refer to Method MB-14:03 and the absence of *Staphylococcus* and *Pseudomonas* studies. Provide a justification for and data to support the incubation of organisms in (b) (4) rather than the (b) (4) defined in USP<62>.
4. Provide a justification for not conducting microbial analysis on routine stability batches to confirm the microbial content through expiry. We note that previous submissions included a commitment to conduct antimicrobial effectiveness testing on stability but that the current stability program does not include antimicrobial effectiveness or microbial enumeration studies after release.
5. Clarify the release and stability specification for methyl and propyl parabens. This submission contains conflicting information on the methyl and propyl parabens content in the stability specification. The minimum (b) (4) content must be established and supported with data from the (b) (4) effectiveness studies.

6. Provide antimicrobial effectiveness test results from 3 batches of drug product with at least one batch at the minimum (b) (4) content from the specification. For example, if the minimum (b) (4) content for methyl parabens is (b) (4)% and the minimum content for propyl parabens is (b) (4)%, and the minimum BHT concentration is (b) (4)% then results should be submitted from at least one batch containing (b) (4)% methylparabens, (b) (4)% propylparabens and (b) (4)% BHT.
7. Provide a copy of deviation (b) (4) from the antimicrobial effectiveness testing on Lot 12G023A.
8. Provide the test method and acceptance criterion to demonstrate the drug product is free of the objectionable microorganism *Burkholderia cepacia*. Your test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested.

Please identify potential sources for introduction of *B. cepacia* during the manufacturing process and describe the steps to minimize the risk of *B. cepacia* complex (Bcc) organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.

As there are currently no compendial methods for detection of Bcc, we have provided a suggestion for a potential validation scheme. However, any validated method capable of detecting *B. cepacia* complex organisms would be adequate. At this point in time, it would be sufficient to precondition representative strain(s) of *B. cepacia* in water and/or your drug product without preservatives and demonstrate that your proposed method is capable of detecting small numbers of Bcc. Your validation studies should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning (minimum 48 hours) of the organisms occurs during these method validation studies.

We refer you to *Envir. Microbiol.* 13(1):1-12, 2011 for more information on the *B. cepacia* complex of organisms. We refer you to *J. Appl. Microbiol.* 1997 Sep;83(3):322-6 for more information on the recovery of *B. cepacia* organisms from pharmaceutical environments.

If you have any questions, please contact, LCDR Kerri-Ann Jennings, Regulatory Business Process Manager, at (301) 796-2919.

Sincerely,

**Moojhong Rhee -S**

Digitally signed by Moojhong Rhee -S  
DN: c=US, o=U.S. Government, ou=FHS, ou=FDA,  
ou=People, cn=Moojhong Rhee -S,  
0.9.2342.19200300.100.1.1=1300041261  
Date: 2015.03.06 13:22:02 -0500

Moo-Jhong Rhee, Ph.D.  
Chief, Branch V  
Office of New Drug Products  
Office of Pharmaceutical Quality  
CDER/FDA

**MEMORANDUM**

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

**DATE:** November 30, 2011

**FROM:** J. David Doleski *David Doleski*  
Acting Director  
Division of Good Manufacturing Practice Assessment  
Office of Manufacturing and Product Quality  
Office of Compliance

**SUBJECT:** Issuance of Consent Decree with Application Integrity Policy provisions

**FIRM:** Hill Dermaceuticals, Inc  
2650 South Mellonville Ave  
Sanford, FL 32773-9311  
CFN Number: 1036365

**APPLICATIONS:**

NDA	Drug	Sponsor	Status
(b) (4)			
NDA 22-259	Tolak (fluorouracil) Cream, 4%	Hill Dermaceuticals, Inc.	Pending/ Complete Response
(b) (4)			

**TO:** Directors,  
Office of New Drugs  
Office of Drug Evaluation I  
Office of Drug Evaluation II  
Office of Drug Evaluation III  
Office of Drug Evaluation IV  
Office of Antimicrobial Products  
Office of Hematology Oncology Drug Products  
Office of Pharmaceutical Science  
Office of New Drug Quality Assessment  
Office of Generic Drugs  
Office of Biotechnology Products

Hill AIP

Page 2

On September 10, 1991, FDA published the "Application Integrity Policy" ("AIP") in the Federal Register (56 FR 46191; "Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities"). For a firm that is impacted by the policy, FDA generally defers substantive scientific review of data in pending applications or supplements while a validity assessment is completed by the Agency to determine the reliability of the submissions.

In the case of Hill Dermaceuticals, FDA inspections uncovered data integrity and significant CGMP problems at the firm. On September 28, 2011, the District Court for the Middle District of Florida entered a Consent Decree of Permanent Injunction that prohibits Hill Dermaceuticals, Inc. and Hill Labs, Inc. located in Sanford, FL (hereafter referred to as Hill) from introducing adulterated drugs into interstate commerce. The decree also included the provisions of FDA's Application Integrity Policy, which are designed to ensure the authenticity of data submitted to the agency.

All pending and approved applications which contain data generated by Hill are affected by implementation of this AIP. Except as noted below, substantive scientific review of any applications or supplements containing data generated at Hill should be suspended pending completion of validity assessments by the Florida District Office. CDER already has conducted a validity assessment for (b) (4) and no data integrity problems were uncovered. Therefore, substantive scientific review should not be suspended for this supplement.

Please note that review of IND applications should not be suspended, as we do not wish to interrupt ongoing clinical trials. The Agency will conduct validity assessments of any INDs containing data generated at the Sanford, FL site, even though the Agency is not at this time suspending substantive scientific review of the INDs.

We will notify you when scientific review should be resumed, where appropriate. We will also inform you of pending or approved applications and supplements deemed unreliable, where non-approval or withdrawal are appropriate.

The firm is aware of the implications of AIP as described in the Consent Decree and has been instructed to work with the Florida District Office with future communications. A current listing of all firms affected by the Agency's Application Integrity Policy, updated to include Hill, can be obtained at the following web address:

<http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/ucm134453.htm>

Should you have any questions regarding this case please contact Shawn Gould, Compliance Officer at (301)796-3759, or Lori Gorski, Project Manager at (301)796-0722.

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

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*/s/*

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LORI M GORSKI

02/24/2012

Hill Consent Decree/AIP internal memo. Hill Derm has been issued a Consent Decree under Application Integrity provisions. All pending and approved applicationd containing data generated by Hill are affected.

# **NDA 22-259**

**Tolak (Fluorouracil) Cream  
4%**

**Hill Dermaceuticals, Inc.**

**Jane L. Chang, Ph.D.**

**Review Chemist**

**Office of New Drug Quality Assessment  
Division of Pre-Marketing Assessment II  
Branch III**

**For Division of Dermatologic and Dental Drug Products  
HFD-540**

# Table of Contents

<b>Table of Contents .....</b>	<b>2</b>
<b>Chemistry Review Data Sheet.....</b>	<b>3</b>
<b>The Executive Summary .....</b>	<b>7</b>
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	10
II. Summary of Chemistry Assessments.....	10
A. Description of the Drug Product and Drug Substance.....	10
B. Description of How the Drug Product Is Intended To Be Used .....	13
C. Basis for Approvability or Not-Approval Recommendation.....	13
III. Administrative.....	13
A. Reviewer’s Signature.....	13
B. Endorsement Block.....	13
C. CC Block.....	13
<b>Chemistry Assessment .....</b>	<b>14</b>
I. Establishment Evaluation.....	14
II. Amendments .....	18
III. Peanut Oil NF Issues.....	34
IV. Labels.....	37
V. Attachment—FDA Form 483 .....	39

## Chemistry Review Data Sheet

# Chemistry Review Data Sheet

1. NDA 22-259
2. REVIEW #: 2
3. REVIEW DATE: 21-MAY-2009
4. REVIEWER: Jane L. Chang
5. PREVIOUS DOCUMENTS:

<u>Documents</u>	<u>Document Date</u>
Original Submission	17-AUG-2007
Amendment (BZ)	10-SEP-2007
Amendment (BC)	11-OCT-2007
Correspondence (C)	15-OCT-2007
Amendment (BZ)	19-NOV-2007
Amendment (BC)	09-JAN-2008
Amendment (BC)	12-FEB-2008
Amendment (BC)	04-MAR-2008
CMC Review #1	31-MAR-2008
CMC Memo to File	18-JUN-2008

6. SUBMISSION(S) BEING REVIEWED:

<u>Submissions Reviewed</u>	<u>Document Date</u>
Amendment (BC)	02-APR-2008
Amendment (WA)	16-JUN-2008
Amendment (BC)	23-JUN-2008
Amendment (BL)	24-JUN-2008
Amendment (BC)	21-JUL-2008
Amendment (BC)	04-AUG-2008

## Chemistry Review Data Sheet

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Hill Dermaceuticals, Inc  
Address: 2650 South Mellonville Avenue  
Sanford, Florida 32773  
Representative: Rosario G (Nini) Ramirez, MD / Director  
Telephone: 407-323-1887

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: TOLAK
- b) Non-Proprietary Name: Fluorouracil Cream
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 5 (New Formulation)
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

## 10. PHARMACOL. CATEGORY: nucleoside metabolic inhibitor

## 11. DOSAGE FORM: Cream

## 12. STRENGTH/POTENCY: 4%

## 13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

## Chemistry Review Data Sheet

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



5-Fluorouracil

2,4(1*H*,3*H*)-Pyrimidinedione, 5-fluoro-Molecular Formula: C<sub>4</sub>H<sub>3</sub>FN<sub>2</sub>O<sub>2</sub>Molecular Weight: 130.0<sup>(b)</sup><sub>(4)</sub>

CAS No: 51-21-8

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	1	Adequate	3/20/2008	By J. Chang
	III			4	N/A		*
	III			4	N/A		*

\*See page 82 of CMC Review #1 under container and closure system for details.

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Chemistry Review Data Sheet

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	69,841	5-Fu (fluorouracil) Cream

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	WITHHOLD WITHHOLD*	6/10/2008 12/18/2008	C. Cruz
Pharm/Tox	N/A		
Biopharm	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
Office of Drug Safety	Acceptable**	5/16/2008	T. Turner, K. Linda, T. Denise
EA	Categorical exclusion (see CMC review #1)	3/30/2008	J. Chang
Microbiology	N/A		

\*See page 14.

\*\*DMETS does not object the use of the proposed proprietary name Tolak.

## Executive Summary Section

# The Chemistry Review for NDA 22-259

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA has not assured identity, strength, purity, and quality due to lack of the cGMP compliance, acceptable drug product stability data, and acceptable labeling. The September 2008 establishment inspection revealed major deficiencies on the drug product stability data. Therefore, this NDA is recommended not to be approved in its present form per a CMC perspective until the following issues are resolved:

1. One of the facilities involved in the submission is deemed not to comply with cGMP requirements. Satisfactory resolution of any deficiencies of the facility is required to assure identity, strength, purity and quality of the drug product.
2. The stability data submitted to date are not adequate to establish a specification for the drug product and an expiration dating period due to the following deficiencies:
  - a. Particle size testing, viscosity, homogeneity, and butylated hydroxytoluene assay are not available for the entire stability studies.
  - b. The validity of data for pH can not be assured.
  - c. The validity of data for methylparaben and propylparaben assays can not be assured because we have concluded that the chromatograms of the method validation study for (b) (4) provided in the original submission and the February 12, 2008 and April 2, 2008 amendments are not from Tolak Cream based on the following reasons:

You were informed on January 14, 2008 via FDA Information Request Letter that the method validation data provided in the original submission were not acceptable because (b) (4) was used in the study. This letter requested you to provide validation data for Tolak Cream. You then submitted the method validation data, which included specificity, accuracy/recovery, and precision/repeatability, in the February 12, 2008 and April 2, 2008 amendments. The method validation protocol was provided only in the April 2, 2008 amendment. (b) (4)

- 1) During the September 2008 establishment inspection, you confirmed that the clinical lot, K050158, was used for evaluation of method precision/repeatability. However, the six chromatograms of the precision/repeatability study (HPLC Bin # 100-105) do not match the release data of Lot K050158 (HPLC Bin # 40-45), but rather they

## Executive Summary Section

resemble (b) (4) Lot G080139 (HPLC Bin # 36-37 and 41-44).

For instance, a small but distinctive peak with the retention time of (b) (4) minutes is present in all (b) (4) chromatograms of the release data for (b) (4) Lot G080139. This peak is also present in all of the Tolak Cream chromatograms for the precision/repeatability study, but it is missing in the release data of Tolak Cream, Lot K050158.

- 2) During the September 2008 establishment inspection, you stated that the “placebo cream” contained 5-fluorouracil and was prepared using the same formulation as that of Tolak Cream except for the absence of methylparaben and propylparaben. You also stated that the chromatograms labeled with “Blank 1” (HPLC Bin # 99) and “Blank 2” (HPLC Bin # 100) were those of “vehicle cream without parabens”.

However, the chromatograms of “vehicle cream without parabens” looked more like (b) (4) than that of Tolak Cream without parabens. For example, a major peak ((b) (4) minutes) prior to the methylparaben is present in the release data of Tolak Cream, Lot K050158, but it is missing in “Blank 1” or “Blank 2”. Since the “vehicle cream without parabens” contains all ingredients in Tolak Cream but the parabens, the chromatograms are expected to resemble that of Tolak Cream except for the absence of the two paraben peaks (retention times at (b) (4) minutes).

- 3) During the September 2008 establishment inspection, you confirmed that four lots of fluorouracil cream varying the amounts of parabens at (b) (4)%, respectively, of the target concentrations in the Tolak formulation, were produced. The differences to make the formula to 100% was added or subtracted (b) (4) in the formula. These four creams were used for evaluation of method accuracy/recovery.

Because the (b) (4) minutes peak is present, the chromatograms of the four creams for the accuracy/recovery study (HPLC Bin # 117-118, 21-22, 58-59, and 63-64) also resemble those of (b) (4), Lot G080139. Furthermore, the HPLC chromatograms of the four creams suggest that they are from (b) (4) diluted at four different target concentrations. This is because the area counts of all other peaks (e.g. (b) (4) minutes) increase along with the increase of paraben concentrations. If the four creams had been prepared in the manner you have claimed, the HPLC chromatograms would have shown an increase of only methylparaben and propylparaben area counts at higher paraben concentrations and the area counts of all other peaks would have remained the same.

Therefore, unless you provide a satisfactory explanation for why you repeatedly provided (b) (4) data for the accuracy/recovery and precision/repeatability

## Executive Summary Section

studies and used (b) (4) data as “placebo cream”, the validity of the data for methylparaben and propylparaben assays can not be assured.

In addition, you will also need to address the following items in order to provide assurance of the validity of your submitted data for methylparaben and propylparaben assays:

- Explain why the validation report dated February 8, 2008, that was submitted in the February 12, 2008 amendment differed from the same validation report dated February 8, 2008, that was submitted in the April 2, 2008 amendment. The differences include, but are not limited to, table of contents, authorized signatories' signatures, and the contents for the specificity study.
- Explain why you provided a validation report without all authorized signatories' signatures in the February 12, 2008 amendment. The report was signed off only by Sarah Reinartz, Quality Assurance Manager, on February 8, 2008. In addition, the “Report Approval” on page 1 was listed as “Protocol Approval” in the Table of Contents. Pages 5 and 6 of this validation report were missing.
- Explain why the method specificity study submitted in both amendments was conducted two years prior to the approval of the validation protocol. The validation protocol was signed off on January 17, 2008 by Nancy Puglia, Plant Manager, Sarah Reinartz, Quality Assurance Manager, Kacy McGee, Quality Assurance, and Ingrid Warner, Regulatory CMC. The method specificity study, which included (b) (4) chromatograms of methylparaben and propylparaben standards (HPLC Bin # 92-96) and (b) (4) chromatograms of “placebo cream”, was conducted on October 25, 2005.
- Explain why deviations from the approved validation protocol were not documented in the validation reports submitted in the February 12, 2008 and April 2, 2008 amendments. The deviations included the date of the specificity study, described above, and missing chromatograms of Tolak Cream for the specificity study as required on page 4 (Actual drug product) of the validation protocol. The validation report submitted in the April 2, 2008 amendment was signed on February 8, 2008, by the same personnel on the validation protocol dated January 17, 2008.
- Explain why laboratory preparations of “vehicle cream without parabens” and the four creams used in the method accuracy/recovery study were not documented.

If the above issues are satisfactorily resolved, then stability data from three new primary batches of Tolak Cream should be provided. 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.

## Executive Summary Section

3. The hold time for the bulk drug product [REDACTED] (b) (4) should be determined and justified. In-process samples taken at the beginning and end of the hold time should be tested per Tolak Cream In-process Product Specification Form (provided in the February 12, 2008 amendment) to justify the hold time.
4. Regarding the peanut oil, NF specification:
  - a. Revise the limit for protein analysis in the peanut oil specification to “for information only”. The analytical method, i.e. DSFS D-12 for Protein Analysis Sample Preparation and Amino Acid Analysis Protocol, has not been validated properly.
  - b. Change the “Approved Manufacturer” from “[REDACTED] (b) (4)” to “[REDACTED] (b) (4)”.
  - c. Several testing facilities are listed as approved testing facilities on your raw material specification forms. For example, Hill Laboratories, Inc., [REDACTED] (b) (4) [REDACTED] are listed as the approved testing facilities in the peanut oil, NF raw material specification form. Please clarify whether all these facilities are involved in the testing of the peanut oil and in what capacity.

**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**

None

**II. Summary of Chemistry Assessments****A. Description of the Drug Product and Drug Substance****(1) Drug Product**

Fluorouracil Cream, 4%, is a white cream indicated for the topical treatment of actinic keratosis. The formulation is [REDACTED] (b) (4) butylated hydroxytoluene NF, cetyl alcohol NF, glycerin USP, isopropyl myristate NF, methyl gluceth-10, methylparaben NF, propylparaben NF, peanut oil NF, stearyl alcohol NF, and stearic acid NF [REDACTED] (b) (4) sodium hydroxide NF [REDACTED] (b) (4) Arlachel-16 [REDACTED] (b) (4)

The proposed specification of peanut oil NF includes a test for protein content with a limit of NMT [REDACTED] (b) (4) ppm. [REDACTED] (b) (4) Analytical

## Executive Summary Section

procedures for the sample preparation (DSFS D-12) and amino acid analysis are poorly written and confusing. Validation data are inadequate due to lack of accuracy, precision, linearity, etc. Detailed deficiencies regarding the analytical methods are listed on page 34. Based on the Agency's current position, these deficiencies are not approvability issues. This is because the peanut oil used in Tolak Cream meets the requirements described in the NF monograph (b) (4)

**Per Dr. Janet Woodcock's memo on March 24, 2009, an assay to determine the level of peanut oil protein is not required as a condition of approval provided that the peanut oil used is fully refined that meets the NF standard. The memo concludes that the use of refined peanut oil meeting the NF standard is adequately safe for drug products.**

**The issue regarding the (b) (4) peanut oil manufacturer should be addressed in the next review cycle.** Hill must make a commitment to submit a prior approval supplement if it wants to change the current peanut oil manufacturer or to make a major manufacturing process change.

**A change of conclusion from CMC Review #1 is made regarding the manufacturing process and process controls.** This is due to the findings from the establishment inspection, which took place from September 15, 2008 to September 29, 2008. Out of specification (OOS) results were reported for the two recent lots of bulk drug and one lot of the packaged product. The OOS results suggested that the manufacturing process is not well controlled. The bulk drug hold time should be determined and justified.

The proposed drug product specification includes description, pH, assay (RP-HPLC), identification (TLC), microbial limits, methylparaben and propylparaben assays (RP-HPLC), ratio (5-FU:salt), particle size testing (microscopic examination), homogeneity (RP-HPLC), related substances (RP-HPLC), butylated hydroxytoluene assay (RP-HPLC), antimicrobial effectiveness test, viscosity, and minimum fill. (b) (4)

Adequate validation data were provided for Method LL-0352, assay for fluorouracil and related substance. Validation data for the RP-HPLC Method (b) (4) for methylparaben and propylparaben were found to be invalid during the September 2008 establishment inspection. The drug product used for the method validation study was not fluorouracil cream as claimed. Instead, the HPLC chromatograms provided resemble those of a commercial product, (b) (4)

**The inspection revealed that the entire method validation data for**

## Executive Summary Section

(b) (4) are invalid. This leads to a change of the conclusion from CMC Review #1.

The drug product will be packaged into a 40 g commercial package size.

Eighteen months real-time and six months accelerated stability data have been provided for the three primary stability batches. A significant change ((b) (4)%) in fluorouracil assay was observed during the accelerated stability studies. The data also showed a decreasing trend for pH. As a result, the ratio of fluorouracil to its sodium salt showed an increasing trend. **Because the September 2008 establishment inspection revealed major deficiencies on the drug product stability data, the submitted stability data provided to date are not deemed adequate to establish a specification for the drug product and an expiration dating period. Particle size testing, viscosity, homogeneity, and butylated hydroxytoluene assay are not available for the entire stability studies, and the validity of data for pH along with methylparaben and propylparaben assays can not be assured. These newly discovered deficiencies during the inspection lead to a change of the conclusion from CMC Review #1. Therefore, stability data from three new primary batches of Tolak Cream should be provided when the NDA is resubmitted.**

**Labeling issues, including lack of Structured Product Labeling, should be addressed in the next review cycle.**

**An overall compliance recommendation of “WITHHOLD” was issued on June 10, 2008 and December 18, 2008 by the Office of Compliance.** The overall recommendation of “withhold” indicates the lack of cGMP compliance in the manufacture of the proposed product. Without an acceptable cGMP compliance, the identity, strength, purity, and quality of the product can not be assured.

## (2) Drug Substance

Fluorouracil is a well-established compendial drug substance whose structure has been fully elucidated. Fluorouracil is marketed in various formulations since 1962. The approved formulations include an injectable solution (50 mg/mL, NDA 12-209) for treatment of cancer, and topical solutions [2% and 5% (NDA 16-831)] as well as topical creams [0.5% (NDA 20-985), 1% (NDA 16-988), and 5% (NDA 16-831)] for the treatment of multiple actinic or solar keratosis.

The drug substance is supplied by (b) (4). The CMC information pertaining to synthesis and control of fluorouracil was presented in the NDA. In addition to the tests listed in the USP monograph, testing for related substances (TLC and RP-HPLC) is included in the drug substance specification.

## Executive Summary Section

**B. Description of How the Drug Product Is Intended To Be Used**

Fluorouracil Cream 4% is indicated for the topical treatment of actinic keratosis lesions of the face, ears, and scalp. It is intended to be applied once daily in an amount sufficient to cover the lesions with a thin film, using the fingertips to gently massage the medication uniformly into the skin. Fluorouracil Cream should be applied for a period of four weeks as tolerated. Hands should be thoroughly washed following Fluorouracil Cream application.

Fluorouracil Cream, 4% is to be stored at controlled room temperature 25°C (77°F). **The final expiration dating period will be determined after stability data of three new primary batches are submitted in the next review cycle.**

**C. Basis for Approvability or Not-Approval Recommendation**

This NDA has not assured identity, strength, purity, and quality. More specifically, the following deficiencies have been identified:

- The manufacture of the proposed product is lack of cGMP compliance. Office of Compliance issued an overall compliance recommendation of “WITHHOLD” on June 10, 2008 and December 18, 2008.
- The drug product stability data provided to date are not adequate to establish a specification for the drug product and an expiration dating period.
- The hold time for the bulk drug product (b) (4) is not determined and justified.
- The proposed limit of NMT (b) (4) ppm for peanut protein and the manufacturer of the peanut oil listed in the peanut oil, NF specification are inappropriate.
- A commitment should be made for asking the Agency’s approval prior to any changes to the manufacturing process and manufacturer for the (b) (4) peanut oil.
- The labeling information is inadequate. To date, Structured Product Labeling (SPL) has not been submitted. Deficiencies have been identified on the immediate container and carton labels submitted on the June 24, 2008 amendment.

**III. Administrative**

- A. Reviewer’s Signature**  
electronically signed in DFS
- B. Endorsement Block**  
electronically signed in DFS
- C. CC Block**  
entered electronically in DFS

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Chemistry Assessment Section

(b) (4)

**IV. Labels**

Since the completion of Review #1, three amendments dated 6/24/2008 (BL), 2/4/2009 (BC), and 3/31/2009 (BL) on labeling were submitted. The last two amendments dated 2/4/2009 and 3/31/2009 were not reviewed during this review cycle (see page 33). Information provided in the 6/24/2008 amendment is summarized below.

**1) Immediate Container**

Labeling Item	Information provided
Trade name	Tolak
Establish name (size at least one half of trade name)	fluorouracil cream
Strength	4%
Net contents	40 g
Lot number per 21 CFR 201.18	(b) (4)
Expiration date per 21 CFR 201.17	(b) (4)
“Rx only” statement per 21 CFR 201.100(b)(1)	provided
Storage	Do not freeze. Maintain at 25°C (77°F), excursion permitted to 15°C - 30°C (59°F - 86°F) during storage and transportation.
NDC number	28105-421-40
Bar Code per 21 CFR 201.25(c)(2)	provided
Name of distributor/manufacturer per 21 CFR 201.1(h)(5)	Hill Dermaceuticals, Inc. Sanford, Florida 32773 USA
Others	For topical use only. Not for Ophthalmic, Oral or Intravaginal Use.

Chemistry Assessment Section

2) Cartons

Labeling Item	Information provided
Trade name	Tolak
Establish name (size at least one half of trade name)	fluorouracil cream
Strength*	4%
Net quantity of dosage form	40 g
Lot number per 21 CFR 201.18	Provided on the bottom flap
Expiry date 21 CFR 201.17	Provided on the bottom flap
“Rx only” statement per 21 CFR 201.100(b)(1)	provided
“See package insert for dosage information”	provided
“Keep out of reach of children”	provided
NDC number	28105-421-40
Storage	Do not freeze. Maintain at 25°C (77°F), excursion permitted to 15°C - 30°C (59°F - 86°F) during storage and transportation.
Bar Code per 21 CFR 201.25(c)(2)	The location of bar code was marked.
Name of distributor/manufacturer per 21 CFR 201.1(h)(5)	Hill Dermaceuticals, Inc. Sanford, Florida 32773 USA

*Reviewer's Assessment: Adequate labeling information was provided in the 6/24/2008 amendment except for the following statements on both immediate and carton labels:*



## Chemistry Assessment Section

(b) (4)

The following revisions are recommended:

- 1) Delete (b) (4) from both the immediate container and carton labels.
- 2) Change the statement of

(b) (4)

to

(b) (4) Active ingredient: fluorouracil USP. Inactive ingredients: arlacel-165, butylated hydroxytoluene NF, cetyl alcohol NF, anhydrous citric acid USP, glycerin USP, isopropyl myristate NF, methyl gluceth-10, methylparaben NF, propylparaben NF, purified water USP, peanut oil NF, sodium hydroxide NF, stearic acid NF, and stearyl alcohol NF.”

Because of other significant CMC deficiencies, labeling issues will be addressed in the next review cycle.

### 3) Drug Listing Data Elements in Structured Product Labeling

The applicant did not submit Structured Product Labeling (SPL).

Reviewer's Assessment: The request for SPL was made on the 74-day letter dated November 2, 2007. However, at the completion of this review, SPL has still yet to be submitted.

## V. Attachment—FDA Form 483

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/s/

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Jane Chang  
5/21/2009 03:09:08 PM  
CHEMIST

Shulin Ding  
5/21/2009 03:12:45 PM  
CHEMIST  
On behalf of Dr. Moo-Jhong Rhee.

## MEMORANDUM

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

**DATE:** June 23, 2008

**TO:** NDA 22-259 Addendum to CMC Review #1

**FROM:** Shulin Ding, Ph.D., Pharmaceutical Assessment Lead  
(ONDQA Division of Pre-Marketing Assessment II)

**THROUGH:** Moo-Jhong Rhee, Ph.D., Chief, Branch III  
(ONDQA Division of Pre-Marketing Assessment II)

**SUBJECT:** **Addendum to Addendum to CMC Review #1: Corrections of Error and Typo**

Addendum to CMC Review #1 was filed in DFS on June 18, 2008. The addendum contains an inadvertent error and a typo in the first sentence of Background section. The error is the NDA number. It should be NDA 22-259 rather than NDA 22-032. Additionally, the acronym, PDUFA, was spelled wrong.

The correct sentence should read "The PDUFA goal date of NDA 22-259 is June, 20, 2008."

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/s/

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Shulin Ding  
6/23/2008 10:52:01 AM  
CHEMIST

Moo-Jhong Rhee  
6/23/2008 01:37:45 PM  
CHEMIST  
Chief, Branch III

# MEMORANDUM

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

**DATE:** June 18, 2008

**TO:** NDA 22-259 CMC Review #1

**FROM:** Shulin Ding, Ph.D., Pharmaceutical Assessment Lead  
(ONDQA Division of Pre-Marketing Assessment II)

**THROUGH:** Moo-Jhong Rhee, Ph.D., Chief, Branch III  
(ONDQA Division of Pre-Marketing Assessment II)

**SUBJECT:** **Change in CMC Recommendation for NDA 22-259 due to Recent Notification of unacceptable cGMP Compliance**

## Background

The PUDUFA goal date of NDA 22-032 is June 20, 2008. CMC Review #1 was closed on March 31, 2008 with a recommendation of Approval pending an acceptable Overall Compliance Recommendation and label/labeling.

Additionally, an issue on peanut oil is also noted in CMC Review #1 (pp. 8, 46, 58, and 63 of 109). Specifically, the issue is with the validity of the proposed assay method on peanut oil proteins. Despite a request of information (IR letterdated Jan. 14, 2008), an adequate response has not been received.

## Reviewer's Evaluation

Concerning cGMP Compliance: The Overall Compliance Recommendation (attachment) from the Office of Compliance regarding facility cGMP status was issued on June 10, 2008, and the recommendation is "Withhold" for this NDA. The overall recommendation of "withhold" indicates the lack of cGMP compliance in the manufacture of the proposed product. Without an acceptable cGMP compliance, the identity, strength, purity, and quality of the product can not be assured.

Concerning label/labeling deficiencies: The deficiencies were conveyed to the applicant in the IR letter dated Jan. 31, 2008. An acceptable revised label/labeling has not been received as of the date of this memorandum. Since CMC recommendation for this NDA is changed to "approvable" (see below Recommendation and Conclusion on Approvability), any future submissions on label/labeling under this NDA will be reviewed in the next cycle of review.

Concerning peanut oil issue: The current Agency's position on the peanut oil issue is that the Agency may approve the NDA if the peanut oil supplier has a tract record that demonstrates that their peanut oil [REDACTED] (b)(4) does not cause significant allergic reaction to the patients (Meeting dated June 6, 2008 with Dr. Janet Woodcock, and Dr. Woodcock's draft letter dated June 6, 2008). Since the current supplier of the peanut oil to this NDA is deemed to have such tract record for producing acceptable peanut oil [REDACTED] (b)(4) [REDACTED] this NDA may be approved per CMC perspective once cGMP issue is resolved. During the second review cycle appropriate post approval commitment will be discussed with the applicant based on the Agency's policy per Dr. Woodcock's letter to the applicant.

#### Recommendation and Conclusion on Approvability

This NDA has not assured identity, strength, purity, and quality due to lack of the cGMP compliance. Therefore, "**Approvable**" action is recommended per CMC perspective.

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 22259/000 Sponsor: HILL DERMAC  
2650 SOUTH MELLONVILLE AVE  
SANFORD, FL 327739311

Org Code: 540

Priority : 5S

Stamp Date: 20-AUG-2007

PDUFA Date : 20-JUN-2008

Action Goal :

District Goal: 21-APR-2008

Brand Name : 4% 5-FLUOROURACIL

Estab. Name:

Generic Name: 4% 5-FLUOROURACIL

Dosage Form: (CREAM)

Strength : 4%

FDA Contacts: L. CHASEY Project Manager (HFC-60) 301-827-8675  
J. CHANG Review Chemist 301-796-1973  
S. DING Team Leader 301-796-1349

-----  
Overall Recommendation: WITHHOLD on 10-JUN-2008 by C. CRUZ (HFD-323) 301-796-3254  
-----

Establishment : CFN : (b) (4) FEI : (b) (4)  
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER  
Profile: CTL OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 22-OCT-07  
Decision: ACCEPTABLE  
Reason: BASED ON PROFILE

-----  
Establishment : CFN : FEI : (b) (4)  
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER  
DRUG SUBSTANCE RELEASE TESTER  
DRUG SUBSTANCE STABILITY TESTER

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile: CSN OAI Status: NONE  
 Last Milestone: OC RECOMMENDATION  
 Milestone Date: 22-OCT-07  
 Decision: ACCEPTABLE  
 Reason: BASED ON PROFILE

-----  
 Establishment : CFN : 1036365 FEI : 1036365

HILL DERMACEUTICALS INC  
 2650 S MELLONVILLE AVE  
 SANFORD, FL 327739311

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER  
 FINISHED DOSAGE LABELER  
 FINISHED DOSAGE MANUFACTURER  
 FINISHED DOSAGE PACKAGER  
 FINISHED DOSAGE RELEASE TESTER  
 FINISHED DOSAGE STABILITY TESTER

Profile: OIN OAI Status: POTENTIAL OAI  
 Last Milestone: OC RECOMMENDATION  
 Milestone Date: 10-JUN-08  
 Decision: WITHHOLD  
 Reason: DISTRICT RECOMMENDATION

-----  
 Establishment : CFN : (b) (4) FEI : (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER  
 FINISHED DOSAGE RELEASE TESTER

Profile : CTL OAI Status: NONE  
 Last Milestone: OC RECOMMENDATION  
 Milestone Date: 22-OCT-07  
 Decision: ACCEPTABLE  
 Reason: BASED ON PROFILE

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/s/

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Shulin Ding  
6/18/2008 02:02:58 PM  
CHEMIST

Moo-Jhong Rhee  
6/18/2008 02:11:08 PM  
CHEMIST  
Chief, Branch III

**NDA 22-259**

**Fluorouracil Cream  
4%**

**Hill Dermaceuticals, Inc.**

**Jane L. Chang, Ph.D.**

**Review Chemist**

**Office of New Drug Quality Assessment  
Division of Pre-Marketing Assessment II  
Branch III**

**For Division of Dermatologic and Dental Drug Products  
HFD-540**

# Table of Contents

<b>Table of Contents .....</b>	<b>2</b>
<b>Chemistry Review Data Sheet.....</b>	<b>4</b>
<b>The Executive Summary.....</b>	<b>8</b>
I. Recommendations.....	8
A. Recommendation and Conclusion on Approvability.....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product and Drug Substance.....	8
B. Description of How the Drug Product is Intended to be Used .....	10
C. Basis for Approvability or Not-Approval Recommendation.....	11
III. Administrative.....	11
A. Reviewer’s Signature.....	11
B. Endorsement Block.....	11
C. CC Block.....	11
<b>Chemistry Assessment .....</b>	<b>12</b>
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data .....	12
S DRUG SUBSTANCE.....	12
S.1 General Information.....	12
S.2 Manufacture .....	13
S.3 Characterization .....	20
S.4 Control of Drug Substance.....	23
S.5 Reference Standards or Materials .....	34
S.6 Container Closure System .....	35
S.7 Stability.....	36
P DRUG PRODUCT.....	45
P.1 Description and Composition of the Drug Product.....	45
P.2 Pharmaceutical Development .....	45
P.3 Manufacture .....	51
P.4 Control of Excipients.....	56
P.5 Control of Drug Product .....	64

P.6 Reference Standards or Materials ..... 81

P.7 Container Closure System ..... 81

P.8 Stability ..... 83

A APPENDICES .....93

A.1 Facilities and Equipment (biotech only) ..... 93

A.2 Adventitious Agents Safety Evaluation ..... 93

A.3 Novel Excipients ..... 93

R REGIONAL INFORMATION .....93

R.1 Executed Batch Records ..... 93

R.2 Comparability Protocols ..... 94

R.3 Methods Validation Package ..... 94

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 ..... 94

A. Labeling & Package Insert.....94

1. Package Insert ..... 94

2. Labels ..... 97

3. Drug Listing Data Elements in Structured Product Labeling ..... 99

B. Environmental Assessment Or Claim Of Categorical Exclusion .....99

III. List Of Deficiencies ..... 100

## Chemistry Review Data Sheet

# Chemistry Review Data Sheet

1. NDA 22-259
2. REVIEW #: 1
3. REVIEW DATE: 25-MAR-2008
4. REVIEWER: Jane L. Chang
5. PREVIOUS DOCUMENTS:

<u>Documents</u>	<u>Document Date</u>
8/16/2004 Pre-IND Meeting Minutes	04-SEP-2004
11/21/2005 EOP2 Meeting Minutes	21-DEC-2005
4/19/2007 Pre-NDA Reviewer Comments by Fax	25-APR-2007

6. SUBMISSION(S) BEING REVIEWED:

<b>Submissions Reviewed</b>	<b>Document Date</b>
Original Submission	17-AUG-2007
Amendment (BZ)	10-SEP-2007
Amendment (BC)	11-OCT-2007
Correspondence (C)	15-OCT-2007
Amendment (BZ)	19-NOV-2007
Amendment (BC)	09-JAN-2008
Amendment (BC)	12-FEB-2008
Amendment (BC)	04-MAR-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Hill Dermaceuticals, Inc  
Address: 2650 South Mellonville Avenue  
Sanford, Florida 32773  
Representative: Rosario G (Nini) Ramirez, MD / Director  
Telephone: 407-323-1887

## Chemistry Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: (b) (4)  
b) Non-Proprietary Name: Fluorouracil Cream  
c) Code Name/# (ONDQA only): N/A  
d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 5 (New Formulation)
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

## 10. PHARMACOL. CATEGORY: (b) (4)

11. DOSAGE FORM: Cream

12. STRENGTH/POTENCY: 4%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#): SPOTS product – Form Completed Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



5-Fluorouracil

2,4(1*H*,3*H*)-Pyrimidinedione, 5-fluoro-Molecular Formula: C<sub>4</sub>H<sub>3</sub>FN O<sub>2</sub>.

Molecular Weight: 130.0 (b) (4)

CAS No: 51-21-8

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYP E	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	1	Adequate	3/20/2008	By J. Chang
	III			4	N/A		*
	III			4	N/A		*

\*See page 82 of this review under container and closure system for details.

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	69,841	5-Fu (fluorouracil) Cream

Chemistry Review Data Sheet

18. STATUS:

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
Biometrics	N/A		
EES	Pending*		
Pharm/Tox	N/A		
Biopharm	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
Office of Drug Safety	Not recommended**	12/14/2007	T. Turner
EA	Categorical exclusion (see review)	10/5/2007	J. Chang
Microbiology	N/A		

\*With the exception of Hill Dermaceuticals, Inc., all other manufacturing and control facilities are acceptable. The inspection of Hill Dermaceuticals, Inc. is still pending.

\*\*DDMAC did not recommend the use of the proposed proprietary name (b) (4). It was stated that the Division of Dermatology and Dental Products concurs with DDMAC's comments. Therefore, DMETS will not proceed with the safety review of the proposed proprietary name, (b) (4).

## Executive Summary Section

# The Chemistry Review for NDA 22-259

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Therefore, this NDA may be approved pending resolution of the following issues:

- An acceptable overall recommendation from the Office of Compliance. Inspection of Hill Dermaceuticals, Inc. facility is still pending.
- Submission of acceptable labeling information including immediate container and carton labels and Structured Product Labeling (SPL). To date, SPL has not been submitted.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product and Drug Substance

##### (1) Drug Product

Fluorouracil Cream, 4%, is a white cream indicated for the topical treatment of actinic keratosis. The formulation is (b) (4) butylated hydroxytoluene NF, cetyl alcohol NF, glycerin USP, isopropyl myristate NF, methyl gluceth-10, methylparaben NF, propylparaben NF, (b) (4) peanut oil NF, stearyl alcohol NF, and stearic acid NF (b) (4) sodium hydroxide NF (b) (4) Arlacel-165 (b) (4)

Protein content in (b) (4) peanut oil is significantly reduced (b) (4). The proposed specification of (b) (4) peanut oil NF includes a test for protein content by amino acid analysis with a limit of NMT

## Executive Summary Section

(b) (4) ppm. Analytical procedure for this test is poorly written and confusing and validation data are inadequate due to lack of accuracy, precision, linearity, etc. **Nevertheless, these issues are not critical as long as no labeling claim is made regarding the level of protein content.**

Acceptable specification has been provided to ensure product identity, strength, purity, and quality at release. The specification includes description, pH, assay (RP-HPLC), identification (TLC), microbial limits, propylparaben and methylparaben assays (RP-HPLC), ratio (5-FU:salt), particle size testing (microscopic examination), homogeneity (RP-HPLC), related substances (RP-HPLC), butylated hydroxytoluene assay (RP-HPLC), antimicrobial effectiveness test, viscosity, and minimum fill. (b) (4)

Adequate validation data were provided for Method LL-0352, assay for fluorouracil and related substance. Validation data for the RP-HPLC Methods (b) (4) and 5FU-8 for the (b) (4) were either inadequate or lacking. Lacking adequate validation data for (b) (4) assays is believed not to have significant impact on the safety of the drug product because fluorouracil likely acts as an anti-microbial agent because of its mechanism of action. In addition, microbiological quality attributes of the drug product can be addressed by other tests such as microbial limits and antimicrobial effectiveness test, which are included in the specification.

The drug product will be packaged into 40 g commercial package size.

Twelve months real-time and six months accelerated stability data have been provided for the three primary stability batches. **The data are not sufficient to support the proposed shelf life of (b) (4) months.** A significant change ((b) (4) %) in 5-fluorouracil assay was observed during the accelerated stability studies. Under long-term condition, the assay showed a slight decrease ((b) (4) %) over 12 months. The data also showed a decreasing trend for pH. As a result, the ratio of fluorouracil to its sodium salt showed an increasing trend. **Per ICH Q1E, a 15-month shelf life for the drug product is granted. As there is no (b) (4) study for the drug product, the storage temperature for the drug product should be maintained at 25°C (77°F), excursion permitted to 15-30°C (59-86°F) (b) (4)**

Even though particle size testing (free of particles and no phase separation) is included in the drug product stability specification, no data were submitted.

## Executive Summary Section

**Complete stability data generated per stability specification shown on page 85 should be submitted and evaluated if an extension of shelf life is requested in the future.**

**(2) Drug Substance**

5-Fluorouracil is a well-established compendial drug substance whose structure has been fully elucidated. 5-Fluorouracil is marketed in various formulations since 1962. The approved formulations include an injectable solution (50 mg/mL, NDA 12-209) for treatment of cancer, and topical solutions [2% and 5% (NDA 16-831)] as well as topical creams [0.5% (NDA 20-985), 1% (NDA 16-988), and 5% (NDA 16-831)] for the treatment of multiple actinic or solar keratoses.

The drug substance is supplied by [REDACTED] <sup>(b) (4)</sup>. The CMC information pertaining to synthesis and control of 5-fluorouracil was presented in the NDA. In addition to the tests listed in the USP monograph, testing for related substances (TLC and RP-HPLC) is included in the drug substance specification.

**B. Description of How the Drug Product is Intended to be Used**

Fluorouracil Cream 4% is indicated for the topical treatment of actinic keratosis lesions of the face, ears, and scalp. It is intended to be applied once daily in an amount sufficient to cover the lesions with a thin film, using the fingertips to gently massage the medication uniformly into the skin. Fluorouracil Cream should be applied for a period of four weeks as tolerated. Hands should be thoroughly washed following Fluorouracil Cream application.

Fluorouracil Cream, 4% is to be stored at controlled room temperature 25°C (77°F). **When stored under the specified conditions, an expiration dating period of 15 months can be applied to the drug product.**

## Executive Summary Section

**C. Basis for Approvability or Not-Approval Recommendation**

Adequate data have been submitted to ensure the drug product's identity, strength, purity, and quality as a topical product for its intended use. This NDA may be approved pending resolution of the following issues:

- An acceptable overall recommendation from the Office of Compliance. Inspection of Hill Dermaceuticals, Inc. facility is still pending.
- Submission of acceptable labeling information. To date, Structured Product Labeling (SPL) has not been submitted. Labeling deficiencies regarding immediate container and carton labels, e.g. lack of Lot number, expiration date, "Rx only" statement, bar code, etc. were conveyed to the applicant on 1/31/2008. However, revised labels have not been submitted. DDMAC does not recommend the proposed proprietary name, (b) (4)

**III. Administrative****A. Reviewer's Signature**

electronically signed in DFS

**B. Endorsement Block**

electronically signed in DFS

**C. CC Block**

entered electronically in DFS

82 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

## Chemistry Assessment Section

(b) (4)

**II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1****A. Labeling & Package Insert**

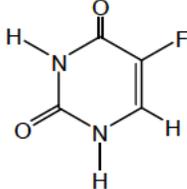
Package insert was submitted in the 9/10/2007 amendment (BZ). Labeling for immediate container and carton was submitted in the 11/19/2007 amendment.

**1. Package Insert****1) *Dosage Forms and Strengths***

Labeling Item	Information provided
Dosage Form	Cream
Strength	4%

## Chemistry Assessment Section

2) *Description*

Labeling Item	Information provided
Proprietary name	Not provided
Established name	5-fluorouracil
Route of Administration	Not provided
Strength	4%
Dosage Form*	Cream
Qualitative ingredient information	Purified water, sodium hydroxide, methyl gluceth-10, glycerin, isopropyl myristate, (b) (4) peanut oil, butylated hydroxytoluene, cetyl alcohol, stearic acid, stearyl alcohol, methylparaben, propylparaben, arlacel-165, (b) (4)
Pharmacological/therapeutic class per 21 CFR 201.57(a)(1)(v)	Not provided
Chemical name, structural formula, molecular weight	 <p>5-fluoro-2,4(1H,3H)-pyrimidinedione Molecular Formula: C<sub>4</sub>H<sub>3</sub>FN<sub>2</sub>O<sub>2</sub> Molecular weight: 130.1</p>

3) *How Supplied*

Labeling Item	Information provided
Strength of dosage form	4%
Units of dosage form	40-gram
NDC number	Not provided
Special handling	None
Storage condition	Store at 25°C (77°F), excursion permitted to 15°C - 30°C (59°F - 86°F).

4) *Patient Counseling Information*

Labeling Item	Information provided
Trade name	Not provided
Distributor's name as qualified by 21 CFR 201.1(h)(5)*	Hill Dermaceuticals, Inc. Sanford, Florida 32773

## Chemistry Assessment Section

Reviewer's Assessment: Adequate labeling information was provided in the 9/10/2007 amendment except for the following items:

*Full Prescribing Information*

- a) In Section 11-DESCRIPTION, proprietary name, route of administration, and pharmacological/therapeutic class were not provided.
- b) In Section 16-HOW SUPPLIED/STORAGE AND HANDLING, NDC number was not included.
- c) In Section 17-PATIENT COUNSELING INFORMATION, the trade name and established name were stated to be "TRADENAME (4% (b)(4)fluorouracil) Cream" under Patient Information.

The following comments were conveyed to the applicant on 1/31/2008:

Please revise the Full Prescribing Information in 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.

At the completion of this review, updated labeling for the package insert has not been provided. However, revisions were incorporated into the draft package insert by this reviewer via the 2/11/2008, 2/25/2008, and 3/19/2008 emails to the clinical team. The revisions included:

- a) Trade name and established name and strength:  
"TRADENAME (fluorouracil) Cream 4%"

Chemistry Assessment Section

b) In Section 11-DESCRIPTION:

*established name: fluorouracil cream*

*route of administration: topical*

*pharmacological/therapeutic class: (b) (4)*

c) In Section 16-HOW SUPPLIED/STORAGE AND HANDLING:

*NDC number: 28105-421-40 for the 40 gram tube.*

*Storage:*

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

2. Labels

1) Immediate Container

Labeling Item	Information provided
Trade name	(b) (4)
Establish name (size at least one half of trade name)	4% fluorouracil cream
Strength	4%
Net contents	40 g
Lot number per 21 CFR 201.18	Not provided
Expiration date per 21 CFR 201.17	Not provided
“Rx only” statement per 21 CFR 201.100(b)(1)	Not provided
Storage	Store at 25°C (77°F), excursion permitted to 15°C - 30°C (59°F - 86°F).
NDC number	28105-421-40
Bar Code per 21 CFR 201.25(c)(2)	Not provided
Name of distributor/manufacturer per 21 CFR 201.1(h)(5)	Hill Dermaceuticals, Inc. Sanford, Florida 32773
Others	For topical use only. Not for Ophthalmic, Oral or Intravaginal Use.

Chemistry Assessment Section

2) *Cartons*

Labeling Item	Information provided
Trade name	(b) (4)
Establish name (size at least one half of trade name)	4% fluorouracil cream (size less than one half of trade name)
Strength*	4%
Net quantity of dosage form	40 g
Lot number per 21 CFR 201.18	Provided on the side panel
Expiry date 21 CFR 201.17	Provided on the side panel
“Rx only” statement per 21 CFR 201.100(b)(1)	Nor provided
“See package insert for dosage information”	provided
“Keep out of reach of children”	provided
NDC number	28105-421-40
Storage	Store at 25°C (77°F), excursion permitted to 15°C - 30°C (59°F - 86°F)
Bar Code per 21 CFR 201.25(c)(2)	Provided
Name of distributor/manufacturer per 21 CFR 201.1(h)(5)	Hill Dermaceuticals, Inc. Sanford, Florida 32773

*Reviewer's Assessment: Adequate labeling information was provided in the 11/19/2007 amendment except for the following items:*

- a) *Strength was included as part of the established name.*
- b) *Lot number, expiration date, “Rx only” statement, and bar code were not provided for the immediate container labeling.*
- c) *“Rx only” statement was not provided for the carton label.*
- d) *The font size of the established name is less than one half of the trade name*  
(b) (4)
- e) *DDMAC does not recommend the use of the proposed proprietary name* (b) (4)

*The following comments were conveyed to the applicant on the 1/31/2008 FDA information request:*

## Chemistry Assessment Section

Please revise the labeling for immediate container and carton:

- 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) 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.

***At the completion of this review, updated immediate container and carton labels have not been submitted.***

### 3. Drug Listing Data Elements in Structured Product Labeling

The applicant did not submit Structured Product Labeling (SPL).

***Reviewer's Assessment:*** The request for SPL was made on the 74-day letter. ***However, at the completion of this review, SPL has still yet to be submitted.***

### B. Environmental Assessment Or Claim Of Categorical Exclusion

A categorical exclusion from the preparation of an environmental assessment (EA) was requested under 21 CFR 25.31(b). The basis of this exclusion is the fact that the estimated concentration of the active ingredient at the point of entry into the aquatic environment will be less than 1 ppb from all products using this material as the active ingredient.

The maximum quantity (number of units) of the drug product manufactured and distributed was estimated to be at the range of (b) (4) units per year, which corresponds to (b) (4) kg of the active moiety ((b) (4)) per year. The expected introduction calculation (EIC) is (b) (4) ppb.

***Reviewer's Assessment:*** Acceptable.

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

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Jane Chang  
3/31/2008 11:28:40 AM  
CHEMIST

Moo-Jhong Rhee  
3/31/2008 11:31:17 AM  
CHEMIST  
Chief, Branch III