

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022259Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

Product Quality Microbiology Review

22 JUL 2015

NDA: 22-259 (Class II resubmission)

Drug Product Name

Proprietary: Tolak

Non-proprietary: 5- fluorouracil

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
17 DEC 2014	18 DEC 2014	03 FEB 2015	06 FEB 2015
06 APR 2015	07 APR 2015	N/A	N/A
15 JUL 2015	16 JUL 2015	N/A	N/A
22 JUL 2015 (email)	22 JUL 2015	N/A	N/A

Applicant/Sponsor

Name: Hill Dermaceuticals, Inc.
Address: 2650 South Mellonville Avenue
Sanford, FL 32773
Representative: Linda Payne
Telephone: 407-323-1887

Name of Reviewer: Jessica G. Cole, PhD

Conclusion: Recommended for Approval.

Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUBMISSION:** Class II resubmission of an original NDA
 - 2. SUBMISSION PROVIDES FOR:** New drug product
 - 3. MANUFACTURING SITE:** Hill Dermaceuticals, Inc.
2650 South Mellonville Avenue
Sanford, FL 32773
 - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
 - 4% topical cream
 - 5. METHOD(S) OF STERILIZATION:** This is a non-sterile drug product
 - 6. PHARMACOLOGICAL CATEGORY:** Treatment of actinic keratosis
- B. SUPPORTING/RELATED DOCUMENTS:** Chemistry review dated 29 May 2009 and 31 March 2008.
- C. REMARKS:** This is an entirely paper resubmission not in the eCTD format. This is a 3 volume submission composed of a collection of multiple submissions dating from 2011-2014. No microbiology review was conducted on the original NDA submission dated 20 August 2007. The original inspection found application integrity policy (AIP) concerns, including issues with the validation of the proposed preservative system. An information request (IR) was sent to the applicant on 06 March 2015, 09 June 2015, and 20 June 2015 and responses were received on 07 April 2015, 16 July 2015, and 22 July 2015 (email). A teleconference was held with the applicant on 09 June 2015. This review contains the IRs and a summary of the applicant's responses.

filename: N022259R1.doc

Executive Summary**I. Recommendations**

- A. Recommendation on Approvability - Recommended for Approval.**
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – Not applicable.**

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – This is a non-sterile preserved topical cream. The drug product is (b) (4) filled into tubes.**
- B. Brief Description of Microbiology Deficiencies – Not applicable.**
- C. Assessment of Risk Due to Microbiology Deficiencies – Not applicable.**
- D. Contains Potential Precedent Decision(s)- Yes No**

III. Administrative

- A. Reviewer's Signature** _____
Jessica G. Cole, PhD
- B. Endorsement Block** _____
Stephen Langille, PhD
Microbiology Acting Branch Chief
- C. CC Block**
In Panorama

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – A non-sterile cream in an aluminum tube.
- **Drug product composition** –

Table 1- Composition of the drug product (Copied from the 31 March 2008 chemistry review page 45/110)

Table P.1.1. Composition of 4% Fluorouracil Cream

Component	Quantity per Batch (b) (4)		Purpose (b) (4)
	%	Kilograms	
5-Fluorouracil USP	4.0		
Purified Water USP	(b) (4)		
(b) (4) Peanut Oil USP ¹			
Isopropyl Myristate NF			
Methyl Gluceth-10 (b) (4)			
Arlacel-165 (b) (4)			
Glycerin USP			
Cetyl Alcohol NF			
Stearyl Alcohol NF			
Sodium Hydroxide NF			
Stearic Acid NF			
Butylated Hydroxytoluene NF			
Methylparaben NF			
Citric Acid USP			
Propylparaben NF			
Total:	100 %	500 kg	(b) (4)

- **Description of container closure system** – The 31 March 2008 chemistry review indicates the drug product is packaged into a 40 gram aluminum tube with end sealant and cap.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Container-Closure and Package integrity** – Not applicable for this multidose non-sterile product.
- **Preservative Effectiveness** – Preservative effectiveness studies were described for a single lot of drug product. AET was initially conducted on stability at release, 12, and 24 months.

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

Jessica Cole -S

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Stephen E. Langille

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