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RESEARCH**

APPLICATION NUMBER:

208183Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

Product Quality Microbiology Review

12 JUNE 2015

NDA: 208-183

Drug Product Name

Proprietary: ULTRAVATE®

Non-proprietary: Halobetasol Propionate Lotion, 0.05%

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
23 DEC 2014	23 DEC 2014	20 JAN 2014	20 JAN 2015
29 MAY 2015	29 MAY 2015	NA	NA

Submission History (for 2nd Reviews or higher) – NA

Applicant/Sponsor

Name: Ferndale Laboratories, Inc.

Address: 780 West Eight Mile Rd.
Ferndale , MI 48220

Representative: Sarah Van Hoof

Telephone: (248) 586-8661

Name of Reviewer: Neal J. Sweeney, Ph.D.

Conclusion: Recommended for approval from the Product Quality Microbiology review perspective.

Product Quality Microbiology Data Sheet

- A. 1. TYPE OF SUBMISSION:** Original New Drug Application
- 2. SUBMISSION PROVIDES FOR:** The manufacture and marketing of a non-sterile topical lotion.
- 3. MANUFACTURING SITE:**
- Ferndale Laboratories, Inc.
780 West Eight Mile Road
Ferndale, MI 48220
- 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
- Dosage Form: lotion
 - Route of Administration: topical
 - Strength/Potency: 0.05% (w/w) packaged in 2 g (b) (4) (professional samples) and 2 oz. HDPE bottles (primary packaging).
- 5. METHOD(S) OF STERILIZATION:** N/A, non-sterile drug product.
- 6. PHARMACOLOGICAL CATEGORY:** Indicated for the treatment of plaque psoriasis in patients 18 years of age and older.
- B. SUPPORTING/RELATED DOCUMENTS:** N/A
- C. REMARKS:**
The Microbiologist's filing review (dated Feb. 18, 2015) identified microbial limits review issues that were conveyed to the applicant via 74 day letter (dated March 18, 2015). The applicant's responses, submitted (May 29, 2015) are incorporated in this review.

filename: N208183R1.docx

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** - Recommended for approval from a quality microbiology perspective.
- B. Recommendations on Phase 4 Commitments and/or Agreements** –N/A.

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – Manufacturing of non-sterile drug product in cGMP facility where the manufacturer (1) performs routine environmental monitoring in the manufacturing and packaging areas, (2) tests ^{(b) (4)} water ^{(b) (4)}

- B. Brief Description of Microbiology Deficiencies** – Based upon the information provided, no microbiology deficiencies were identified.
- C. Assessment of Risk Due to Microbiology Deficiencies** – NA
- D. Contains Potential Precedent Decision(s)** - Yes No

III. Administrative

- A. Reviewer's Signature** _____
Neal J. Sweeney, Ph.D.
Microbiology Reviewer
- B. Endorsement Block** _____
Bryan S. Riley, Ph.D.
(Acting) Division 4 Branch Chief
- C. CC Block**
N/A

Product Quality Microbiology Assessment

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

S DRUG SUBSTANCE - NA

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product – Halobetasol Propionate Lotion, 0.05% is a non-sterile, white to off-white (b) (4) topical lotion (b) (4) with propyl paraben and butylparaben, and filled in (b) (4) (professional sample) and HDPE bottles. .
- Drug product composition – Halobetasol Propionate Lotion, 0.05% contains halobetasol propionate in a lotion base consisting of water, diisopropyl adipate, octyldodecanol, ceteth-20, poloxamer 407, cetyl alcohol, stearyl alcohol, propylparaben, butylparaben, glycerin, propylene glycol, carbomer homopolymer, and sodium hydroxide for (b) (4). The drug product composition is summarized below in Table 1:

Table 1: Drug Product Composition

Ingredient	Purpose	Composition (% w/w)
Halobetasol Propionate USP	API	0.05
Diisopropyl Adipate	(b) (4)	(b) (4)
Octyldodecanol, NF		
Ceteth-20		
Poloxamer 407, NF		
Cetyl Alcohol, NF		
Stearyl Alcohol, NF		
Propylparaben, NF		
Butylparaben, NF		
Propylene Glycol, USP		
Glycerin, USP		
Carbomer Homopolymer, NF		
Sodium Hydroxide, NF (b) (4)		
(b) (4) Water, USP		

Table 1 was reproduced in part from applicant’s untitled Table presented in Section 3.2.P.1, Description and Composition of Drug Product, page 1.

- Description of container closure system – The product will be supplied in 2 g professional sample (b) (4) with polypropylene (PP) caps, and 2 oz.

white oval tapered HDPE bottles (b) (4) with PP disc top caps..

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- Container-Closure and Package integrity – N/A
- Antimicrobial Effectiveness Test (AET) – Formulation containing 75% of the theoretical levels of butylparaben and propylparaben (b) (4) content (formulation R9861) met USP <51> AET category 2 acceptance criteria:

Bacteria: Not less than (b) (4) reduction from the initial count at 14 days , and no increase from the 14 days' count at 28 days.

Yeast and Mold: No increase from the initial count at 14 and 28 days

The provided AET results for formulation R9861 showed (b) (4) reduction of *E. coli*, *P. aeruginosa*, and *S. aureus* by day 14, and no increase from the day 14 count at 28 days. A (b) (4) reduction of *C. albicans* was observed by day14, and no increase in *C. albicans* counts were detected at 28 days. No increase from initial counts were detected for *A. niger* at 14 and 28 days.

(b) (4) content acceptance criteria for both propylparaben and butylparaben are (b) (4) (release) and (b) (4) (stability). Additionally, antimicrobial effectiveness was performed for stability testing of primary stability batches, and is also included in the post-approval stability protocol.

- Justification for not having a microbial limit specification for a non-sterile drug product – The finished drug product has a microbial limit specification.

-ADEQUATE-

REVIEWER COMMENT – Antimicrobial effectiveness of the drug product formulated with 75% of the theoretical levels of butylparaben and propylparaben (b) (4) content met USP <51> AET category 2 acceptance criteria. Additionally the description of drug product and pharmaceutical development information were consistent with the FDA Guidances for Industry: (1) Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, and (2) Q8(R2) Pharmaceutical Development.

P.3 Manufacture

P.3.1 Manufacturer

Ferndale Laboratories, Inc.
780 West Eight Mile Road
Ferndale, MI 48220

P.3.3 Description of the Manufacturing Process and Process Controls

Drug product manufacturing, packaging, labeling, testing and product release operations are performed at the cGMP-compliant Ferndale Laboratories, Inc. facility.

**ADEQUATE**

REVIEWER COMMENT – The drug product, drug product manufacturing, and process controls were sufficiently described for the reviewer to determine which data are needed for sections P.5 (Specifications) and P.8 (Stability) below.

P.5 Control of Drug Product**P.5.1 Specifications****P.5.2 Analytical Procedures**

- Endotoxin – NA
- Sterility – NA
- Microbial Limits -
 - Specification:
 - Total Aerobic Microbial Counts: NMT (b) (4)
 - Total Yeast and Mold Counts: NMT (b) (4)

- Absence of *S. aureus*, *P. aeruginosa*, clinically significant Gram negative bacilli and beta-hemolytic *Streptococcus* spp.
- Methods:
 - QM-105: Total Aerobic Microbial Count Method and Total Yeasts and Molds Count Method (Complies with USP <61> and, and European Pharmacopoeia 2.6.12)
 - QM-110: Method for Verifying the Absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* in Products, and for Screening for Gram Negative Bacilli and Beta-Hemolytic *Streptococcus* spp. (Complies with USP <62> and European Pharmacopoeia 2.6.12)

Additional product quality microbiology-related release/stability tests include package integrity (Method QG-1043, No evidence of unusual distortion, swelling or container bloating. No evidence of discoloration, leakage or perforation), and (b) (4) content for propylparaben and butylparaben ((b) (4) of claim for release, and (b) (4) of claim for stability).

Microbiology Information Request (dated March 18, 2015):

1. *Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganisms of the Burkholderia cepacia complex (Bcc). 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 these species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. Your test method should be validated and a discussion of those methods should be provided. Test methods validation should address multiple strains of Bcc and cells that are acclimated to the product and the environments (e.g., warm or cold water) that may be tested.*
2. *Provide study results verifying the suitability of the following microbiological test methods for the Halobetasol Propionate, 0.05% drug product:*
 - a. *SOP QM-105: Total Aerobic Microbial Count Method and Total Yeasts and Molds Count Method*
 - b. *SOP QM-110: Method for Verifying the Absence of Staphylococcus aureus and Pseudomonas aeruginosa in Products, and for Screening for Gram Negative Bacilli and Beta-Hemolytic Streptococcus spp.*

Applicant's Response (May 29, 2015):

The drug product is tested according to SOPs QM-105 and QM-110, which respectively comply with current USP test procedures, <61> *Microbiological Examination of Non Sterile Products: Microbial Enumeration Tests* and <62> *Microbiological Examination of Non Sterile Products: Tests for Specified Microorganisms*, as well as EP 2.6.12 and 2.6.13. The applicant submitted Validation Report VP/QM-613-00/RO,

entitled “Validation of Non-sterile Products Tested by the harmonized USP (<61> and <62>) and EP (2.6.12, 2.6.13) Microbial Enumeration Test and Test for Specified organisms: Halobetasol Propionate Lotion, 0.05%”.

Microbiologist’s Review of Applicant’s May 29, 2015 Response:

The applicant’s SOP’s include testing for the presence / absence of gram negative bacilli in product and the acceptance criterion for the absence of clinically significant gram negative bacilli in Halobetasol Lotion 0.05%, would include *Burkholderia cepacia* complex (Bcc). Method suitability of microbial limits test methods QM-105 and QM-110 included demonstration that the product was non-inhibitory (≥ 70 recovery of average control counts) in the enumeration of *S. aureus*, *P. aeruginosa*, *E. coli*, *B. subtilis*, *S. pyogenes*, *C. albicans*, and *A. niger*, as well as *Burkholderia cepacia*, *B. vietnamiensis*, and *B. stabilis* at the 10^{-1} test dilution. Additionally method suitability verification results for tests for specified organisms demonstrated that the drug product did not inhibit growth recovery of *S. aureus*, *P. aeruginosa*, *E. coli*, *S. pyogenes*, and *Burkholderia cepacia*, *B. vietnamiensis*, and *B. stabilis* at the 10^{-1} and 10^{-2} test dilutions

Additionally the applicant/manufacturer (1) performs routine environmental monitoring in the manufacturing and packaging areas, (2) tests (b) (4) water (b) (4)

-ADEQUATE-

REVIEWER COMMENT – Drug product microbial limits harmonized USP/EP <61> and <62> and Ph. Eur. 2.6.12 and Ph. Eur. 2.6.13 microbial limits test method suitabilities were respectively verified for the non-sterile drug product. Additionally drug product and in-process testing comply with the OPQ/OPF/DMA (initially OPS/IO/NDMS) product quality review policy on *Burkholderia cepacia* complex (Bcc) testing non-sterile aqueous products.

P.7 Container Closure System – see section P.1 above.

P.8 Stability

P.8.1 Stability Summary and Conclusion

MAINTENANCE OF MICROBIOLOGICAL CONTROL AND QUALITY: STABILITY CONSIDERATIONS

Based on the available results from the following stability studies a tentative 24 month expiration period is proposed.

The following primary stability studies were initiated:

- Temperature Cycle Studies: $4^{\circ}\text{C} \pm 2^{\circ}\text{C}/40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ (2 oz. commercial bottle only)
 - Microbial limits (TAMC, TYMC, specified microorganisms) testing not included
 - (b) (4) content (for both propylparaben and butylparaben) testing at 0 and 14 days.
 - (b) (4) Effectiveness testing not included
- Long term: $25 \pm 2^{\circ}\text{C}/60 \pm 5\% \text{RH}$ (2 g professional sample and 2 oz. commercial bottle)
 - Microbial limits (TAMC, TYMC, specified microorganisms) testing at 0, 12, 24, 30 and 36 months
 - (b) (4) content (for both propylparaben and butylparaben) testing at 0, 3, 6, 9, 12, 18, 24, and 36 months.
 - (b) (4) Effectiveness testing at 0, 12, 24, 30 and 36 months
- Intermediate: $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{RH} \pm 5\% \text{RH}$ (2 oz. commercial bottle only)
 - Microbial limits (TAMC, TYMC, specified microorganisms) testing at 0 12 and 24 months
 - (b) (4) content (for both propylparaben and butylparaben) testing at 0, 6, 9, 12, and 24 months.
 - (b) (4) Effectiveness testing at 0, 12, and 24 months
- Accelerated: $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{RH}$ (2 g professional sample and 2 oz. commercial bottle)
 - Microbial limits (TAMC, TYMC, specified microorganisms) testing at 0 and 6 months
 - (b) (4) content (for both propylparaben and butylparaben) testing at 0, 2, 4, and 6 months.
 - (b) (4) Effectiveness testing at 0 and 6 months

P.8.2 Post-Approval Stability Protocol and Stability Commitment

The applicant commits to conduct stability testing on the first three marketed drug product lots and on one lot yearly thereafter. .

The post-approval stability protocol (for $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{RH} \pm 5\% \text{RH}$ storage conditions) includes the following product quality microbiology-related test stations:

Table 2: Microbiology-Related Testing Included in Post-Approval Stability Protocol

Test	Interval (months)						
	0	3	6	9	12	18	24
Package Integrity	X	X	X	X	X	X	X
Propylparaben Assay	X	X	X	X	X	X	X
Butylparaben Assay	X	X	X	X	X	X	X
Total Aerobic Microbial Count	X				X		X
Microbial Limits (test for specified microorganisms)	X				X		X
Total Yeasts and Molds Count	X				X		X
(b) (4) Effectiveness	X				X		X

Table 2 was reproduced in part from applicant's untitled Table presented in Section 3.2.P.8.2, page 2.

P.8.3 Stability Data

Stability data were provided for nine drug product lots: 10028B, 13010A, 13082A, 13193A, 13193B, 13194A, 13194B, 13195A, and 13195B. All microbiology-related test results meet the established acceptance criteria.

-ADEQUATE-

REVIEWER COMMENT – The submitted stability protocol, commitment and data comply with FDA Guidances for Industry: (1) Q1A(R2) Stability Testing of New Drug Substances and Products, and (2) Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.

A APPENDICES - NA

R REGIONAL INFORMATION

R.1 Executed Batch Record

Executed batch records were provided for drug product lots 10028B, 13010A, 13082A, 13193A, 13193B, 13194A, 13194B, 13195A, and 13195B, as well as placebo lots 13081A and 13081.

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT - NA

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

(None)

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

/s/

NEAL J SWEENEY
06/25/2015

BRYAN S RILEY
06/25/2015
I concur.