

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208183Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

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

Date: November 3, 2015
From: Yichun Sun, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
Office of New Drug Products

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: CMC Review #1 of NDA 208183

Subject: Final Approval Recommendation for NDA 208183

At the time when the CMC review #1 was written, the NDA was recommended for approval from the ONDP's perspective. However, to eliminate the potential user confusion between Ultravate cream, Ultravate ointment and Ultravate lotion, it was decided that the labels and package insert (PI) for Ultravate lotion (NDA 208183) should be consistent with previously approved Ultravate products so describe the net content of Ultravate lotion, 0.05% as 60 mL (59 g) and maximum dosage as 50 grams per week.

Label/Labeling

The package insert and the container carton labels were revised and submitted on October 29, 2015 by the NDA applicant. The CMC sections of the final package insert, and mock-up container and carton labels have been reviewed by Dr. Hitesh Shroff and found acceptable. The review of the CMC sections of the final package insert, and mock up container and carton labels is attached (**Attachment - 1**).

Recommendation:

The revised package insert and mock-up container and carton labels are acceptable from the CMC perspective, and therefore, the previous **Approval** recommendation for this application remains valid. An expiration dating period of **24 months** is granted for the drug product of NDA 208183.

Application Technical Lead's Assessment and Signature

The NDA is recommended for approval from quality perspective.

Yichun Sun, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
11/3/2015

Attachment - 1 (Review of CMC Sections of the Finalized Labeling and Labels)

Memorandum

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

Date: November 2, 2015

From: Hitesh Shroff
Senior CMC Reviewer
Office of New Drug Products
Branch V/DNDP II

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Office of New Drug Products
Branch V/DNDP II

To: CMC Review #1 of NDA 208183

Subject: Revised Label

Review #1 indicated that label/labeling issues were satisfactorily resolved and therefore made an Approval recommendation was made. However, because of the following reason, the label was revised and got an agreement with the applicant.

Ultravate cream, 0.05% and Ultravate ointment, 0.05% are previously approved and supplied in 50 g tubes. The total allowed dosage is 50 grams per week. In accordance with CFR and USP the amount of drug product is described in grams in all labels and PI.

The drug product in the current NDA, Ultravate solution, 0.05%, is supplied in 60 mL bottles. The earlier labels and PI stated net content as 60 mL and maximum allowed dosage as 50 mL/week in accordance with CFR and USP.

However, to eliminate the potential user confusion between Ultravate cream, Ultravate ointment and Ultravate lotion it was decided in the labeling meeting that the labels and PI for Ultravate lotion should be consistent with previously approved ULTRAVATE products so describe the net content of ULTRAVATE lotion, 0.05% as 60 mL (59 g) and maximum dosage as 50 grams per week.

The package insert and the container carton labels were revised and submitted on October 29, 2015. The label/labeling is revised satisfactorily from the CMC perspective (**Attachment 1**).

Recommendation:

The revised label is acceptable from the CMC perspective, and therefore, the previous **Approval** recommendation for this application remains valid.

1. Package Insert

The strength is revised from [REDACTED]^{(b) (4)} to 0.5 mg/g.

(a) “Highlights” Section

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ULTRAVATE[®] lotion safely and effectively. See full prescribing information for ULTRAVATE lotion.

ULTRAVATE (halobetasol propionate) lotion
Initial U.S. Approval: 1990

-----DOSAGE FORMS AND STRENGTHS-----
Lotion: 0.05% (0.5 mg/g). (3)

(b) “Full Prescribing Information” Section

#3. Dosage Form and Strength

3. DOSAGE FORMS AND STRENGTHS

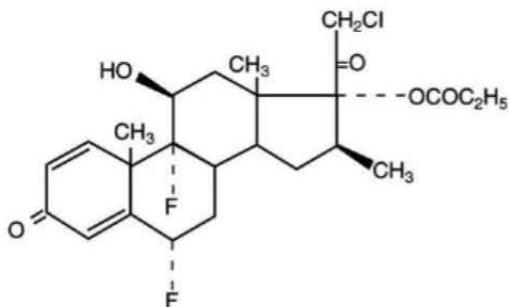
ULTRAVATE (halobetasol propionate) lotion, 0.05% is a white to off-white lotion. Each gram of ULTRAVATE lotion contains 0.5 mg of halobetasol propionate.

#11. Description

The ingredients in [REDACTED]^{(b) (4)} is revised to *Each gram*

11. DESCRIPTION

ULTRAVATE (halobetasol propionate) lotion, 0.05% for topical use contains a corticosteroid, halobetasol propionate. The chemical name of halobetasol propionate is 21-chloro-6 α , 9-difluoro-11 β , 17-dihydroxy-16 β -methylpregna-1, 4-diene-3-20-dione, 17-propionate. Halobetasol propionate is a white to off-white crystalline powder with a molecular weight of 484.96 and a molecular formula of C₂₅H₃₁ClF₂O₅. It is practically insoluble in water and freely soluble in dichloromethane and in acetone. It has the following structural formula:



Each gram of ULTRAVATE lotion contains 0.5 mg of halobetasol propionate in a white to off-white lotion base consisting of diisopropyl adipate, octyldodecanol, ceteth-20, poloxamer 407, cetyl alcohol, stearyl alcohol, propylparaben, butylparaben, propylene glycol, glycerin, carbomer homopolymer, sodium hydroxide, and water.

#16 How Supplied/storage and Handling

The net content is revised from 60 mL to 60 mL (59 g).

16. HOW SUPPLIED/STORAGE AND HANDLING

ULTRAVATE lotion, 0.05 % is white to off-white lotion. It is supplied in an oval tapered white high-density polyethylene bottle with a white polypropylene disc cap. Each bottle contains 60 mL (59 g) of ULTRAVATE lotion.

NDC 10631-122-04

60 mL (59g) bottle

Store at 25°C (77°F); excursions permitted to 15°C and 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Do not freeze.

2. Labels

60 mL (59 g) Bottle

The net content is revised from *60 mL* to *60 mL (59 g)*. The ingredients in  ^{(b) (4)} is revised to *Each gram*. The maximum dosage is *50 grams per week*.



60 mL (59 g) Carton

The net content is revised from *60 mL* to *60 mL (59 g)*. The ingredients in (b) (4) is revised to *Each gram*. The maximum dosage is *50 grams per week*.

(b) (4)

2 mL (2 g) Sample (b) (4) label

The net content is revised from 2 mL to 2 mL (2 g). The maximum dosage is 50 grams per week.



2 mL(2 g) Sample (b) (4) Carton Label

The net content is revised from 2 mL to 2 mL (2 g).

(b) (4)

Reviewer's Assessment and Signature:

The final label and labeling submitted on October 29, 2015 are satisfactory from ONDP perspective.

Reviewer's Signature:

Hitesh Shroff, Ph.D.

Branch V

Division of New Drug Products II/ONDP

**Hitesh N.
Shroff -S**

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Secondary Review Comments and concurrence:

Moojhong Rhee -S

Supervisor's Signature:

Moo-Jhong Rhee, Ph.D.

Branch V

Division of New Drug Products II/ONDP

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Recommendation: This 505(b)(2) NDA is recommended for **APPROVAL** with the expiration dating period of 24 months recommended for the drug product.

NDA 208183 Review #1

Drug Name/Dosage Form	Halobetasol propionate lotion
Strength	0.05%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Femdale Laboratories, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original submission	December 23, 2014
Amendment	29-MAY-2015
Amendment	26-August-2015
Amendment	03-SEP-2015
Amendment	28-SEP-2015
Amendment	29-Sep-2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sam Bain	Branch II/Division of New Drug API
Drug Product	Hitesh Shroff	Branch V/Division of New Drug Products II
Process	Xueli Zhu	Branch VIII/Division of Process Assessment III
Microbiology	Neal Sweeney	Branch II/Division of Microbiology Assessment
Facility	Denise M. DiGiulio	Branch II/Division of Inspection Assessment
Biopharmaceutics	Vidula Kolhatkar	Branch II/Division of Biopharmaceutics
Project/Business Process Manager	Melinda Bauerlien	Branch I/Division of Regulatory and Business Process Management
Application Technical Lead	Yichun Sun	Branch V/Division of New Drug Products II
Laboratory (OTR)	NA	NA
ORA Lead	Paul Perdue	Division of Medical Products & Tobacco Operations
Environmental Assessment (EA)	N/A	NA

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Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION:
2. RELATED/SUPPORTING DOCUMENTS:
 - A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE D	STATUS ¹	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate	04-AUG-2015	N/A
	Type III (if applicable)			N/A	N/A	N/A
	Type III			N/A	N/A	N/A
	Type III			N/A	N/A	N/A
	Type III			N/A	N/A	N/A

¹ Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
EOP2 meeting minutes	(b) (4)	Discussion of the clinical development plan for IND (b) (4)
Pre-NDA meeting minutes		Discussion of the planned NDA submission for halobetasol propionate lotion, 0.05%
Letter of authorization	NDA 19967	Ranbaxy authorizes the FDA to refer to all relevant data in their approved NDA 019967 for Ultravate [®] (halobetasol propionate) Cream, 0.05% in support of the submission for Halobetasol Propionate Lotion, 0.05% by Ferndale Laboratories, Inc.
Letter of authorization	NDA 19968	Ranbaxy authorizes the FDA to refer to all relevant data in their approved NDA 019967 for Ultravate [®] (halobetasol propionate) Ointment, 0.05% in support of the submission



QUALITY ASSESSMENT
A/NDA # 208183



		for Halobetasol Propionate Lotion, 0.05% by Ferndale Laboratories, Inc.
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3. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	----	N/A	----	----
Pharmacology/Toxicology	----	N/A	----	----
CDRH	----	N/A	----	----
Clinical	----	N/A	----	----
Other	----	N/A	----	----

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has provided sufficient CMC information to assure the identity, purity, strength and quality of the drug substance and drug product.

The facility review team from the Office of Facility and Process has issues "Approval" recommendation for the facilities involved in this application.

The issues on labels/labeling are completely resolved at this time.

Therefore, from the OPQ perspective, this NDA is recommended for approval with the expiration dating period of 24 months.

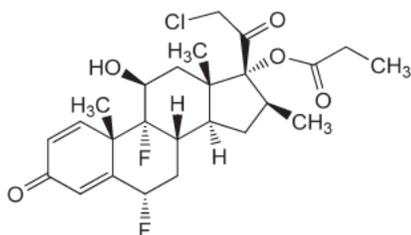
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

The drug substance/active pharmaceutical ingredient (API) used in the drug product, (halobetasol propionate lotion), is halobetasol propionate. The drug substance is chemically produced (b) (4). The chemical name of halobetasol propionate is: 21-Chloro-6 α ,9-difluoro-11 β ,17-dihydroxy-16 β -methylpregna-1,4-diene-3,20-dione 17-Propionate. It has the following structural formula:



Halobetasol propionate is a white to off-white crystalline powder with a molecular weight of 484.96 and a molecular formula of C₂₅H₃₁ClF₂O₅. It is practically insoluble in water and freely soluble in dichloromethane and in acetone. Halobetasol propionate is packaged in (b) (4) bottles. (b) (4)

(b) (4) Detailed CMC information for halobetasol propionate is referred to DMF # (b) (4). The DMF has been reviewed and found adequate in supporting (b) (4)

the use of the drug substance in the NDA. The recommended retest period for halobetasol propionate is (b) (4) months when stored (b) (4) .

B. Drug Product [Established Name] Quality Summary

The drug product, ULTRAVATE (halobetasol propionate) Lotion, is an (b) (4) containing 0.05% (w/w) halobetasol propionate. Halobetasol propionate is a corticosteroid indicated for the topical treatment of plaque psoriasis in patients eighteen (18) years of age and older. The drug product is a white to off-white lotion. Each gram of ULTRAVATE Lotion contains 0.5 mg of halobetasol propionate in a lotion (b) (4) consisting of diisopropyl adipate, octyldodecanol, ceteth-20, poloxamer 407, cetyl alcohol, stearyl alcohol, propylparaben, butylparaben, propylene glycol, glycerin, carbomer homopolymer, sodium hydroxide, and water.

The lotion is prepared by (b) (4)



The identity, strength, purity including microbial limits, and quality of the drug product are deemed assured by the drug product specification. An in vitro release test (IVRT) of halobetasol propionate lotion has not been developed and validated.

The expiration dating period of 24 months is recommended for the drug product when stored at 20 - 25°C based on the 18-month long-term and 6-month accelerated stability data obtained from 3 registration batches of the drug product.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	ULTRAVATE
Non Proprietary Name of the Drug Product	Halobetasol propionate lotion

Non Proprietary Name of the Drug Substance	Halobetasol propionate
Proposed Indication(s) including Intended Patient Population	ULTRAVATE Lotion is a corticosteroid indicated for the topical treatment of plaque psoriasis in patients eighteen (18) years of age and older.
Duration of Treatment	2 consecutive weeks.
Maximum Daily Dose	Apply a thin layer of ULTRAVATE Lotion to the affected skin twice daily (b) (4) for up to two weeks and rub in gently. Do not use with occlusive dressings unless directed by a physician.
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Classification:

- Drug Substance: N/A
- Drug Product: N/A

2. Biowaivers/Biostudies

- Biowaiver Requests: N/A
- PK studies: N/A
- IVIVC: N/A
- IVRT:

The applicant submitted IVRT method development and validation reports which are not complete per the Agency's standard. An advice letter was sent to the applicant regarding the IVRT method development. The Agency recommend that the applicant continue work on the development and validation of the IVRT method. Once the method development and validation are complete, the applicant needs to test the production batches with that method and propose to the Agency an IVRT release specification based on the data from at least 6 production batches. The applicant is expected to report in vitro release data that support the selection of their IVRT method parameters (paddle speed, synthetic membrane, receptor medium, and sampling time points) to the Agency at their earliest convenience, but by the first Annual Report time being the latest.

E. Novel Approaches

N/A

F. Any Special Product Quality Labeling Recommendations

Protect from freezing.

G. Process/Facility Quality Summary (see Attachment A)

H. Life Cycle Knowledge Information (see Attachment B)



**QUALITY ASSESSMENT
A/NDA # 208183**



Application Technical Lead's Assessment and Signature

The NDA is recommended for approval from quality perspective.

Yichun Sun, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
10/13/2015

Yichun
Sun -S

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ASSESSMENT OF THE BIOPHARMACEUTICS

18. Are the in-vitro dissolution test and acceptance criteria adequate for assuring consistent bioavailability of the drug product?

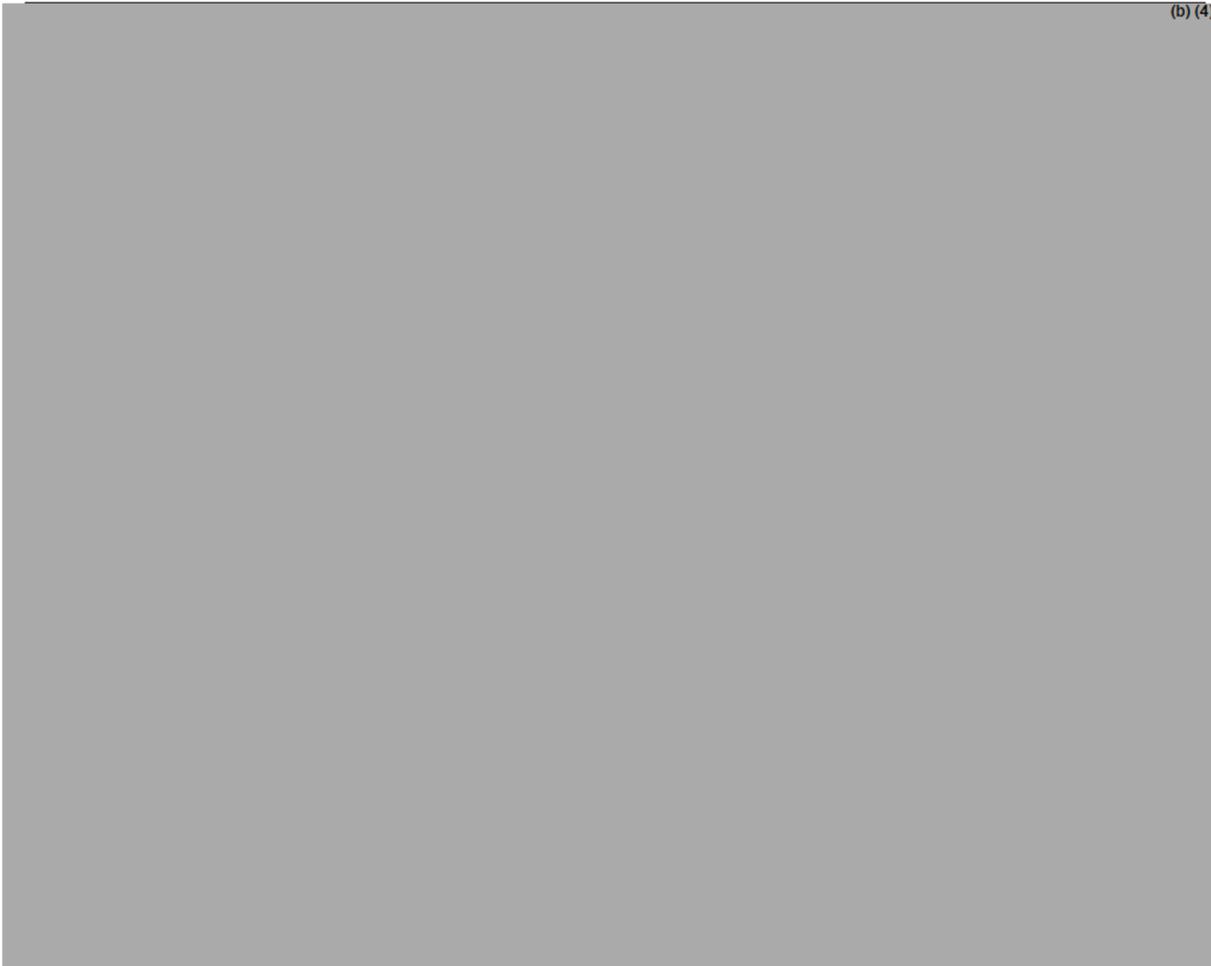
The applicant did not submit in vitro release testing data for this product. The Division of Biopharmaceutics recommended that the applicant develop and validate an in vitro release testing method for the drug product and propose in vitro release acceptance criteria. The applicant submitted information supporting their in vitro release method in the amendments received August 26 and September 03, 2015.

19. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

The formulation used in all seven of the clinical studies is the same formulation that will be used for the to-be-marketed product.

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

(b) (4)



OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS**Reviewer's Assessment and Signature:**

Additional data are needed for the IVRT method validation. The adequacy of the proposed IVRT method and proposed in vitro release acceptance criteria will not affect the approvability of this NDA.

The applicant did not propose any IVRT specification for release and stability. The applicant submitted IVRT method development and validation reports which are not complete per the Agency's standard. We recommend that the sponsor continue work on the development and validation of the IVRT method, specifically addressing the Agency's concerns listed below. Once the method development and validation are complete, the applicant should test the production batches with that method and propose to the Agency an IVRT release specification based on the data from at least 6 production batches. The sponsor is expected to report the results to the Agency at their earliest convenience, but by the first Annual Report time being the latest.

The following comments were conveyed to the Applicant in an Advice letter:

You did not propose any IVRT specification for release and stability. You submitted IVRT method development and validation reports which are not complete per the Agency's standard. We recommend that you continue work on the development and validation of the IVRT method. Once the method development and validation are complete, you need to test the production batches with that method and propose to the Agency an IVRT release specification based on the data from at least 6 production batches. You are expected to report in vitro release data that supports the selection of your IVRT method parameters (paddle speed, synthetic membrane, receptor medium, and sampling time points) to the Agency at your earliest convenience, but by the first Annual Report time being the latest. Ensure that you provide the in vitro release data in the appropriate units (e.g. mcg/cm² for amount of drug released per unit membrane area, and mcg/cm²/hr^{1/2} for release rate).

Reviewer's Signature

Vidula Kolhatkar, Ph.D.
Branch II
Division of Biopharmaceutics/ONDP
9/25/2015

Vidula R.
Kolhatkar -S

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Supervisor Comments and Concurrence:

I have reviewed the Biopharmaceutics Assessment and concur with the Reviewer's conclusions.

Supervisor's Signature

Kelly Kitchens, Ph.D.
QAL, Branch II
Division of Biopharmaceutics/ONDP
9/25/2015

Kelly M.
Kitchens -S

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ASSESSMENT OF MICROBIOLOGY

20. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Antimicrobial Effectiveness Test (AET) – Formulation containing 75% of the theoretical levels of butylparaben and propylparaben (b) (4) content (b) (4) 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 (b) (4) 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 day 14, 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.

-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.

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.

(b) (4)

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 **Specifications** and **Stability** sections below.

Drug Product Specifications**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/manufacture (1) performs routine environmental monitoring in the manufacturing and packaging areas, (2) tests (b) (4) water (b) (4)

[Redacted]

-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.

Stability

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

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°C ± 2°C/60% RH ± 5% RH storage conditions) includes the following product quality microbiology-related test stations:

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

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

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.

Applicant’s Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer’s Assessment: The information provided in support of drug product quality microbiology for NDA 208183/N000 is acceptable.

2.3.P.6 Reference Standards or Materials

21. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: N/A From a quality microbiology perspective container closure is not a critical attribute for non-sterile topical dosage forms.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

22. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: No materials are obtained or derived from animal sources.

23. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:
There were no quality microbiology deficiencies identified in the information



**QUALITY ASSESSMENT
A/NDA # 208183**



provided. The application is recommended for approval from a quality microbiology perspective.

Reviewer's Signature

**Neal J. Sweeney, Ph.D.
Acting Microbiology Quality Assessment Lead
Branch II
Division of Microbiology Assessment/OPF
8/23/15**

**Neal J.
Sweeney
-S**

Digitally signed by Neal J. Sweeney -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300109587, cn=Neal J. Sweeney -S
Date: 2015.10.16 13:54:30 -04'00'

Supervisor Comments and Concurrence:

I concur with the recommendation for approval.

Supervisor's Signature

**Bryan S. Riley, Ph.D.
Acting Chief, Branch II
Division of Microbiology Assessment/OPF
9/4/2015**

**Bryan S.
Riley -S**

Digitally signed by Bryan S. Riley -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Bryan S. Riley -S, 0.9.2342.19200300.100.1.1=1300138775
Date: 2015.10.15 19:52:17 -04'00'

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

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

a) Carton and Container Labels

Immediate container label for 60 ml bottle



Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The drug product name is presented correctly. Satisfactory
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Displayed 0.05% is presented correctly Satisfactory
Net contents (21 CFR 201.51(a))	Displayed correctly Satisfactory
“Rx only” displayed prominently on the main panel	The statement is displayed prominently Satisfactory
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	NDC number is displayed as NDC 10631-122-04 Satisfactory
Lot number and expiration date (21 CFR 201.17)	Displayed Satisfactory
Storage conditions	Storage condition is displayed correctly. Satisfactory
Bar code (21CFR 201.25)	Barcode is displayed. Satisfactory
Name of manufacturer/distributor	The name of manufacturer is displayed correctly. Satisfactory
And others, if space is available	N/A

Evaluation: Adequate.

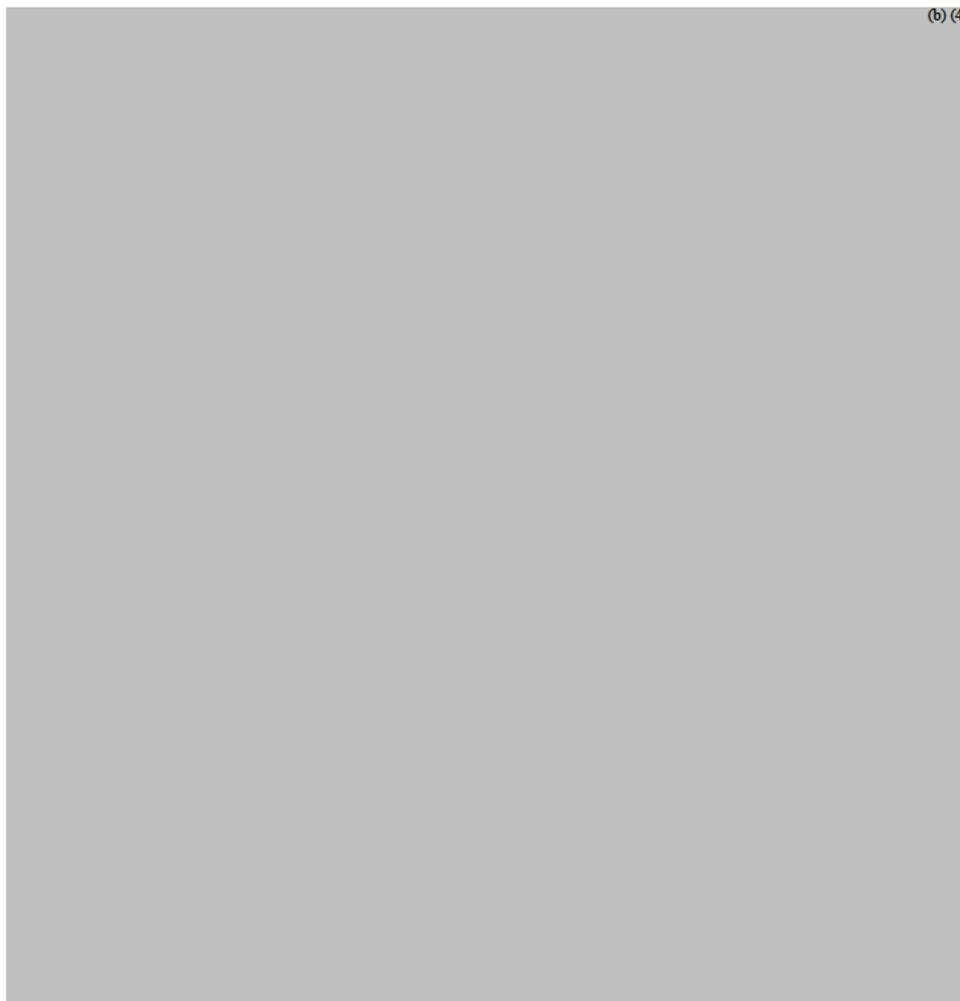
Immediate container label for 2 ml samples



Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The drug product name is presented correctly. Satisfactory
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Displayed 0.05% is presented correctly Satisfactory
Net contents (21 CFR 201.51(a))	Displayed correctly. Satisfactory
“Rx only” displayed prominently on the main panel	The statement is displayed prominently Satisfactory
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	NDC number is displayed as NDC 10631-122-XX Satisfactory
Lot number and expiration date (21 CFR 201.17)	Printed on tube crimp. Satisfactory
Storage conditions	Storage condition is displayed correctly. Satisfactory
Bar code (21CFR 201.25)	No required for samples. Satisfactory
Name of manufacturer/distributor	The name of manufacturer is displayed correctly. Satisfactory
And others, if space is available	N/A

Evaluation: Adequate.

60 ml Container Carton label

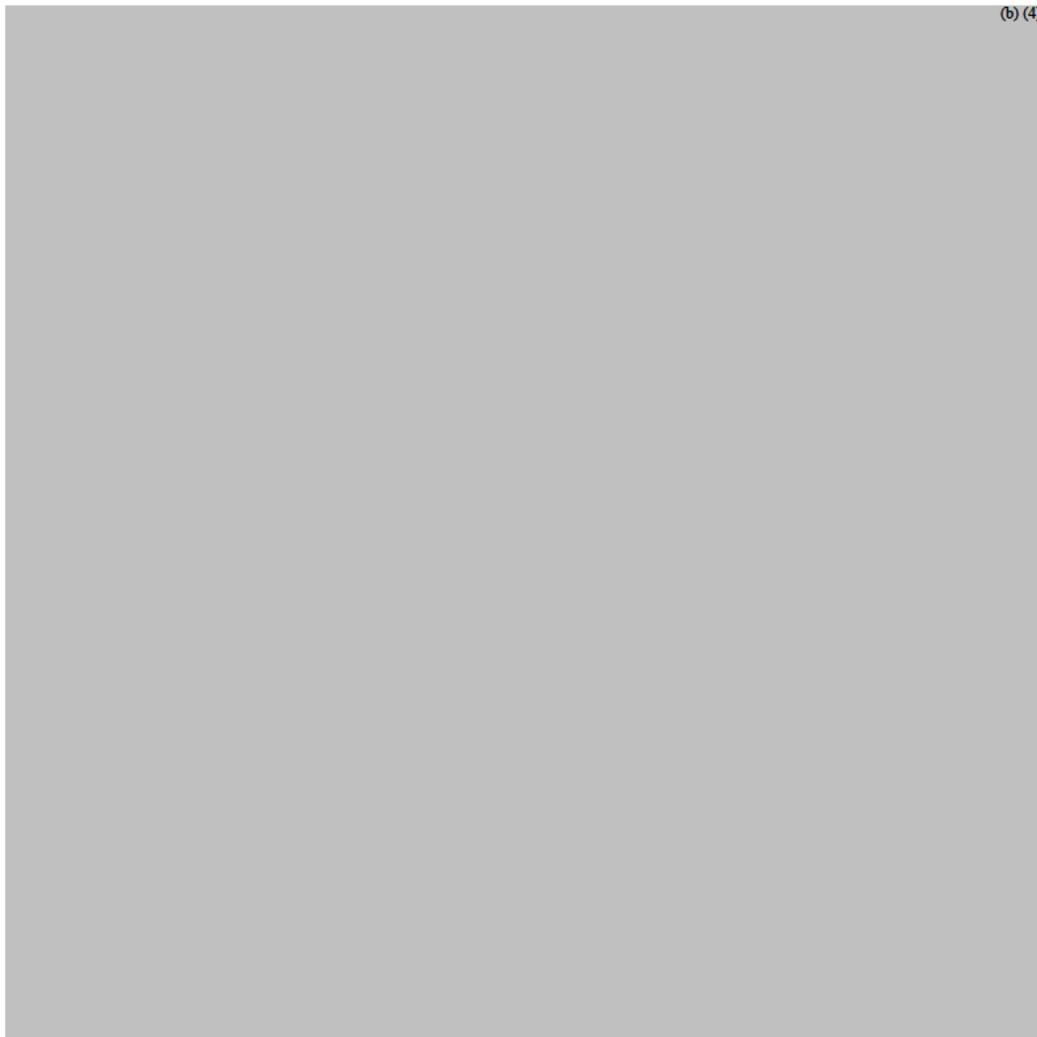


Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size, prominence) (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	The drug product name is presented correctly. Satisfactory
Dosage strength (21CFR 201.10(d)(1), 21CFR 201.100(b)(4))	Dosage strength as 0.05% is presented correctly Satisfactory
Net quantity of dosage form (21 CFR 201.51(a))	Displayed correctly. Satisfactory
“Rx only” displayed prominently on the main panel (21 CFR 201.100 (b)(1))	The statement is prominently displayed. Satisfactory
Expiration date and lot number (21 CFR 201.17 and 21 CFR 201.18)	A space is allocated for this information. Satisfactory
Storage conditions	Storage condition is correctly described. Satisfactory
Bar code (21CFR 201.25)	Is displayed Satisfactory
NDC number (21 CFR 201.2, 21 CFR	NDC number is indicated as 10631-122-04.

207.35(b)(3)(i)	Satisfactory
Manufacturer/distributor's name 21CFR201.1(a)	The name of manufacturer is correctly described. Satisfactory
The list of inactive ingredients, 21CFR 201.10(a), if not oral dosage form; and quantitative ingredient information, if parenteral injection. 21CFR 201.100(b)(5)(iii)	The inactive ingredients are displayed correctly. Satisfactory
Statement of being sterile (if applicable)	N/A
"See package insert for dosage information" (21 CFR 201.55)	This statement is displayed as "See package insert for complete prescribing information" Satisfactory
"Keep out of reach of children" (Required for OTC but Optional for Rx drugs)	N/A
Route of Administration (21 CFR 201.100(b))	Indicated as "For external use only. Not for eye use." Satisfactory

Evaluation: Adequate.

2 ml Sample Container Carton label



Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size, prominence) (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	The drug product name is presented correctly. Satisfactory
Dosage strength (21CFR 201.10(d)(1), 21CFR 201.100(b)(4))	Dosage strength as 0.05% is presented correctly Satisfactory
Net quantity of dosage form (21 CFR 201.51(a))	Displayed correctly. Satisfactory
“Rx only” displayed prominently on the main panel (21 CFR 201.100 (b)(1))	The statement is prominently displayed. Satisfactory
Expiration date and lot number (21 CFR 201.17 and 21 CFR 201.18)	A space is allocated for this information. Satisfactory
Storage conditions	Storage condition is correctly described. Satisfactory
Bar code (21CFR 201.25)	Is displayed Satisfactory
NDC number (21 CFR 201.2, 21 CFR 207.35(b)(3)(i))	NDC number is indicated as 10631-122-XX. Satisfactory
Manufacturer/distributor's name (21CFR201.1(a))	The name of manufacturer is correctly described. Satisfactory
The list of inactive ingredients, 21CFR 201.10(a), if not oral dosage form; and quantitative ingredient information, if parenteral injection. 21CFR 201.100(b)(5)(iii)	The inactive ingredients are displayed correctly. Satisfactory
Statement of being sterile (if applicable)	N/A
“See package insert for dosage information” (21 CFR 201.55)	This statement is displayed as “See package insert for complete prescribing information” Satisfactory
“Keep out of reach of children” (Required for OTC but Optional for Rx drugs)	N/A
Route of Administration (21 CFR 201.100(b))	Indicated as “For external use only. Not for eye use.” Satisfactory

Evaluation: Adequate.

Labeling Review

The following is a summary of the labeling review.

1. Package Insert

(a) “Highlights” Section (21CFR 201.57(a))

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ULTRAVATE® lotion safely and effectively. See full prescribing information for ULTRAVATE lotion.

ULTRAVATE (halobetasol propionate) lotion
Initial U.S. Approval: 1990

-----DOSAGE FORMS AND STRENGTHS-----
Lotion: 0.05% (0.5 mg/mL). (3)

Item	Information Provided in NDA	Reviewer’s Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	ULTRAVATE (halobetasol propionate) Lotion	The proprietary name and established names are displayed correctly Satisfactory
Dosage form, route of administration	Lotion	Dosage form described as lotion is correct. However, the route of administration for lotion is understood to be topical therefore it is not required to be displayed. Satisfactory
Controlled drug substance symbol (if applicable)		Not applicable
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Lotion, 0.05% (0.5 mg/g),	The dosage form as lotion and strength as 0.05% are described correctly. Satisfactory
Whether the drug product is scored (If the product is not scored, do not say “not scored.”)		The product is not scored.

Evaluation: Satisfactory.

(b) “Full Prescribing Information” Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

3. DOSAGE FORMS AND STRENGTHS

ULTRAVATE (halobetasol propionate) lotion, 0.05% is a white to off-white lotion. Each (b) (4) of ULTRAVATE lotion contains 0.5 mg of halobetasol propionate.

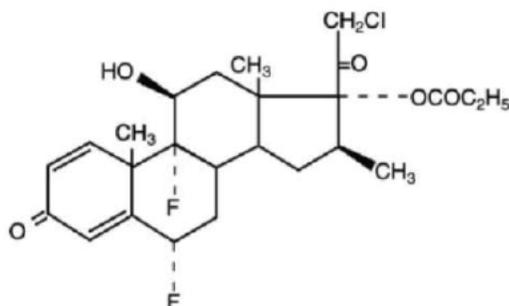
Item	Information Provided in NDA	Reviewer’s Assessment
Available dosage forms	lotion	Dosage form described correctly as lotion. Satisfactory
Strengths: in metric system	0.05%. Each (b) (4) of ULTRAVATE lotion contains 0.5 mg of halobetasol propionate	The strength is described correctly. Satisfactory
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	White of off white lotion	The lotion is described correctly. Satisfactory

Evaluation: Satisfactory.

#11: Description (21CFR 201.57(c)(12))

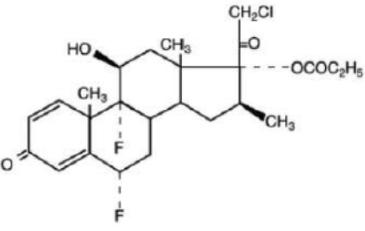
11. DESCRIPTION

ULTRAVATE (halobetasol propionate) lotion, 0.05% for topical use contains a corticosteroid, halobetasol propionate. The chemical name of halobetasol propionate is 21-chloro-6 α , 9-difluoro-11 β , 17-dihydroxy-16 β -methylpregna-1, 4-diene-3-20-dione, 17-propionate. Halobetasol propionate is a white to off-white crystalline powder with a molecular weight of 484.96 and a molecular formula of C₂₅H₃₁ClF₂O₅. It is practically insoluble in water and freely soluble in dichloromethane and in acetone. It has the following structural formula:



Each (b) (4) of ULTRAVATE lotion contains 0.5 mg of halobetasol propionate in a white to off-white lotion base consisting of diisopropyl adipate, octyldodecanol, ceteth-20, poloxamer 407, cetyl alcohol, stearyl alcohol, propylparaben, butylparaben, propylene glycol, glycerin, carbomer homopolymer, sodium hydroxide, and water.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	ULTRAVATE (halobetasol propionate) lotion, 0.05 %	The drug product name described properly. Satisfactory
Dosage form and route of administration	lotion	Satisfactory
Active moiety expression of strength with equivalence statement for salt (if applicable)		N/A
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Inactive ingredients are listed as follows: of diisopropyl adipate, octyldodecanol, ceteth-20, poloxamer 407, cetyl alcohol, stearyl alcohol, propylparaben, butylparaben, propylene glycol, glycerin, carbomer homopolymer, sodium hydroxide, and water	Information for inactive ingredients is provided correctly. Satisfactory
Statement of being sterile (if applicable)		Not applicable
Pharmacological/ therapeutic class	corticosteroid	Pharmacological class is correctly described. Satisfactory

<p>Chemical name, structural formula, molecular weight</p>	<p>Chemical Name: 21-chloro-6α, 9-difluoro-11β, 17-dihydroxy-16β-methylpregna-1, 4-diene-3-20-dione, 17-propionate</p> <p>Its empirical formula is C₂₅H₃₁ClF₂O₅ and its structural formula is:</p> 	<p>The chemical name and the structural formula are correct.</p> <p>Satisfactory</p>
<p>If radioactive, statement of important nuclear characteristics.</p>		<p>Not applicable</p>
<p>Other important chemical or physical properties (such as pKa, solubility, or pH)</p>	<p>Halobetasol propionate is a white to off-white crystalline powder with a molecular weight of 484.96 and a molecular formula of C₂₅H₃₁ClF₂O₅. It is practically insoluble in water and freely soluble in dichloromethane and in acetone.</p>	<p>The appearance and the solubility of the drug substance in various solvents is described.</p> <p>Satisfactory</p>

Evaluation: Satisfactory.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16. HOW SUPPLIED/STORAGE AND HANDLING

ULTRAVATE lotion, 0.05 % is white to off-white lotion. It is supplied in an oval tapered white high-density polyethylene bottle with a white polypropylene disc cap. Each bottle contains 60 mL of ULTRAVATE lotion.

NDC xxxx-yyy-zz 60 mL bottle

Store at 25°C (77°F); excursions permitted to 15°C and 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Do not freeze.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Lotion, 0.05 %	This information is provided. Satisfactory
Available units (e.g., bottles of 100 tablets)	60 ml bottle	This information is provided correctly. Satisfactory
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Whit to off-white color NDC xxxx-yyyy-zz	The lotion color is provided but the NDC numbers will be provided. Satisfactory
Special handling (e.g., protect from light, do not freeze)	(b) (4)	Information provided. Satisfactory
Storage conditions	Store at 25°C (77°F); excursions permitted to 59°F and 86°F (15°C to 30°C) [see USP Controlled Room Temperature].	Information provided correctly. Satisfactory

Evaluation: Satisfactory.

Manufacturer/distributor name listed at the end of PI, following Section #17

Manufactured for Ranbaxy Laboratories, Inc., Jacksonville, FL 32257

By: Ferndale Laboratories, Inc., Ferndale MI 48220

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured by Ranbaxy Laboratories, Inc. By: Ferndale Laboratories, Inc. Ferndale MI 48220	Information provided. Satisfactory

II. List of Deficiencies To Be Communicated

- A. Drug Substance: None.
- B. Drug Product: None.
- C. Process/FacilityL: None.
- D. Biopharmaceutics: None.
- E. Microbiology: None.
- F. Label/Labeling: None.



**QUALITY ASSESSMENT
A/NDA # 208183**



III. Attachments

A. Facility

OVERALL RECOMMENDATION:				
DRUG SUBSTANCE				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
(b) (4)				
DRUG PRODUCT				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
(b) (4)	Ferndale Lab	1811212	high	acceptable
(b) (4)				

B. Facility

OVERALL RECOMMENDATION: “Approve” recommendation was entered in Panorama on Aug 24, 2015.

Facility Alerts

This report displays the Alerts associated with facilities on the selected applications
Time run: 9/23/2015 3:59:40 PM

Facility FEI	Facility DUNS	Issue Name	Alert Type	Status	Entry Date	Entered By
(b) (4)	(b) (4)	OAI/POAI Alert:	Potential Official Action Indicated	NEW	4/1/2015	MERIDETH ROSE

Facility Status View for NDA 208183 Original 1

Displays information for the facilities that are associated to NDA 208183 Original 1. It also shows the Overall Manufacturing Inspection Recommendation for the application and the associated OPF Facility Recommendations.
Time run: 9/23/2015 3:59:40 PM

Overall Manufacturing Inspection Recommendations for NDA 208183 Original 1

Project Name	Sponsor Name	Overall Manufacturing Inspection Recommendation	Overall Manufacturing Inspection Task Status	Overall Manufacturing Inspection Recommendation Task Completion Date
NDA 208183-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)	FERNDALE LABORATORIES INC	Approve	Complete	8/24/2015

OPF Facility Recommendations for Facilities on NDA 208183 Original 1



QUALITY ASSESSMENT

A/NDA # 208183



Project Name	FEI	DUNS	Facility Name	Profile	OPF Facility Recommendation	OPF Facility Recommendation Task Status	OPF Facility Recommendation Task Completion Date
(b) (4)							
NDA 208183-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)	1811212	005320536	FERNDALDE LABORATORIES INC.	(b) (4)	Approve Facility	Complete	8/24/2015
(b) (4)							

C. Lifecycle Knowledge Management

a) Drug Product

Risk Assessment:

Risk Assessment for halobetasol propionate Lotion, 0.05%

Product Attribute/CQA	Factors that can impact the CQA	FMECA RPN Number	Justification	Risk Mitigation Approach	Final Risk
Assay (halobetasol propionate)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	L	The content of the drug substance in bulk drug product, at release and during stability studies is determined using an HPLC or UPLC method.	The HPLC/UPLC method for DS assay is commonly used for assay determination. It is adequately validated for precision, accuracy, linearity, and selectivity. There are no interfering peaks from degradants in the chromatogram. It is deemed to be stability indicating method.	The drug product is expected to be safe for topical administration during the entire shelf life from product quality perspective. Low to None
Impurities and degradation products	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	L	The impurities of the drug substance are determined using an UPLC method at release and during stability studies.	The HPLC/UPLC method for degradants assessment is adequately validated for precision, accuracy, linearity, robustness, specificity, LoD and LoQ. The degradants peaks were well separated in the chromatogram. It is deemed to be stability indicating method.	The impurities in the drug products are controlled and are within the acceptance limits at release and storage. The drug product should be safe for topical administration (b) (4) months at room temperature. Low to None

content (Butylparaben and Propylparaben)	(b) (4) <ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	L	Butylparaben and propylparaben are used as (b) (4). The level of the (b) (4) is monitored by an HPLC or UPLC method at release and during stability studies.	The (b) (4) effectiveness tests were performed to determine the final amounts of (b) (4). The HPLC/UPLC method for DS assay and (b) (4) contents is commonly used for assay determination. It is adequately validated for precision, accuracy, linearity, and selectivity. There are no interfering	The (b) (4) levels are accurately measured and controlled at release and stability. Low to None
Microbial Limits	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	M	Butylparaben and propylparaben are used as (b) (4) Microbial limit tests are included in the drug product specifications used for the bulk drug product, at release and during stability studies.	The antimicrobial (b) (4) effectiveness (PET) tests were performed per USP <51> and microbial limits testing was performed per USP <61> and USP <62>.	The microbial contaminants are within the acceptance limits at the DP release and during stability testing as indicated by three registration batches Low to None

pH	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	M	pH of the drug product is monitored for the bulk drug product, at release and during stability studies.	pH is measured by an analytical method with a pH meter per USP <791>. The pH is controlled by DP release and stability specification.	The pH is well controlled by DP specification. Low to None
Apparent Viscosity (cps)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	M	Apparent viscosity of the drug product is monitored for the bulk drug product, at release and during stability studies. The clinical performance of the drug product can be affected by the viscosity of the lotion.	The viscosity is measured using a viscometer. The viscosity is controlled by release and stability specification. The viscosity remained within the acceptance level in the registration batches.	The viscosity is controlled during release and storage by DP specification. Low to None
Droplet Size	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	M	Droplet size of the drug product is monitored for the bulk drug product, at release and during stability studies. The clinical performance of the drug product can be affected by the viscosity of the lotion, which is related to the droplet size of the (b) (4).	The droplet size is controlled by DP specification.	Low to None
Minimum Fill	<ul style="list-style-type: none"> • Process parameters • Scale/equipment • Site 	L	Conform to USP <755>	This test is performed per USP <755>.	Low to None

IV. Administrative

A. Reviewer's Signature

B. Endorsement Block

Reviewer Name/Date: [*Same date as draft review*]

Secondary Reviewer Name/Date:

Project Manager Name/Date: