

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209354Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

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

Date: February 20, 2019
From: Hamid Shafiei, 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 209354

Subject: Final Recommendation for NDA 209354

At the time when the CMC Review #1 was completed on April 13, 2018, the CMC label/labeling issues were not completely resolved and therefore, the application was not recommended for approval from the label/labeling perspective.

The applicant submitted an amendment on February 11, 2019, to address the pending label/labeling issues. The drug product reviewer, Dr. Carolyne Strasinger has reviewed this amendment and has noted that the pending label-labeling issues have been satisfactorily resolved and recommended the approval of this application.

Recommendation:

This NDA is now recommended for Approval from the OPQ perspective.

Application Technical Lead's Assessment and Signature

The NDA is recommended for Approval from the OPQ perspective.

Hamid Shafiei, Ph.D.
Application Technical Lead,
Branch V, Division of New Drug Products II
February 20, 2019



Hamid
Shafiei

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Memorandum

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

Date: February 20, 2019

From: Caroline Strasinger, Ph.D.
Reviewer, 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: Labeling Review #1 of NDA 209354

Subject: Final Recommendation

Labeling Review #1 had noted the following pending issues:

Regarding the Carton and Container

Adjust the font size and prominence of the proprietary name to established name to be consistent with 21 CFR 201.10(g)(2) for all primary container (tube) and carton configurations.

Because of the above deficiency in Labeling Review #1, this NDA was not recommended for approval from the labeling perspective.

On February 11, 2019, the deficiency was agreed to by the applicant. Updated carton and containers were submitted. A representative carton is included as an attachment below.

OVERALL ASSESSMENT AND RECOMMENDATION:

This NDA is now recommended for approval from the labeling perspective.

LABELING

R. Regional Information

I. Package Insert

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

1) Title

DUOBRII (halobetasol propionate and tazarotene) Lotion, (b) (4) for topical use
Initial U.S. Approval: XXXX

2) DOSAGE FORMS AND STRENGTHS

Lotion: 0.01%/0.045% (3)

Each gram of DUOBRII Lotion contains 0.1mg (0.01%) halobetasol propionate and 0.45 mg (0.045%) tazarotene. (3)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Drug name (201.57(a)(2))		
Proprietary name and established name	Duobrii Established Name: halobetasol propionate and tazarotene lotion	Adequate
Dosage form, route of administration	Dosage: lotion Route: for topical use	Adequate
Controlled drug substance symbol (if applicable)		NA
Dosage Forms and Strengths (201.57(a)(8))		
Summary of dosage form and strength	Lotion, 0.01%/0.045%	Adequate

Reviewer Assessment: **ADEQUATE**

2. "FULL PRESCRIBING INFORMATION

#3: DOSAGE FORM AND STRENGTHS

3 DOSAGE FORMS AND STRENGTHS

Lotion: 0.01%/0.045%

Each gram of DUOBRII Lotion contains 0.1 mg (0.01%) halobetasol propionate and 0.45 mg (0.045%) tazarotene in a white to off-white lotion.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Available dosage forms	Lotion	Adequate
Strengths: in metric system	0.01%/0.045%	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	0.1 mg (0.01%) 0.45 mg (0.045%)	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	White to off-white lotion	Adequate

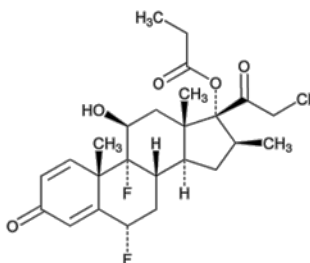
Reviewer Assessment: ADEQUATE

#11: DESCRIPTION

11 DESCRIPTION

DUOBRII Lotion is a combination product with halobetasol propionate and tazarotene as the active ingredients in a white to off white lotion formulation intended for topical use.

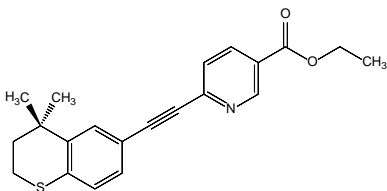
Halobetasol propionate is a synthetic corticosteroid. The chemical name for halobetasol propionate is [(6S,9R,16S,17R)-17-(2-chloroacetyl)-6,9-difluoro-11-hydroxy-10,13,16-trimethyl-3-oxo-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-17-yl] propanoate. The structural formula for halobetasol propionate is represented below:



Molecular Formula: $C_{25}H_{31}ClF_2O_5$ Molecular Weight: 484.96

Tazarotene is a member of the acetylenic class of retinoids. The chemical name for tazarotene is 6-[(3,4-dihydro-4,4-dimethyl-2H-1-benzothiopyran-6-yl)ethynyl]-3-pyridinecarboxylic acid ethyl ester. The structural formula for tazarotene is represented below:

Tazarotene:



Molecular Formula: C₂₁H₂₁NO₂S Molecular Weight: 351.46

Each gram of DUOBRII Lotion contains 0.1 mg (0.01%) halobetasol propionate and 0.45 mg (0.045%) tazarotene in a white to off-white lotion base consisting of carbomer copolymer type B, carbomer homopolymer type A, diethyl sebacate, edetate disodium dihydrate, light mineral oil, methylparaben, propylparaben, purified water, sodium hydroxide, sorbitan monooleate and sorbitol solution, 70%.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name	DUOBRII Lotion halobetasol propionate and tazarotene	Adequate
Dosage form and route of administration	lotion; for topical use	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	N/A	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	carbomer copolymer type B, carbomer homopolymer type A, diethyl sebacate, edetate disodium dihydrate, light mineral oil, methylparaben, propylparaben, purified water, sodium hydroxide, sorbitan monooleate and sorbitol solution, 70%.	Adequate (ingredients are correctly listed in alphabetical order)
Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	corticosteroid/retinoid	Adequate
Chemical name, structural formula, molecular weight	Structure, molecular weight, formula presented	Adequate
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa or pH)	White to off-white lotion	Adequate

Reviewer Assessment: ADEQUATE

#16: HOW SUPPLIED/STORAGE AND HANDLING

16 HOW SUPPLIED/STORAGE AND HANDLING

DUOBRII (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045% is a white to off-white lotion supplied in a white aluminum tube as follows:

- 45 g (NDC 0187-0653-45)
- 60 g (NDC 0187-0653-60)
- 100 g (NDC 0187-0653-01)

Storage and Handling Conditions

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from freezing.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Strength of dosage form	0.01%/0.045%	Adequate
Available units (e.g., bottles of 100 tablets)	45 g, 60 g, 100 g	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	white to off-white lotion in a white aluminum tube. NDC numbers present	Adequate
Special handling (e.g., Dispense in tight and light resistant container as defined in USP)	Protect from freezing	Adequate
Storage conditions	Store at 20°C – 25°C (68°F – 77°F); excursions permitted to 15°C-30°C (59°F-86°F) [See USP Controlled Room Temperature]	Adequate
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for:  (b) (4) Bridgewater, NJ 08807	Adequate

Reviewer Assessment: ADEQUATE

II. Labels (Provided November 9, 2018)

1. IMMEDIATE CONTAINER LABEL

The immediate container labels (for a tube) include a 45 g, 60 g, 100 g, and then a 3 g sample tube. The labels are identical except for the Net Wt. amount. The comments below are applicable to all presentations and strengths.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Duobrii (halobetasol propionate and tazarotene) lotion	Inadequate Size and prominence should be adjusted
Dosage strength Active moiety expression of strength with equivalence statement (if applicable), if space is available	0.01% and 0.045%	Adequate
Net contents	3 g, 45 g, 60 g, 100 g	Adequate
“Rx only” displayed prominently on the main panel	Rx only	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Present	Adequate
Lot number and expiration date (21 CFR 201.17)	Place Reserved on crimp	Adequate
Storage conditions Special handling, e.g., “Dispense in tight and light resistant container as defined in USP”.	Store at 20°C – 25°C (68°F – 77°F); excursions permitted to 15°C-30°C (59°F-86°F) [See USP Controlled Room Temperature] Protect from Freezing	Adequate
Bar code (21CFR 201.25)	Present	Adequate
Name of manufacturer/distributor	(b) (4)	Adequate
And others, if space is available	Not for Eye Use	

Reviewer Assessment: INADEQUATE

Adjust the font size and prominence of the proprietary name to established name to be consistent with 21 CFR 201.10(g)(2)

2. CARTON LABELS:

The Applicant proposes a carton for all sizes of tubes and are identical except for Net Wt. amounts. The carton review below is applicable to the sample carton 3 g and 45 g, 60 g, 100 g sizes; a 100 g carton has been provided as an example.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	Duobrii (halobetasol propionate and tazarotene) lotion	Inadequate Size and prominence should be adjusted
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	0.01% and 0.045%	Adequate
Net quantity of dosage form	3 g, 45 g, 60 g, 100 g	Adequate
"Rx only" displayed prominently on the main panel	Displayed on front and back panel	Adequate
Lot number and expiration date	Each end of carton	Adequate
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store at 20°C – 25°C (68°F – 77°F); excursions permitted to 15°C-30°C (59°F-86°F) [See USP Controlled Room Temperature]. Protect from freezing.	Adequate
Bar code (21CFR 201.25)	Side panel	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Multiple panels	Adequate
Manufacturer/distributor's name	Side panel	Adequate
Quantitative ingredient information (injectables) (21 CFR 201.100 (b))	Ingredient list in alphabetical order on side panel	Adequate
Statement of being sterile (if applicable)	NA	Adequate
"See package insert for dosage information"	Side Panel	Adequate
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Side Panel	Adequate

Reviewer Assessment: INADEQUATE

Adjust the font size and prominence of the proprietary name to established name to be consistent with 21 CFR 201.10(g)(2)

III. LIST OF DEFICIENCIES:

Adjust the font size and prominence of the proprietary name to established name to be consistent with 21 CFR 201.10(g)(2) for all primary container (tube) and carton configurations.

IV. OVERALL ASSESSMENT AND RECOMMENDATION:

The Label (container and carton) of NDA 209354 is not adequate.

At this time, the NDA is not recommend for approval from the Label and Labeling Perspective.

Primary Labeling Reviewer Name and Date:

Caroline Strasinger, PhD 16-JAN-2019

OPQ, ONDP, DNDP II, BV

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I agree with Dr. Strasinger's assessment on the labeling and labels and concur with her recommendation that this application is not ready for approval as of this review.

Moo-Jhong Rhee, Ph.D. 16-JAN-2019

Chief, Branch V

DNDP II/ONDP

Integrated Quality Assessment (IQA) for NDA 209354

Office of Pharmaceutical Quality (OPQ)



Executive Summary for NDA 209354

APPEARS THIS WAY ON ORIGINAL

Recommendation:

From the OPQ perspective, this 505(b)(2) NDA is *not* deemed ready for approval as of this review in its present form per 21CFR 314.125(b)(6) (**Note:** Labels/Labeling are not reviewed in this review cycle because the NDA will be recommended for CR due to failed clinical bridging.).

**NDA 209354
Review # 1**

Drug Name/Dosage Form	DUOBRII™ (halobetasol propionate and tazarotene) Lotion, for Topical Use
Strength	0.01%/0.045% (w/w)
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Dow Pharmaceutical Sciences, Inc. Sean Humphrey Suite C, 1330 Redwood Way Petaluma, CA 94954
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original submission	08-18-2017	All
Amendment	10-27-2017	Drug product manufacturing process
Amendment	02-14-2018	Drug substance
Amendment	03-23-2018	Drug product manufacturing process

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Ramsharan Mittal	Branch II/Division of New Drug API
Drug Product	Caroline Strasinger	Branch V/Division of New Drug Products II
Process	Jingbo Xiao	Branch V/Division of Process Assessment III
Microbiology	Vinayak Pawar	Branch I/Division of Microbiology Assessment
Facility	Laurie Nelson	Branch III/Division of Inspection Assessment
Biopharmaceutics	Vidula Kolhatkar	Branch III/Division of Biopharmaceutics
Regulatory Business Process Manager	Bamidele (Florence) Aisida	Branch I/Division of Regulatory and Business Management I/Office of Program and Regulatory Operations
Application Technical Lead	Yichun Sun	Branch V/Division of New Drug Products II

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	1	March 22, 2018	Adequate
	Type II		3	October 19, 2017	Adequate	
	Type III		4	N/A	N/A	

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")

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
End-of-Phase 2 Meeting Minutes	IND 111218	Discussions of development plan for halobetasol propionate and tazarotene Lotion
Pre-NDA Meeting Minutes	IND 111218	Discussions of the content and format of the proposed NDA submission.

2. 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 and Conclusion on Approvability

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

The facility review team from the Office of Process and Facility (OPF) has issued an “Acceptable” recommendation for the facilities involved in this application.

However, labels/labeling have not been reviewed at this time because the NDA will be recommended for CR due to failed clinical bridging.

Therefore, from the OPQ perspective, this NDA is *not* ready for approval in its present form per 21 CFR 314.125(b)(6) until the labels/labeling are reviewed and found acceptable.

II. Summary of Quality Assessments

A. Product Overview

The NDA of DUOBRII™ (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045% for topical use is submitted as a 505(b)(2) application by Dow Pharmaceutical Sciences, Inc. (a subsidiary of Valeant Pharmaceutical International). The listed drugs used for the basis of this 505(b)(2) application are NDA 019967 [Ultravate (halobetasol propionate) Cream, 0.05%] and NDA 021184 [Tazorac (tazarotene) Cream, 0.05%].

The indication and recommended dose of the drug product are summarized in the following Table.

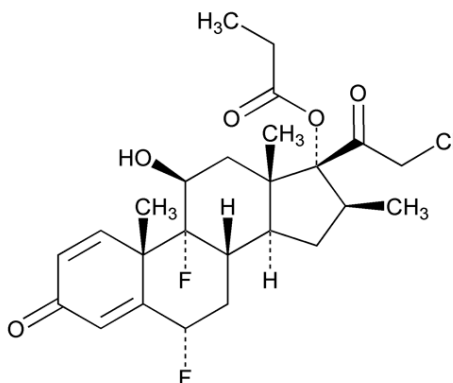
Proposed Indication(s) including Intended Patient Population	Duborii Lotion is a combination of halobetasol propionate and tazarotene indicated for the topical treatment of plaque psoriasis in patients of 18 years and older.
Duration of Treatment	Long term
Maximum Daily Dose	The total dosage should not exceed approximately 50 g per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance

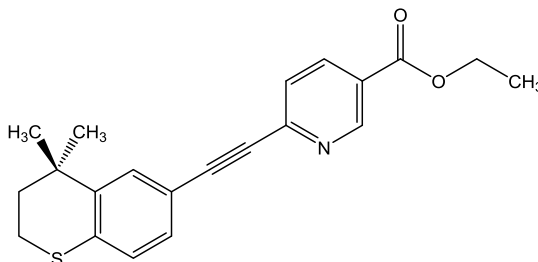
Duborii lotion is a combination product containing 0.01% (w/w) halobetasol propionate and 0.045% (w/w) tazarotene.

Halobetasol propionate, is a synthetic corticosteroid. The chemical name for halobetasol propionate is 21-chloro-6 α , 9-difluoro-11 β , 17-dihydroxy-16 β -methylpregna-1, 4-diene-3,20-dione 17-propionate. The chemical structure of halobetasol propionate is:



It has a molecular formula of $C_{25}H_{31}ClF_2O_5$ and a molecular weight of 484.96 g/mol. Halobetasol propionate is a white to off-white crystalline powder. It is practically insoluble in water, freely soluble in dichloromethane and in acetone. The drug substance is manufactured by (b) (4). Detailed CMC information of halobetasol propionate drug substance for this NDA is referred to DMF # (b) (4).

Tazarotene is a member of the acetylenic class of retinoids. Tazarotene is a retinoid pro-drug, which is converted to its active form, the cognate carboxylic acid of tazarotene, by rapid de-esterification in vivo. The chemical name for tazarotene is 6-[(3,4-Dihydro-4,4-dimethyl-2H-1-benzothiopyran-6-yl)ethynyl]-3-pyridinecarboxylic acid ethyl ester. The structural formula for tazarotene is:



It has a molecular formula of $C_{21}H_{21}NO_2S$ and a molecular weight of 351.46. Tazarotene drug substance is a pale yellow to brownish powder. It is insoluble in water, slightly soluble in ethanol, very soluble in benzyl alcohol. The drug

substance is manufactured by (b) (4). Detailed CMC information of tazarotene drug substance for this NDA is referred to DMF # (b) (4)

DMF # (b) (4) was reviewed by Dr. Ramsharan Mittal on March 22, 2018 and found adequate in supporting the approval of this NDA. DMF # (b) (4) has been adequate since last review conducted by Dr. Xingding Hu on October 19, 2017 and no new information has been added to the DMF since then. The review on the CMC information of the drug substance in the NDA has been conducted by Dr. Ramsharan Mittal. The NDA is recommended for **approval** from drug substances perspective (See **CHAPTER I: Review of Drug Substance**).

Drug Product

The drug product, DUOBRII™, is a topical lotion which contains 0.01% (w/w) halobetasol propionate and 0.045% (w/w) tazarotene. The inactive ingredients used in the drug product include: carbomer copolymer type B, carbomer homopolymer type A, diethyl sebacate, edetate disodium dihydrate, light mineral oil, methylparaben, propylparaben, purified water, sodium hydroxide, sorbitan monooleate and sorbitol solution, 70%. The inactive ingredients are of compendial grade. The drug product is packaged as a nominal 3, 45, 60 or 100 g fill size in a (b) (4) aluminum tube with (b) (4) cap.

The specification for the halobetasol propionate and tazarotene lotion is adequate to ensure the identity, strength, purity, and quality of the drug product during its expiration dating period. The long-term stability data up to 12 months for the three registration batches of the drug product produced at (b) (4) kg scale are provided in the NDA submission. The stability data submitted are sufficient to support the proposed expiration dating period of 24 months when stored at room temperature. The results of in-use studies support that the product can be continuously used (b) (4) with no undesirable trends to physical, chemical or microbial characteristics. The estimated EIC for both drug substances is well below 1 ppb. The claim of categorical exclusion is acceptable per 21 CFR 25.31 (b).

The drug product is recommended for **approval** from the drug product perspective. The recommended expiration dating period of the drug product is 24 months. The review on the CMC information of the drug product has been conducted by Dr. Caroline Strasinger (See **CHAPTER II: Review of Drug Product**).

Labeling and Labels

The sections of the Package Insert related to CMC, and container/carton labels of the drug product of the NDA are not reviewed in this review cycle because the NDA will be recommended for CR due to failed clinical bridging.

Drug Product Manufacturing Process

The (b) (4) drug product is prepared by

(b) (4)

(b) (4)

(b) (4)

The manufacturing process of the halobetasol propionate and tazarotene lotion includes the following steps:

(b) (4)

(b) (4)



Additionally, a list of tests with acceptance criteria is added to the drug product manufacturing process to ensure the quality of the (b) (4) drug product (b) (4)

The tests included in the specification are: appearance, pH, viscosity, assay for halobetasol propionate, assay for tazarotene, (b) (4) and lotion droplet size.

The batch formula, manufacturing process parameters, and in-process controls are found to be adequate to ensure the robustness of the drug product manufacturing process. The NDA is recommended for **approval** from the perspective of drug product manufacturing process. The review on the drug product manufacturing process has been conducted by Dr. Jingbo Xiao (See **CHAPTER III: Review of Drug Product Manufacturing Process**).

Biopharmaceutics

The applicant is seeking approval for halobetasol propionate and tazarotene lotion, 0.01%/0.045%. The applicant was advised to develop an in vitro release methodology and propose in vitro release test with acceptance criteria for the proposed drug product to be used routinely at batch release and during stability as a quality control test. (b) (4)

(b) (4)

(b) (4)

From the biopharmaceutics perspective, developing an IVRT method with acceptance criteria as a quality control tool is a recommendation in this case and not a requirement. The lack of an IVRT method and acceptance criteria will not affect the approvability of this NDA.

There was a manufacturing site change during development of the product. Phase 2 clinical batch was manufactured at Dow Pharmaceutical Sciences facility in Petaluma, CA. Phase 3 clinical batch was manufactured at Valeant Pharmaceuticals International, Inc. facility at Laval, Canada (proposed commercial site). Per 21 CFR 300.50 fixed-combination prescription drugs for humans, the batch of the drug product used in Phase 2 clinical study should be the same as the Phase 3 and commercial batches. A comparative in vitro release testing was not conducted demonstrating the “sameness” between Phase 2 and Phase 3 clinical batches of the drug product after manufacturing site change. However, considering that pivotal Phase 3 studies were conducted with batches manufactured at the proposed commercial site and other physicochemical characteristics (pH, viscosity) are comparable between batches manufactured at the two sites, additional information is not deemed necessary from a Biopharmaceutics perspective.

The NDA is recommended for **Approval** from the perspective of Biopharmaceutics. The review on Biopharmaceutics of the drug product of the NDA has been conducted by Dr. Vidula Kolhatkar (See **CHAPTER IV: Review of Biopharmaceutics**).

Quality Microbiology

The drug product is a non-sterile lotion containing 0.01%/ halobetasol propionate and 0.045% tazarotene Lotion. (b) (4)

The antimicrobial effectiveness dose response study was designed to evaluate (b) (4) at the 60, 80 and 100% levels per USP <51>. The study results indicate that at a (b) (4) concentration of (b) (4)%, the lower specification limit for the (b) (4) adequate (b) (4) was observed for the test article to meet the USP <51> antimicrobial effectiveness Category 2 criteria for this lotion. The results also indicate that the test article continues to meet the USP <51> antimicrobial criteria, even at lower levels of (b) (4) i.e. down to (b) (4)%.

Validation results of microbial limits tests indicated that the current USP methods for microbial enumeration (TAMC and TYMC) and specified organisms (P. aeruginosa and S. aureus) are suitable to be used for microbial limit tests of the drug product. Validation results for the test method of B. Cepacia Complex (Bcc) indicated that tests for Bcc organisms will require (b) (4)

(b) (4)

[REDACTED]. The suitability of the method used for monitoring *Burkholderia cepacia* complex (BCC) is acceptable for this product.

The results of stability studies indicated that the levels of [REDACTED] (b) (4) [REDACTED] in the stability samples of the drug product remained within the specification limit [REDACTED] (b) (4) (%) for up to 12 months under long-term test conditions, for up to 6 months under accelerated test conditions. Additionally, free-thaw and cold-warm cycles stress conditions did not dramatically change the concentration of the [REDACTED] (b) (4) in the test samples of the drug product. The concentrations of the [REDACTED] (b) (4) in the stability samples met the acceptance criteria. Since the [REDACTED] (b) (4) levels are monitored through the expiration dating period of the drug product, it is acceptable that the applicant will not perform microbial limits testing on stability batches of the drug product.

The NDA is recommended for **Approval** from the perspective of quality microbiology. The review on microbiology controls of the drug product of the NDA has been conducted by Dr. Vinayak Pawar (See **CHAPTER V: Review of Quality Microbiology**).

Facilities

Facilities Related to Drug Substance Manufacturing and Testing:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Facilities Related to Drug Product Manufacturing and Testing:

Valeant Pharmaceuticals International, Inc., Laval, Quebec, Canada (FEI: #3002807186) is responsible for manufacturing, packaging, labeling, release and stability testing of the finished drug product, halobetasol propionate and tazarotene lotion (DUOBRII). A review of the site dossier indicates Valeant Pharmaceuticals International is currently registered as a manufacturer and tester of human prescription and non-prescription drug products. The drug listing includes finished drug products of oral solids, powders, liquids and creams. OPF recommends approval of Valeant Pharmaceuticals International, Inc. as the manufacturing site with the functions listed for the finished drug product, halobetasol propionate and tazarotene lotion (DUOBRII).

Dow Pharmaceutical Sciences, Inc., Petaluma, California (FEI: #1000135370) is an alternative release and stability testing facility for the finished drug product. A review of this firm indicates the firm is capable of performing release and stability testing of the finished drug product. OPF recommends approval of Dow Pharmaceutical Sciences, Inc. as an alternative release and stability testing facility for the drug product.

(b) (4)



All the facilities are deemed acceptable in their identified functions and responsibilities to support the **approval** of NDA 209354. The facility review of

the NDA has been conducted by Consumer Safety Officer, Laurie Nelson (See **CHAPTER VI: Review of Facilities**).

C. Special Product Quality Labeling Recommendations

N/A

D. Final Risk Assessment (Attachment I)

E. List of Deficiencies (Attachment II)

None.

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessments - NDA

a) Drug Product

Final Risk Assessment for NDA 209354 [DUOBRII™ (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045%, for Topical Use]

Product Attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay halobetasol propionate and its degradation products	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	4	3	36	An HPLC method is used to quantitate the content (halobetasol propionate assay) and its degradation products in the drug product at release and during stability studies. The assay results ranged from 90.1 to 103.5% were observed in stability samples of all testing conditions. However, no reportable peaks were observed for individual unspecified impurities (degradants) in stability samples stored in all testing conditions.
Assay tazarotene and its degradation products	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	4	3	36	An HPLC method is used to quantitate the content (tazarotene assay) and its degradation products in the drug product at release and during stability studies. The assay results ranged from 91.0 to 104.9% in the stability samples of all testing conditions. The highest level of (b) (4) reached to (b) (4)%. However it was still within the specification limit, (b) (4)%.
Assay – (b) (4)	• Formulation • Raw materials	3	3	2	18	(b) (4)

	• Process parameters • Scale/equipment • Site					(b) (4)	
Assay – (b) (4)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	3	2	18		
Uniformity in containers – halobetasol propionate	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	4	3	24		The test is conducted per USP <3> at release and during stability studies. All stability samples met the requirements for stage 1 testing: (b) (4) % of label claim with a maximum difference within each tube of not more than (NMT) (b) (4)%.
Uniformity in containers – tazarotene	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	4	3	24		The test is conducted per USP <3> at release and during stability studies. All stability samples met the requirements for stage 1 testing: (b) (4) % of label claim with a maximum difference within each tube of not more than (NMT) (b) (4)%.
(b) (4) Droplet Size	• Formulation • Raw materials	2	4	3	24		Single Particle Optical Sensing. D10 = NMT (b) (4) μm D50 = NMT (b) (4) μm

	• Process parameters • Scale/equipment • Site					D90 = NMT (b) (4) μm The droplet size distribution of the lotion showed no significant trending during stability studies in all testing conditions.
Microbial Testing	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	2	3	18	Microbiological examination tests per USP <61> and USP <62>. An in-house method is used to test <i>Bulkholderia Cepacia Complex</i> (Bcc) in the drug product. However, the tests were not performed during stability studies as antimicrobial effectiveness test was conducted and the test results indicated that the levels of (b) (4) in the drug product were adequate to inhibit microorganism growth.
pH	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	2	3	12	The pH of the drug product is monitored at release and during stability studies. No significant change in pH value was observed for the stability samples stored under all testing conditions.
Viscosity	• Formulation • Raw materials • Process parameters • Scale/equipment	2	2	3	12	Viscosity of the drug product is monitored at release and during stability studies. The viscosity of the stability samples ranged from (b) (4) cP and meet the specification after stored for 12 months at 25°C/60%RH, for 6 months at 40°C/75%RH.
Minimum Fill	• Site • Formulation • Raw materials • Process parameters • Scale/equipment • Site	2	2	3	12	The test is performed per USP <755> and is only conducted at release.
Package Integrity	• Formulation • Container components • Process parameters	3	2	2	12	Visual check. This test is only performed during stability studies. No deterioration was observed on the stability samples of all testing conditions.

RPN: Risk Priority Number

$$RPN = \begin{bmatrix} 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{bmatrix} O \times \begin{bmatrix} 5 \\ 4 \\ 3 \\ 2 \\ 1 \end{bmatrix} S \times \begin{bmatrix} 1 \\ 2 \\ 3 \\ 4 \\ 5 \end{bmatrix} D$$

Low Risk- $RPN \leq 25$

Moderate Risk - $25 < RPN \leq 60$

High Risk - $RPN > 60$

OVERALL ASSESSMENT AND SIGNATURES:**Application Technical Lead's Assessment and Signature**

From the OPQ perspective, the NDA is not deemed ready for approval as of this review in its present form per 21CFR 314.125(b)(6).

Yichun Sun, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
4/13/2018



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Rhee

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CHAPTERS: Primary Quality Assessment

CHAPTER IV: Review of Biopharmaceutics

CHAPTER VI: BIOPHARMACEUTICS

[IQA Review Guide Reference](#)

Product Background:**NDA: 209354****Drug Product Name / Strength: Halobetasol propionate and tazarotene Lotion,
0.01%/0.045%****Route of Administration: Topical****Formulation: Lotion****Applicant Name: Dow Pharmaceutical Sciences, Inc.****Indication: Treatment of plaque psoriasis*****Review Recommendation: Adequate***

Review Summary: The applicant is seeking approval for Halobetasol propionate and tazarotene Lotion, 0.01%/0.045%. In the Information Request (IR) communicated on October 10, 2017, the Agency recommended that the Applicant develop an in vitro release test (IVRT) and propose in vitro release acceptance criteria for the proposed drug product to be used at release and during stability as a quality control parameter.

(b) (4)

[REDACTED]. IVRT as a QC tool was a recommendation in this case and does not affect approvability of the application.

There was a manufacturing site change during development of the product. Phase 2 batches were manufactured at Dow Pharmaceutical Sciences facility in Petaluma, CA. Phase 3 batches were manufactured at Valeant Pharmaceuticals International, Inc. facility at Laval, Canada (proposed commercial site). Comparative in vitro release testing was not conducted comparing the Phase 2 and Phase 3 batches. However, considering that pivotal Phase 3 studies were conducted with batches manufactured at the proposed commercial site and other physicochemical characteristics (pH, viscosity) are comparable between batches manufactured at the two sites additional information is not needed from a Biopharmaceutics perspective.

From the Biopharmaceutics perspective, NDA 209354 is recommended for APPROVAL.

Concise Description of Outstanding Issues Remaining: None

BCS Designation

Reviewer's Assessment: This is a topical product; BCS designation is not pertinent to this application.

Dissolution: See below In-Vitro Release Testing (IVRT) for Semi-Solid Products.

Dissolution Method and Acceptance Criteria

Reviewer's Assessment: See below In-Vitro Release Testing (IVRT) for Semi-Solid Products.

In-Vitro Release Testing (IVRT) for Semi-Solid Products

Reviewer's Assessment:

The applicant was advised to develop an in vitro release methodology and propose in vitro release acceptance criteria for the proposed drug product to be used routinely at batch release and during stability as a quality control test. (b) (4)

[REDACTED]. From the biopharmaceutics perspective, developing an IVRT method and acceptance criteria as a quality control tool is a recommendation in this case and not a requirement. The lack of an IVRT method and in vitro release acceptance criteria will not affect the approvability of this NDA.

Bridging of Formulations

Reviewer's Assessment: {Adequate/Inadequate} Adequate

There was a manufacturing site change from Dow Pharmaceutical Sciences facility in Petaluma, CA to Valeant Pharmaceuticals International, Inc. facility at Laval (Canada) prior to Phase 3 clinical trials. The applicant was requested to submit

comparative in vitro release data for the batches manufactured at Dow facility in California and batches manufactured in Valeant Pharmaceuticals International, Inc. facility in Laval in an Information Request (October 10, 2017)

In their response dated October 27, 2017, the applicant stated that nine of the eleven clinical studies were conducted with supplies manufactured at the proposed commercial manufacturer, Laval. Specifically, the two pivotal phase 3 studies, the one year long term safety study, the two phase 2 safety and efficacy bridging studies and the pharmacokinetic bridging study required for a 505(b)(2) NDA, as well as the two dermal safety studies and the potency study were conducted with lots manufactured at Laval. The two studies that used batches manufactured at Dow Pharmaceutical Sciences were the proof-of-concept (POC) study (DPSI-IDP-118-P2-01) and the phase 2 study V01-118A-201 which primarily served as early POC and to power the phase 3 studies, respectively.

Per 21 CFR 300.50 fixed-combination prescription drugs, two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effect. The phase 2 study comparing the drug product (with both APIs) to each of the monads (Study V01-118A-201) was conducted with Batch DP1615 manufactured at Dow at a (b) (4) kg scale.

It should be noted that the clinical and ICH registration lots were manufactured at (b) (4) kg scale at Laval.

The following was considered to determine that information to bridge this manufacturing site change is not needed from Biopharmaceutics perspective:

- Pivotal phase 3 studies were conducted with batches manufactured at the proposed commercial site (Laval),
- There were no formulation changes between Phase 2 and Phase 3 batches, Manufacturing process changes were minimal between the sites (as discussed with the process reviewer Dr. Jingbo Xiao at internal meeting on March 19, 2018) and
- Other physicochemical characteristics such as viscosity and pH were comparable between Phase 2 batch DP 1615 and other phase 3 batches
Lot no DP1615 manufactures at Dow facility: pH: 5.1, viscosity: 11854 cP
Phase 3 lots manufactured at Laval facility: pH: 5.4, viscosity: 12118 cP (average of four batches, each tested at beginning, middle and end)

Biowaiver Request

Reviewer's Assessment: N/A

List of Deficiencies:

None

From the Biopharmaceutics perspective, NDA 209354 is recommended for approval.

Primary Biopharmaceutics Reviewer Name and Date:

Vidula Kolhatkar, Ph.D. March 30, 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Okpo Eradiri, Ph.D. April 4, 2018



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Kolhatkar

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CHAPTER V: Review of Quality Microbiology

MICROBIOLOGY

Product Background:

The applicant/sponsor submits an original new drug application per Section 505(b)(2) and 21 CFR 314.50, for DUOBRII™ (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045%, for the topical treatment of plaque psoriasis. Proposed proprietary name “Duobrii” has been conditionally accepted for NDA 209354 by the Agency on 11/13/2017. A method was developed and validated to confirm the absence of *B. cepacia* complex as requested by the Agency in the pre-NDA meeting (02/15/2017).

NDA: 209354**Drug Product Name / Strength:** DUOBRII™ (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045%**Route of Administration:** Topical Lotion**Applicant Name:** Valeant Pharmaceuticals North America, LLC, a Dow Pharmaceutical Science subsidiary.**Manufacturing Site:** Valeant Pharmaceuticals International, Inc., Laval, Quebec, Canada H7L 4A8. FEI: 3002807186. DUNS: 245141858**Method of Sterilization:** N/A. Non-sterile Drug product.**Review Recommendation:** Adequate**Theme (ANDA only):** Choose an item.**Justification (ANDA only):** Choose an item.

Review Summary: This non-sterile drug product is administered topically. Adequate information is provided from microbiological perspective in support of product quality. The product is expected to maintain microbial quality over shelf life based on the (b) (4) efficacy studies as well as demonstration for the absence of *B. cepacia* complex.

List Submissions Being Reviewed:

Submit	Received	Review Request	Assigned to Reviewer
August 17, 2017	August 18, 2017	N/A	August 23, 2017

Highlight Key Outstanding Issues from Last Cycle: N/A**Remarks:** None

Concise Description Outstanding Issues Remaining: N/A

Supporting Documents: None

List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance – N/A

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – The DUOBRII™ (halobetasol propionate and tazarotene) Lotion, 0.01%/0.045%, is proposed for topical administration for the treatment of (b) (4) plaque psoriasis in patients 18 years of age and older.
- **Drug product composition** – Qualitative and Quantitative composition is provided in Table 1(copied from Table 3.2.P.1-1)

Table 1. Qualitative and quantitative composition of drug product

Component	Reference to Quality Standard	Function	Concentration (% w/w)
Halobetasol propionate	USP	Active	0.01
Tazarotene	In-house	Active	0.045
Diethyl sebacate	NF	(b) (4)	
Light mineral oil	NF		
Sorbitan monooleate	NF		
Sorbitol solution, 70%	USP		
Methylparaben	NF		
Propylparaben	NF		
Edetate disodium dihydrate	USP		
Carbomer copolymer type B (b) (4)	NF		
Carbomer homopolymer type A (b) (4)	NF		
Sodium hydroxide	NF		
Purified water	USP		

USP = United States Pharmacopeia
 NF = National Formulary
 qs = quantity sufficient

- **Description of container closure system** – Drug product is packaged as a nominal 3, 45, 60 or 100 g fill size in a (b) (4) aluminum tube with (b) (4) cap. Component details and description of the packaging system was referenced in Section 3.2.P.7.

Reviewer’s Assessment: *Adequate*

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