CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209483Orig1s000

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: **Oct 26, 2017**

From: **Zhengfang Ge, Ph.D.**
ONDP/Division II/Branch V

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, ONDP/Division II/Branch V

To: **Labeling Review #1 of NDA 209483**

Subject: **Final labeling/labels**

The Labeling review #1 has noted that Section 16 of the Package Insert should be revised to include 1) Strength of the drug product, 2) A statement "Do not freeze", before approval of this application.

On Oct 7, 2017, the applicant amended the labeling and the above issues are satisfactorily resolved.

In addition, carton/container labels were also modified in the amendment submitted on Oct 16,2017 based on the recommendation from DMEPA (see the **Attachment**). These changes are acceptable from CMC perspective.

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

Attachment: Final labeling and labels

Highlight

IMPOYZ (clobetasol propionate) Cream, 0.025%, for topical use

——DOSAGE FORMS AND STRENGTHS——

Cream, 0.025% (3)

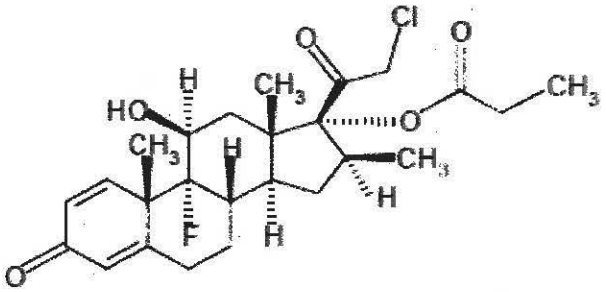
3 DOSAGE FORMS AND STRENGTHS

Cream, 0.025%: each gram contains 0.25 mg of clobetasol propionate in a white to off-white cream base

11 DESCRIPTION

IMPOYZ (clobetasol propionate) Cream, 0.025% for topical use contains clobetasol propionate, a synthetic and fluorinated corticosteroid.

Chemically, clobetasol propionate is 21-chloro-9-fluoro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl propanoate, and it has the following structural formula:



Clobetasol propionate has a molecular formula of $C_{25}H_{32}ClFO_5$ and a molecular weight of 467. It is a white to cream-colored crystalline powder practically insoluble in water.

Each gram of IMPOYZ ™ Cream contains 0.25 mg clobetasol propionate. It is an oil-in-water emulsion intended for topical application and contains the following inactive ingredients: butylated hydroxytoluene, cetostearyl alcohol, cyclomethicone, diethylene glycol monoethyl ether, glyceryl stearate and PEG 100 stearate, isopropyl myristate, methyl paraben, propyl paraben, purified water and white wax.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

IMPOYZ Cream, 0.025% is a white to off-white cream, supplied as follows:

60 g aluminum tube	NDC 67857-811-57
112 g aluminum tube	NDC 67857-811-58

16.2 Storage

Store at 20°C - 25°C (68 °F - 77°F); excursions permitted to 15°C-30°C (59°-86°F) [see USP Controlled Room Temperature]. Do not freeze.

(b) (4)

[redacted]

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Zhengfang Ge

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Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 10/26/2017 09:55:34AM
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Integrated Quality Assessment (IQA) for NDA 209483

Office of Pharmaceutical Quality (OPQ)

QUALITY ASSESSMENT

Recommendation:

This 505(b)(1) NDA is ***not*** deemed ready for approval as of this review in its present form per 21CFR 314.125(b)(6).

NDA 209483
Review # 1

Drug Name/Dosage Form	Trade Name (Clobetasol Propionate) Cream
Strength	0.025%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Promius Pharma, LLC.
US agent, if applicable	Hari Nagaradona, Ph.D. 107 College Road East Princeton, NJ

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original submission	01-30-2017	All
Amendment	04-11-2017	Biopharmaceutics
Amendment	05-12-2017	Biopharmaceutics
Amendment	05-16-2017	Drug product
Amendment	07-10-2017	Quality microbiology, drug product, product manufacturing process
Amendment	07-31-2017	Drug product
Amendment	08-25-2017	Drug product
Amendment	09-05-2017	Product manufacturing process and drug product

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Lawrence Perez	Branch II/Division of New Drug API
Drug Product	Zhengfang Ge	Branch V/Division of New Drug Products II
Process	Youmin Wang	Branch V/Division of Process Assessment III
Microbiology	Maria G. (Gema) MartinManso	Branch III/Division of Microbiology Assessment
Facility	Krishnakali Ghosh	Branch III/Division of Inspection Assessment
Biopharmaceutics	Kalpana Paudel	Branch II/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)		3	September 29, 2016	Adequate
	Type III			4	N/A	N/A

n 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
IND Written Response	110799	Discussions of the development plan for the IND.
Pre-NDA Meeting Minutes	110799	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, the issues on labels/labeling are ***not*** completely resolved at this time.

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 aforementioned issues are satisfactorily resolved (See the **List of Deficiencies** on p. 17).

II. Summary of Quality Assessments

A. Product Overview

Clobetasol propionate cream, 0.025%, which has been developed by Promius Pharma, LLC., is included in this 505b(1) NDA. Promius has obtained a right of reference from Fougera Pharmaceuticals Inc., for all of the Temovate NDAs (NDAs 019322, 019323, 019966, 020337 and 020340) and will rely on these NDAs for the nonclinical safety data of clobetasol propionate.

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

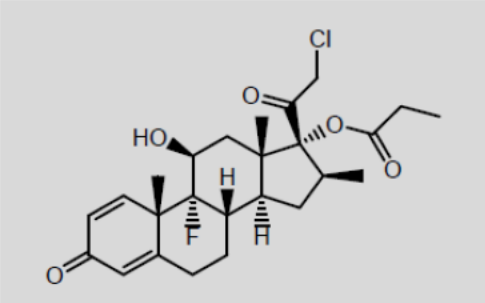
Proposed Indication(s) including Intended Patient Population	Clobetasol propionate cream 0.025% is indicated for the treatment of moderate to severe plaque psoriasis in patients 18 years of age and older.
Duration of Treatment	Use the cream for up to 2 consecutive weeks for treatment.
Maximum Daily Dose	Apply a thin layer of the cream to the affected skin areas twice daily and rub in gently and completely.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance

The active pharmaceutical ingredient (API) used in the drug product, clobetasol propionate cream, 0.025%, is clobetasol propionate. Clobetasol propionate is a corticosteroid of the glucocorticoid class used to treat various skin disorders. The chemical name for clobetasol propionate is 21-chloro-9-fluoro-11β-hydroxy-16β-

methyl-3,20-dioxopregna-1,4-dien-17-yl propanoate. The chemical structure of clobetasol propionate is:



It has a molecular formula of $C_{25}H_{32}ClFO_5$ and a molecular weight of 467.0 g/mol. The drug substance is being manufactured by [redacted] (b) (4) . as a white to cream, crystalline powder and it is non-hygroscopic. Clobetasol propionate as manufactured by [redacted] (b) (4) has only one polymorphic form and is chiral with 8 stereogenic centers. Clobetasol propionate from [redacted] (b) (4) has been shown to be physically and chemically stable at room temperature (25°C/60% RH) and has a retest period of [redacted] (b) (4) months.

Clobetasol propionate is a compendial drug substance. For this NDA application, the specification for the drug substance complies with the current USP monograph. The production of clobetasol propionate is detailed in DMF [redacted] (b) (4) which contains information on the manufacturer, method of manufacturing, characterization, specification and stability of the drug substance. The DMF has been found **Adequate** as per Chemistry Review #3 of DMF [redacted] (b) (4) by Jizhou Wang, Ph.D. dated 29-Sep-2016.

The NDA applicant, Promius Pharma LLC., has provided sufficient information to ensure identity, strength, purity and quality for the clobetasol propionate drug substance. Based upon the assessment of information of the drug substance in NDA submission, a recommendation of **approval** is made for clobetasol propionate as formulated in the drug product, clobetasol propionate cream 0.025%.

The review on the CMC information of the drug substance has been conducted by Dr. Lawrence Perez (See **CHAPTER I: Review of Drug Substance**).

Drug Product

The NDA of clobetasol propionate cream, 0.025% is submitted as a 505 (b)(1) application by Promius Pharma, LLC. The drug product, clobetasol propionate cream, is an oil-in-water emulsion containing 0.25 mg clobetasol propionate per gram of the cream. The inactive ingredients used in the cream are: butylated hydroxytoluene, cetostearyl alcohol, cyclomethicone, diethylene glycol

monoethyl ether, glyceryl stearate and PEG 100 stearate, isopropyl myristate, methyl paraben, propyl paraben, purified water and white wax.

The drug product is packaged in (b) (4) aluminum tubes with net weights of 2.5, 60 and 112 g of the cream, respectively. The 2.5 g tubes are intended for physician's samples and the package sizes of 60 and 112 g tubes are sought for marketing.

Specification for the clobetasol propionate cream is adequate to ensure the identity, strength, purity, and quality of the drug product during its expiration dating period. Stability data from the stability samples packaged in the proposed commercial container closure systems support an expiration dating period of **24 months** when stored at controlled room temperature, 20 to 25°C (68 to 77°F), excursions permitted between 15°C and 30°C (59 - 86°F). The aluminum tubes were found to be adequate to preserve the quality of the cream specifically with respect to the exposure to light based on the results of photostability study. The drug product should not be frozen based on the results of freeze-thaw stability study (b) (4)

(b) (4)

A claim for categorical exclusion from the environmental assessment has been submitted by the NDA applicant and the request is granted.

The drug product is recommended for **approval** from the drug product perspective. The review on the CMC information of the drug product has been conducted by Dr. Zhengfang Ge (See **CHAPTER II: Review of Drug Product**).

Labeling and Labels

The sections of the Package Insert related to CMC, and container labels of the drug product of the NDA have been reviewed by Dr. Zhengfang Ge. Labeling and label issues have ***not*** been resolved satisfactorily as of this review (See **CHAPTER III: Review of Labeling and Labels**). **Note:** Dr. Ge stated that the container and carton labels for the 2.5 g and 112 g packaging configurations have been reviewed but not included in the review as they are deemed similar to the labels of the 60 g packaging configuration.

Drug Product Manufacturing Process

The clobetasol propionate cream is prepared by (b) (4)

(b) (4)

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Quality Microbiology

The information provided by the applicant regarding [redacted] (b) (4) microbiological examination, finished product specification and stability studies meets regulatory expectations and is sufficient to support the drug product manufacturing process from the standpoint of product quality microbiology.

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. Maria Martin Manso (See **CHAPTER VI: Review of Quality Microbiology**).

Facilities

[redacted] (b) (4)

All the facilities are deemed **acceptable** in their identified functions and responsibilities to support the approval of NDA 209483. The facility review of the NDA has been conducted by Dr. Krishna Ghosh (See **CHAPTER VII: Review of Facilities**).

C. Special Product Quality Labeling Recommendations

N/A

D. Final Risk Assessment (Attachment I)

E. List of Deficiencies (Attachment II)

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

Risk Assessment for NDA 209483 [Trade name (clobetasol propionate) Cream, 0.025%]

Product Attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Assay (Clobetasol propionate)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	4	3	36	(b) (4)
Clobetasol propionate (b) (4) (b) (4)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	4	3	36	
	• Formulation • Raw materials • Process parameters	3	3	3	27	(b) (4)

						(b) (4)
	• Scale/equipment • Site					
(b) (4)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	3	3	27	
Microbial Limits (b) (4)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	3	3	27	
Globule size distribution	• Formulation • Raw materials	3	3	3	27	

(b) (4)

	• Process parameters • Scale/equipment • Site					
pH	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	4	3	36	
Apparent Viscosity (cps)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	3	3	27	
Homogeneity – Clobetasol propionate	• Formulation • Raw materials • Process parameters	4	4	2	32	

	• Scale/equipment • Site					
Package integrity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	2	2	12	Seal integrity or leak testing is recommended for topical drug products packaged in tubes.
Minimum fill	• Process parameters • Scale/equipment	3	2	2	12	Minimul fill is a required test on creams according to USP <755>.
(b) (4)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	4	3	2	24	Aluminum tubes with (b) (4) (b) (4) screw caps are used as the primary packaging components for clobetasol propionate cream, 0.025%.

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 ≤ 25

Moderate Risk - $25 < RPN \leq 60$

High Risk - $RPN > 60$

ATTACHMENT II: List of Deficiencies

A. Labeling Deficiencies:

A. **Package Insert**

#16: How Supplied/Storage and Handling

- Strength of the drug product needs to be included.
- A statement, "Do not freeze" should be added.

B. Container Label Deficiencies:

- The container and carton labels need to be updated after the trade name of the drug product proposed is deemed acceptable. Currently, the trade name of the drug product is still under review by DMEPA (Division of Medical Error Prevention and Analysis).

OVERALL ASSESSMENT AND SIGNATURES:

Application Technical Lead's Assessment and Signature

From quality 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
9/27/2017

Yichun Sun

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Moo Jhong Rhee

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LABEL FOR NDA 209483

I. PI

1. *Highlights of Prescribing Information*

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use (b) (4) Cream safely and effectively. See full prescribing information for (b) (4) Cream.
(b) (4) (clobetasol propionate) Cream, 0.025%, for Topical Use
Initial U.S. Approval: 1985

INDICATIONS AND USAGE
(b) (4) Cream is a corticosteriod indicated for the treatment of moderate to severe plaque psoriasis in patients 18 years of age and older. (1)

DOSAGE AND ADMINISTRATION
Apply a thin layer of (b) (4) Cream to the affected skin areas twice daily and rub in gently and completely. Wash hands after each application. Use (b) (4) Cream for up to 2 consecutive weeks of treatment. (2)
Discontinue (b) (4) Cream when control is achieved. (2)
Do not use if atrophy is present at the treatment site. (2)
Do not bandage, cover, or wrap the treated skin area unless directed by a physician. (2)
Avoid use on the face, scalp, axilla, groin, or other intertriginous areas. (2)
(b) (4) Cream is for topical use only. It is not for oral, ophthalmologic, or intravaginal use. (2)

DOSAGE FORMS AND STRENGTHS
Cream, 0.025% (3)

Item	Information Provided in NDA	Reviewer's Assessment
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))		
Proprietary name and established name	(b) (4) **(clobetasol propionate) Cream, 0.025%, for Topical Use**	**Adequate**
Dosage form, route of administration	Cream, for topical use	**Adequate**
Controlled drug substance symbol (if applicable)	N/A	
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))		
Summary of the dosage form and strength	cream, 0.025%	**Adequate**

2. *Section 2 Dosage and Administration*

2 DOSAGE AND ADMINISTRATION

Apply a thin layer of [redacted] Cream to the affected skin areas twice daily and rub in gently and completely. Wash hands after each application. Use [redacted] Cream for up to 2 consecutive weeks of treatment.

Discontinue [redacted] Cream when control is achieved.

Do not use if atrophy is present at the treatment site.

Do not bandage, cover, or wrap the treated skin area unless directed by a physician.

Avoid use on the face, scalp, axilla, groin, or other intertriginous areas.

[redacted] Cream is for topical use only. It is not for oral, ophthalmologic, or intravaginal use.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))		
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	[redacted] Cream is for topical use only. It is not for oral, ophthalmologic, or intravaginal use.	**Adequate**

3. *Section 3 Dosage Forms and Strengths*

3 DOSAGE FORMS AND STRENGTHS

Cream, 0.025%

Each gram of [redacted] Cream contains 0.25 mg of clobetasol propionate [redacted] in a white to off-white cream base.

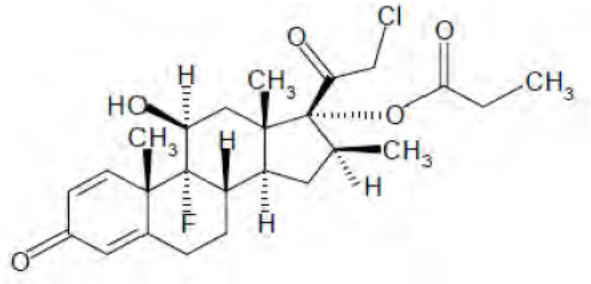
Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))		
Available dosage forms	cream	**Adequate**
Strengths: in metric system	0.025%	**Adequate**
Active moiety expression of strength with equivalence statement (if applicable)	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	white to off-white cream	**Adequate**

4. *Section 11 Description*

11 DESCRIPTION

[redacted] (clobetasol propionate) Cream, 0.025% contains clobetasol propionate a synthetic, and fluorinated corticosteroid.

Chemically, clobetasol propionate is 21-chloro-9-fluoro-11β-hydroxy-16β-methyl-3,20-dioxopregna-1,4-dien-17-yl propanoate, and it has the following structural formula:



Clobetasol propionate has the molecular formula $C_{25}H_{32}ClFO_5$ and a molecular weight of 467. It is a white to cream-colored crystalline powder practically insoluble in water.

Each gram of [redacted] Cream, contains 0.25 mg clobetasol propionate [redacted]. It is an oil-in-water emulsion cream intended for topical application and contains the following inactive ingredients: butylated hydroxytoluene, cetostearyl alcohol, cyclomethicone, diethylene glycol monoethyl ether, glyceryl stearate and PEG 100 stearate, isopropyl myristate, methyl paraben, propyl paraben, purified water and white wax.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))		
Proprietary name and established name	(b) (4) (clobetasol	**Adequate**
Dosage form and route of administration	cream intent for topical application	**Adequate**
Active moiety expression of strength with equivalence statement (if applicable)	N/A	
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	All inactive ingredients are listed.	**Adequate**
Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	clobetasol propionate a synthetic, and fluorinated corticosteroid	**Adequate**
Chemical name, structural formula, molecular weight	Provided	**Adequate**
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	It is a white to cream-colored crystalline powder practically insoluble in water.	**Adequate**

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

16 **HOW SUPPLIED/STORAGE AND HANDLING**

16.1 How Supplied

(b) (4) Cream is a white to off-white cream, supplied as follows:

60-g aluminum tube NDC 67857-811-57

112-g aluminum tube NDC 67857-811-58

16.2 Storage

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

16.3 Handling

Keep out of reach of children.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))		
Strength of dosage form	not provided	**Inadequate**
Available units (e.g., bottles of 100 tablets)	60-g aluminum tube 112-g aluminum tube	**Adequate**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	cream	**Adequate**
Special handling (e.g., Dispense in tight and light resistant container as defined in USP)	N/A	**Inadequate** This section should include "Do not freeze" statement based on the results of freeze thaw study
Storage conditions	Store at 25°C (77°F) with excursions permitted from 15°C to 30°C (59°F-86°F) [see USP Controlled Room Temperature]	**Adequate**
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Provided after "**17 Patient Counseling Information**"	**Adequate**

Deficiency:

The section 16 should be revised as follows:

1. Strength of the drug product needs to be listed.
2. A statement, "Do not freeze" should be included.

II. Labels:

1. **Immediate Container Label**


(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	(b) (4) (clobetasol propionate)	**Adequate**
Dosage strength Active moiety expression of strength with equivalence statement (if applicable), if space is available	0.025%	**Adequate**
Net contents	60 g, 112 g	**Adequate**
"Rx only" displayed prominently on the main panel	Provided	**Adequate**
NDC number (21 CFR 207.35(b)(3)(i))	Provided	**Adequate**
Lot number and expiration date (21 CFR 201.17)	It is indicated "see Crimp for lot number and expiration date"	**Adequate**
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Provided Store between 20° C to 25° C (68° F to 77° F), excursions permitted 15° C to 30° C (59° F to 86° F). [See USP Controlled Room Temperature].	**Add "Do not freeze"** **Inadequate**
Bar code (21CFR 201.25)	Provided	**Adequate**
Name of manufacturer/distributor	Provided	**Adequate**
And others, if space is available	**IMPORTANT:** Do not use if seal has been punctured or is not visible. **TO OPEN:** Remove the cap and puncture the seal by placing the opposite end of the cap and press gently.	**Adequate**

Deficiencies:

- Add "Do not Freeze"

2. Carton Label


(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	(b) (4) (clobetasol propionate)	**Adequate**
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	0.025%	**Adequate**
Net quantity of dosage form	60 g, 112 g	**Adequate**
"Rx only" displayed prominently on the main panel	provided	**Adequate**
Lot number and expiration date	Not provided	**Inadequate**
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Provided Store between 20° C to 25° C (68° F to 77° F), excursions permitted 15° C to 30° C (59° F to 86° F). [See USP Controlled Room Temperature].	**Inadequate** **Add "Do not freeze"**
Bar code (21CFR 201.25)	Provided	**Adequate**
NDC number (21 CFR 207.35(b)(3)(i))	Provided	**Adequate**
Manufacturer/distributor's name	Provided	**Adequate**
Quantitative ingredient information (injectables)	Each gram contains clobetasol propionate 0.25 mg	**Adequate**
Statement of being sterile (if applicable)	N/A	**Adequate**
"See package insert for dosage information"	**USUAL DOSAGE:** See package insert for complete prescribing information.	**Adequate**
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	**WARNING : KEEP OUT OF REACH OF CHILDREN.** **IMPORTANT:** Do not use if seal has been punctured or is not visible. **TO OPEN:** Remove the cap and puncture the seal by placing the opposite end of the cap and press gently.	**Adequate**

Deficiencies:

- Add Lot No and expiration date
- Add "Do not freeze"

Revised Labels Submitted in Amendment Dated 31-July-2017

As shown in the following labels, the applicant added the lot No and expiration date, as well as the "do not freeze" statement. The revised carton and container labels are acceptable from the CMC perspective. The trade name is under review in DMEPA.

Carton Label

(b) (4)

Container Label

(b) (4)

List of Deficiencies:

Section 16 of the Package Insert should be revised as follows:

1. Strength of the drug product should be included.
2. A statement "Do not freeze" should be added.

Overall Assessment and Recommendation:

The applicant revised carton/container labels according to the Agency's recommendation. However, the trade name is still under review by DMEPA. Section 16 of the Package Insert should be revised as shown above before approval of this application.

Primary Labeling Reviewer Name and Date:

Zhengfang Ge, Ph. D.

Reviewer, BRANCH V/DIVISION II

OFFICE OF NEW DRUG PRODUCT

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

I agree with Dr. Ge for her assessment on the labels and labeling and that those deficiencies delineated above need to be resolved before approval of this application.

Moo-Jhong Rhee, Ph. D.

Branch Chief, BRANCH V/DIVISION II

OFFICE OF NEW DRUG PRODUCT

Zhengfang Ge

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Moo Jhong Rhee

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BIOPHARMACEUTICS

Product Background:

NDA/ANDA: NDA 209483

Clobetasol Propionate Cream, 0.025% is indicated for topical treatment of moderate to severe plaque psoriasis. On January 30, 2017, the Applicant submitted NDA 209483 via 505 b1 pathway for approval of Clobetasol Propionate Cream, 0.025%.

Drug Product Name / Strength: Clobetasol Propionate Cream, 0.025% (b) (4)

Route of Administration: Topical

Applicant Name: Promius Pharma, LLC.

Review Recommendation: **Adequate**

Review Summary:

The Applicant has developed and validated an in-vitro release testing (IVRT) method (b) (4) to establish a baseline for any post-approval manufacturing changes. The analytical method and its validation report are adequate. The IVRT method is acceptable. In an IR sent during the filing review cycle, the Agency recommended the Applicant to propose in vitro release acceptance criteria (range) for the proposed drug product. In response, Applicant has stated that they will provide the proposed in-vitro acceptance criteria based on data from at least three production batches (to-be-marketed batches of the drug product) in the first annual report. The applicant's response is acceptable, this is not an approvability issue.

List Submissions being reviewed (table): IVRT method and validation; IVRT method development

(b) (4)

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None

BCS Designation

Reviewer's Assessment: N/A

Solubility: N/A

Permeability: N/A

Dissolution: N/A

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

1. Composition of proposed drug product:

The quantitative composition of each component of Clobetasol Propionate Cream USP, 0.025% is listed in Table 1.

Table 1: Clobetasol Propionate Cream USP, 0.025% formulation

Ingredients	Reference / Standard	% w/w	Function
Clobetasol propionate	USP	0.025	Active
Cetostearyl alcohol	NF	(b) (4)	(b) (4)
Glyceryl stearate & PEG 100 stearate	IH*		
White wax	NF		
Diethylene glycol monoethyl ether	NF		
Butylated hydroxytoluene	NF		
Isopropyl myristate	NF		
Cyclomethicone	NF		
Methylparaben	NF		
Propylparaben	NF		
Purified water Q.S.	USP		

(b) (4)

2. IVRT Method Development:

The Applicant has developed and validated the following IVRT method (b) (4)

(b) (4)

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Reviewer's comments:

On April 4, 2017, the Applicant responded to the above deficiencies as follows. The responses are acceptable.

(b) (4)

[redacted]

Primary Biopharmaceutics Reviewer Name and Date: Kalpana Paudel, Ph.D. 06/01/2017; 08/31/2017

***Secondary Reviewer Name and Date (and Secondary Summary, as needed*:**
Vidula Kolhatkar, Ph.D., September 18, 2017

Kalpana Paudel

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Vidula Kolhatkar

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CHAPTER VI: Review of Quality Microbiology

MICROBIOLOGY

IQA Review Guide Reference

Product Background: (b) (4) cream is a topical corticosteroid indicated for the treatment of moderate to severe plaque psoriasis in patients 18 years of age and older.

NDA: 209483

Drug Product Name
Proprietary: (b) (4) cream
Non-proprietary: Clobetasol propionate cream
Strength: 0.025 %

Route of Administration: Topical

Applicant Name:
Promius Pharma, LLC.
107 College Road East
Princeton, NJ 08540

Manufacturing Site:
(b) (4)

Method of Sterilization: Not applicable. Non-sterile dosage form

Review Recommendation: The submission **is recommended** for approval on the basis of microbiological quality.

Review Summary: The information provided by the applicant regarding (b) (4) microbiological examination, finished product specification and stability studies meets regulatory expectations and is sufficient to support the drug product manufacturing process from the standpoint of product quality microbiology. The proposed analytical procedures are adequate, and the verification / validation studies acceptable.

List Submissions Being Reviewed:

Submit	Received	Review Request	Assigned to Reviewer
30 January 2017	30 January 2017	N/A	21 February 2017
16 May 2017	16 May 2017*	N/A	N/A
10 July 2017	10 July 2017**	N/A	N/A

*Quality / Stability Information
** Quality / Response to Information Request

Highlight Key Outstanding Issues from Last Cycle: Not applicable. This is a first cycle review.

Remarks: NDA-209483 was electronically submitted via gateway and provided in CTD format. All Module, Section, and pdf documents in this product quality microbiology review are from the submission dated 30/January/2017 unless otherwise noted.

Concise Description Outstanding Issues Remaining: Based on the information submitted in the application, no microbiology deficiencies were identified.

Supporting Documents: Not applicable

List Number of Comparability Protocols (ANDA only): Not applicable

S Drug Substance

Reviewer's Assessment: ***{Adequate}***

The drug substance (*i.e.* Clobetasol propionate, 0.025 % w/w, USP) manufacturing process is not the subject of this product quality microbiology review (b) (4) No microbial limits have been provided. However, the active pharmaceutical ingredient is a powder and therefore, it poses low risk for microbial proliferation. (b) (4)

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** The drug product is a white to off-white oil-in-water emulsion cream and is supplied in multi dose aluminum tubes containing 2.5 g (*i.e.* physician's samples), 60 g or 112 g with 0.25 mg of clobetasol propionate USP per g of cream. The drug solution is indicated for topical use.

- **Drug product composition –**
(Module 2.3.P, drug-prod.pdf page 2/45)

Table 1. Qualitative and quantitative composition of (b) (4) cream

Ingredients	Reference / Standard	% w/w	Function
Clobetasol propionate	USP	0.025	Active
Cetostearyl alcohol	NF	(b) (4)	
Glyceryl stearate & PEG 100 stearate	IH*		
White wax	NF		
Diethylene glycol monoethyl ether	NF		
Butylated hydroxytoluene	NF		
Isopropyl myristate	NF		
Cyclomethicone	NF		
Methylparaben	NF		
Propylparaben	NF		
Purified water Q.S.	USP		

(b) (4)

- **Description of container closure system –**
(Module 3.2.P.1, description-and-composition.pdf page 3/4)

Table 2. Description of the primary container closure system

Component	Packaging Material Description	Fill weight	Manufacturer / Supplier	DMF
Aluminum tubes with (b) (4) caps	Aluminum tubes (b) (4) Dimensions: 1/2" X 2-7/16"	2.5 g	(b) (4)	Type III DMF (b) (4)
	Aluminum tubes (b) (4) Dimensions: 1-1/4"X 5-5/16"	60 g		
	Aluminum tubes (b) (4) Dimensions: 1-1/2"X 6-1/2"	112 g		
	HDPE Cap	-		

Table 2 was reproduced from Module 3.2.P.1 (description-and-composition.pdf page 3/4, Table 3.2.P.1.3-1)

Reviewer's Assessment: ***{Adequate}***

The information provided by the applicant regarding the description of the drug product meets regulatory expectations.

P.2 Pharmaceutical Development

(b) (4)

(b) (4)

(b) (4)

Reviewer's Assessment: *{Adequate}*

(b) (4)

(b) (4)

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(b) (4)

Reviewer's Assessment: *{Adequate}*

(b) (4)

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(Module 3.2.P.8.1, stability-summary.pdf, 16/May/2017; module 3.2.P.5.1, specifications.pdf)

The applicant provided stability data up to 24 months for the three registration batches / package size that support the proposed shelf life of 24 months when stored at 20 ºC -25 ºC (68 ºF -77 ºF).

(b) (4)

Table 7. Acceptance criteria for the stability studies

Test	Acceptance Criteria
(b) (4)	

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

(Module 3.2.P.8.2, postapproval-stability.pdf)

The applicant commits to (b) (4) The post-approval stability testing protocol will include (b) (4), tests for specified microorganisms and tests for (b) (4) performed at (b) (4) months.

P.8.3 Stability Data

The applicant provided stability data up to 24 months for the three registration batches / package size and the results met the acceptance criteria for (b) (4) (b) (4)

Reviewer's Assessment: ***{Adequate}***

The information provided by the applicant regarding stability meets regulatory expectations.

A Appendices

A.2 Adventitious Agents Safety Evaluation

(Module 2.3.A, adv-agen-saf-eval.pdf)

The applicant states that there are no adventitious agents in Clobetasol propionate cream, 0.025 % w/w. All the excipients used in the manufacturing of the subject drug product are transmissible and bovine spongiform encephalopathy free.

Reviewer's Assessment: ***{Adequate}***

List of Deficiencies:

There are no microbiology deficiencies identified.

Primary Microbiology Reviewer Name and Date:
Maria Gema Martin Manso, Ph.D., 07/14/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
John W. Metcalfe, Ph.D., 7/14/2017

Maria
Martin Manso

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John
Metcalfe

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