

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210566Orig1s000

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: May 23, 2018
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 210566

Subject: Final Approval Recommendation for NDA 210566

At the time when the CMC review #1 was written, resolution of issues on Labels and Labeling was pending.

Label/Labeling

On May 21, 2018, the NDA applicant submitted an amendment providing the mock up container and carton labels. Additionally, the applicant also agreed to all the CMC changes made to the package insert. All the label/labeling issues except NDC number and proprietary name of the drug product are now satisfactorily resolved. The labeler/distributor of the product needs to be changed and the new labeler/distributor has not been identified. Thus, the proprietary name and NDC number of the product can not be provided for the time being. The applicant proposed to use placeholders for a proprietary name, an NDC number and a distributor in the package insert, and the container and carton labels. The applicant will update the package insert, and the container and carton labels with the approved proprietary name and NDC number, and information of the distributor of the drug product prior to commercial distribution. The applicant's proposal is deemed acceptable from a quality perspective. The review of the CMC sections of the package insert, and mock up container and carton labels has been conducted by Dr. Zhengfang Ge, and her final labeling review is attached below (**Attachment - 1**).

Recommendation:

The revised package insert, and mock-up container and carton labels are now deemed satisfactory from the CMC perspective. Therefore, from the OPQ's perspective, this NDA is recommended for **APPROVAL** with a 36-month expiration dating period for the drug product in the commercial package, and a ^{(b) (4)} month expiration dating period for the physician sample when stored at room temperature.

Application Technical Lead's Assessment and Signature

The NDA is recommended for approval from a quality perspective.

Yichun Sun, Ph.D.

Application Technical Lead, Branch V

Division of New Drug Products II

5/23/2018

Attachment - 1 (Addendum to Labeling Review #1 of NDA 210566)

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

Date: May 21, 2018
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 210566
Subject: Final labeling/labels

The Labeling review #1 has noted the following pending issues:

For the Labeling insert

1. The section 11 should be revised to:
 - 1) The Proprietary name and established name should be written as Tradename (halobetasol propionate) foam in the beginning of the paragraph
 - 2) (b) (4) The excipients should be included as: alcohol (specifically denatured alcohol [SDA]), benzoic acid, cetostearyl alcohol, emulsified wax, polyoxyl 20 cetostearyl ether, propylene glycol, purified water
 - 3) Include a description of the propellant reading as: Tradename is dispensed from an aluminum can pressurized with a hydrocarbon (isobutane and propane) propellant
2. The section 16 should be revised to:
 - 1) The "TRADENAME is a white to off-white foam" should be revised to: TRADENAME (halobetasol propionate) foam, 0.05% is a white to off-white foam
 - 2) (b) (4)

For the Container Labels:

1. "Topical" should be removed from dosage form
2. Include bar code on the container labels
3. For the ingredients section:

- 1) [REDACTED] (b) (4) Remove [REDACTED] (b) (4) for the inactive ingredients.
- 2) The excipients should be included in alphabetical order.
- 3) Add "a hydrocarbon (isobutane and propane) propellant"

For the Carton Labels:

1. For the ingredients section:
 - 1) [REDACTED] (b) (4) Remove [REDACTED] (b) (4) for the inactive ingredients.
 - 2) The excipients should be included in alphabetical order.
 - 3) Add "a hydrocarbon (isobutane and propane) propellant"
2. Provide carton mock up for physician samples

And because of these deficiencies, in the Labeling Review #1, this NDA was not recommended for approval from the labeling perspective.

The above requests have been implemented in the revised labeling. Based on the recently published Agency's draft product title guidance, a dosage form of "topical foam" should be used in place of [REDACTED] (b) (4) that was previously used. Therefore, [REDACTED] (b) (4) has been changed to "topical foam" in labeling/labels.

On May 11, 2018, the applicant informed the Agency that the company may not have the right to use the proposed proprietary name. Therefore, the company has proposed to revise the drug product name, dosage form and strength as "Halobetasol Propionate topical foam, 0.05%". The change is acceptable from CMC perspective. The revised carton/container labels are provided in the Attachment.

Recommendation:

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



Zhengfang
Ge

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Moo Jhong
Rhee

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Date: 5/21/2018 04:36:54PM
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Yichun
Sun

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Moo Jhong
Rhee

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Recommendation:

From the OPQ perspective, 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 210566
Review # 1**

Drug Name/Dosage Form	(b) (4) (Halobetasol Propionate) Foam
Strength	0.05% (w/w)
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Therapeutics Inc. Garet Heintz 9025 Balboa Ave. San Diego, CA 92123
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original submission	07-28-2017	All
Amendment	10-16-2017	Quality microbiology
Amendment	11-09-2017	Quality microbiology
Amendment	11-29-2017	Drug product manufacturing process
Amendment	12-01-2017	Quality microbiology
Amendment	12-27-2017	Device - CDRH
Amendment	02-01-2018	Drug product
Amendment	02-26-2018	Drug product and Quality microbiology
Amendment	02-27-2018	Drug substance and Drug product

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Jeffrey Medwid	Branch II/Division of New Drug API
Drug Product	Zhengfang Ge	Branch V/Division of New Drug Products II
Process	Yumin Wang	Branch V/Division of Process Assessment III
Microbiology	Jennifer Patro	Branch I/Division of Microbiology Assessment
Facility	Allison Aldridge	Branch III/Division of Inspection Assessment
Biopharmaceutics	Sandra Suarez Sharp	Branch III/Division of Biopharmaceutics
CDRH Device Reviewer	Carolyn Dorgan	General Hospital Devices Branch/Division of Anesthesiology, Gen Hospital, Infection Control, & Dental Devices/Office of Device Evaluation/CDRH
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 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	107302	Discussions of development plan for halobetasol propionate foam, 0.05%.
Pre-NDA Meeting Minutes	107302	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	Complete	Approval	1/16/2018	Carolyn Dorgan
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.

The consult review on the device component of the container closure system of the drug product has been conducted by the Office of Device Evaluation, Center for Devices and Radiological Health (CDRH). The device constituent part of this combination product is recommended for approval by CDRH.

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 pp. 18-19).

II. Summary of Quality Assessments

A. Product Overview

The NDA of (b) (4) (Halobetasol Propionate) Foam, 0.05% is submitted as a 505(b)(1) application by Therapeutics Inc. The applicant provided a letter of authorization from the holder (Sun Pharma) of NDA 19967 (Ultravate[®] (halobetasol propionate) Cream, 0.05%,) and NDA 19968 (Ultravate[®] (halobetasol propionate) Ointment, 0.05%) for the right to reference the relevant data in these NDAs.

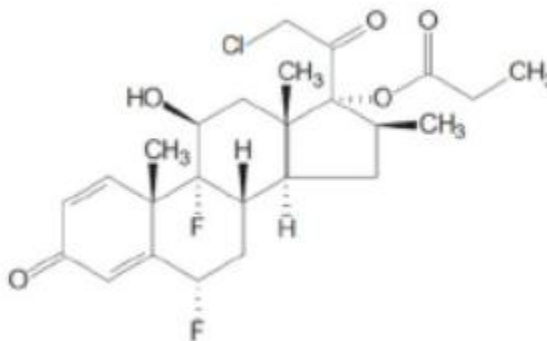
The indication and recommended dose of the drug product are summarized in the following Table.

Proposed Indication(s) including Intended Patient Population	(b) (4) (Halobetasol Propionate) Foam, 0.05% is indicated for the topical treatment of plaque psoriasis in patients eighteen (18) years of age and older.
Duration of Treatment	Treatment beyond two weeks is not recommended and the total dosage should not exceed 50 grams (one can) per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis.
Maximum Daily Dose	The total dosage should not exceed 50 grams (one can) per week.
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance

The active pharmaceutical ingredient (API) used in the drug product, (b) (4) (Halobetasol Propionate) Foam, 0.05%, is halobetasol propionate. Halobetasol propionate is a 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 C₂₅H₃₁ClF₂O₅ 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.

(b) (4)

Detailed CMC information of halobetasol propionate drug substance for this NDA is referred to DMF # (b) (4)

The DMF was reviewed and found adequate to support the **approval** of this NDA by Dr. Jeffrey B. Medwid on March 22, 2018. The review on the CMC

information of the drug substance in the NDA has been also conducted by Dr. Jeffrey B. Medwid (See **CHAPTER I: Review of Drug Substance**).

Drug Product

The drug product, (b) (4) (Halobetasol Propionate) Foam, 0.05%, is a topical foam, which contains 0.05% w/w halobetasol propionate as the active ingredient. The inactive ingredients used in the drug product include: ethanol, water and propylene glycol (b) (4); emulsifying wax, polyoxyl 20 cetostearyl ether and cetostearyl alcohol (b) (4) and benzoic acid (b) (4). The inactive ingredients are of compendial grade. The product will be supplied as physician samples in 35×70 mm aluminum cans (b) (4) and as the commercial configuration in 38×106 mm aluminum cans (b) (4) (b) (4) isobutane and propane (b) (4) is used as the propellant for the foam.

Specification for the halobetasol propionate foam 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 36 months for the three registration batches of the drug product produced at (b) (4) scale are provided in the NDA submission. The stability data submitted are sufficient to support the proposed expiration dating period of 36 months when stored at room temperature. The results of the in-use stability study indicate that the foam is stable and conforms to specification under simulated in-use conditions for two weeks.

The drug product is recommended for **approval** from the drug product perspective. The recommended expiration dating period of the drug product is 36 months. The review on the CMC information of the drug product has been conducted by Dr. Zhengfang Ge (See **CHAPTER II: Review of Drug Product**).

Device (aluminum cans with (b) (4) actuator)


The drug product, halobetasol propionate (HBP) foam, 0.05% is a pressurized aerosol foam, embodying the same fundamental design as is used for common consumer products such as shaving cream and other prescription pharmaceutical products. It is comprised of three major components – the bulk drug (HBP 0.05% in a hydroethanolic solution); **the container closure system (consisting of a (b) (4) aluminum canister, (b) (4), an actuator, and cover cap);** and (b) (4) hydrocarbon propellant (b) (4)

The primary packaging container closure of the halobetasol propionate foam, 0.05%, commercial configuration consists of a 38 mm×106 mm aluminum can with (b) (4) actuator with cover cap. The same (b) (4) actuator/cover cap assembly are also used for the physician

samples. Container closure components meet FDA food grade requirements for direct contact.



The applicant provides engineering drawings which control the aerosol canister physical requirements adequately. The applicant also provides adequate information to demonstrate the selected aerosol can functions per drug product specifications. The verification includes analysis of design output specifications of the finished foam product, as well as verification of the cans after interaction with the contents. In addition to the analysis, the applicant is proposing to apply similar design verification techniques to marketed products up to 36 months.

The device constituent part of this product in the NDA is recommended for **approval** from the device perspective. The review on device constituent part of the drug product has been conducted by Mrs. Carolyn C. Dorgan (See **CHAPTER III: Review of the Device Component of the Container Closure System**  (b) (4))

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 IV: Review of Labeling and Labels**).

Drug Product Manufacturing Process

The manufacturing process of the halobetasol propionate Foam, 0.05%, includes the following steps:

(b) (4)

The manufacturing process is adequately developed. The in-process controls and tests are deemed adequate to ensure that the drug product can be manufactured reproducibly. 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. Youmin Wang (See **CHAPTER V: Review of Drug Product Manufacturing Process**).

Biopharmaceutics

The drug product is a topical aerosol foam (hydro-ethanolic foam) proposed for the treatment of psoriasis. It contains 0.05% w/w halobetasol propionate as the active ingredient in a solution of ethanol and water with (b) (4)% propylene glycol.

This 505(b)(1) application relies on PK and pivotal Phase 3 studies to support its approval. The phase 3 clinical and to-be-marketed (TBM) HBP Foam formulation (338-13-6) is similar to the one (Formulation (b) (4)) used in the vasoconstriction study. (b) (4)

(b) (4)

The manufacturing site for the clinical and commercial batches of the drug product is Pharmasol Corporation, in Massachusetts, USA. The drug product is a hydroethanolic foam where the API and all the excipients are in a solution. Therefore, the assurance of the quality of the drug product relies on drug product specifications (other than in vitro release testing) and in process controls of the characteristics of topical aerosol foam formulation.

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. Sandra Suarez Sharp (See **CHAPTER VI: Review of Biopharmaceutics**).

Quality Microbiology

The drug product is a non-sterile foam containing 0.05% w/w halobetasol propionate as the active ingredient in a solution of ethanol ((b) (4))% w/w) and water with propylene glycol, emulsifying wax, polyoxyl 20 cetostearyl ether, and cetostearyl alcohol. The drug product is supplied in 35 × 70 mm aluminum cans as physician samples and 38 × 106 mm aluminum cans as the commercial configuration. (b) (4) is used as the propellant for the aerosol foam.

Antimicrobial effectiveness testing (AET) of the formulation vehicle (b) (4) (b) (4) was performed according to USP <51>. The AET testing concludes that (b) (4) halobetasol propionate 0.05% foam then the product is self-preserving and will not promote microbial growth from microorganisms inadvertently introduced to the product. The drug product manufacturing process is deemed adequate for a topical, nonsterile product. The applicant provided sufficient information regarding the microbiological tests and sampling frequency for the stability program. The suitability of the method used for monitoring *Burkholderia cepacia* complex (BCC) is acceptable for this product. The applicant commits to include microbial limits testing at release in the post approval stability protocol according to USP <61> and <62>. Additionally, the applicant commits to conduct Antimicrobial Effectiveness Testing (AET) at the end of stability testing. The commitments reduce the risk of not including microbial limits testing in the release specifications.

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. Jennifer Patro (See **CHAPTER VII: Review of Quality Microbiology**).

Facilities

Facilities Related to Drug Substance Manufacturing and Testing:

The active ingredient, halobetasol propionate, is manufactured by (b) (4)

(b) (4)
(b) (4)
(b) (4)

(b) (4) There is reasonable assurance that the quality systems of the facility will support this application and it appears that the facility is acceptable to manufacture halobetasol propionate drug substance.

(b) (4)

(b) (4)

Facilities Related to Drug Product Manufacturing and Testing:

The finished drug product, halobetasol propionate foam, 0.05% is manufactured at **Pharmasol Corporation** (FEI# 1250001). (b) (4)

The overall risk was medium because of the low drug content and the noted deficiencies in recent inspections. There are no recalls or FARs associated with this facility. The facility is listed in several approved applications and has experience with foam products. There is reasonable assurance that the quality systems of the facility will support this application and it appears that the facility is acceptable to manufacture the drug product.

(b) (4)

All the facilities are deemed acceptable in their identified functions and responsibilities to support the **approval** of NDA 210566. The facility review of the NDA has been conducted by Consumer Safety Officer, Allison Aldridge (See **CHAPTER VIII: Review of Facilities**).

C. Special Product Quality Labeling Recommendations

Contents under pressure. Do not puncture or incinerate. Do not expose to heat or store at temperatures above 120°F (49°C). Do not freeze.

D. Final Risk Assessment (Attachment I)**E. List of Deficiencies (Attachment II)**

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessments - NDA

a) Drug Product

Final Risk Assessments for NDA 210566 [(b) (4) (Halobetasol Propionate) Foam, 0.05% (w/w)]

Product Attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Microscopic Analysis of Collapsed Foam (essentially free of any foreign particulates and Essentially free of any crystals)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	2	3	3	(b) (4)	The test is used to ensure that the drug remains in solution of the vehicle. No crystals were observed in the stability samples of registration stability studies.
Assay, Halobetasol Propionate and Degradation Products	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	3	4	3		An HPLC method is used to quantitate the content (assay) and degradation products of the drug product at release and during stability studies. The trend of increasing levels of degradants and total degradation products was observed in the samples of long-term, intermediate and accelerated stability studies.
pH, 10% Dispersion	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	2	2	3		The pH of the drug product is monitored at release and during stability studies. No trend was observed for the pH of the stability samples stored under long-term test conditions for 36 months.

Foam Collapse and Foam Stiffness	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	2	2	3	(b) (4)	<p>These are the physical tests performed on halobetasol propionate foam, 0.05% at release and during stability studies. No trend was observed for foam collapse and foam stiffness of the stability samples stored under long-term test conditions for 36 months.</p>
Delivered Amount	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	2	2	3		<p>Total amount of foam that can be delivered from a can is monitored at release and during stability studies. No trend was observed for delivered amount of the foam from the stability samples stored under long-term test conditions for 36 months.</p>
Can Pressure	<ul style="list-style-type: none"> • Process parameters • Scale/equipment • Site 	2	3	3		<p>The pressure of filled cans is monitored at release and during stability studies. No trend was observed for can pressure of the stability samples stored under long-term test conditions for 36 months.</p>
Leak Rate % (w/w) per year (release) and Weight Loss % (w/w) per year (stability)	<ul style="list-style-type: none"> • Process parameters • Scale/equipment • Site 	2	3	3		<p>The test is performed according to USP <604>. No trend was observed for leak rate/weight loss of the stability samples stored under long-term test conditions for 36 months.</p>
Minimum Fill	<ul style="list-style-type: none"> • Container components 	2	2	2		<p>The test is performed per USP <755>. This test is only conducted at release.</p>

	<ul style="list-style-type: none"> • Process parameters 				(b) (4)	
Package Integrity	<ul style="list-style-type: none"> • Formulation • Container components • Process parameters 	3	2	2		(b) (4)
Delivery Rate	<ul style="list-style-type: none"> • Formulation • Container components • Process parameters 	3	3	2		<p>The test method is based on USP <603> method. No trend was observed for delivery rate of the stability samples stored under long-term test conditions for 36 months.</p>

RPN: Risk Priority Number

(b) (4)



ATTACHMENT II: List of Deficiencies

Labeling Deficiencies:

A. Package Insert

b) Full Prescribing Information

#11: Description

1. The Proprietary name and established name should be written as Tradename (halobetasol propionate) foam in the beginning of the paragraph.
2. [REDACTED] (b) (4) The excipients should be included as: alcohol (specifically denatured alcohol [SDA]), benzoic acid, cetostearyl alcohol, emulsified wax, polyoxyl 20 cetostearyl ether, propylene glycol, and purified water.
3. Include a description of the propellant reading as: Tradename is dispensed from an aluminum can pressurized with a hydrocarbon (isobutane and propane) propellant.

#16: How Supplied/Storage and Handling

1. The “TRADENAME is a white to off-white foam.” should be revised to: TRADENAME (halobetasol propionate) foam, 0.05% is a white to off-white foam.
2. [REDACTED] (b) (4)

B. Container Label

1. “Topical” should be removed from dosage form.
2. Include bar code on the container labels
3. For the ingredients section:
 - a. [REDACTED] (b) (4) Remove [REDACTED] (b) (4) for the inactive ingredients.
 - b. The excipients should be included in an alphabetical order.
 - c. Add “a hydrocarbon (isobutane and propane) propellant”

C. Carton Labels

1. For the ingredients section:
 - a. (b) (4) Remove (b) (4) for the inactive ingredients.
 - b. The excipients should be included in an alphabetical order.
 - c. Add “a hydrocarbon (isobutane and propane) propellant”.
2. Provide carton mock up for the physician sample.

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
4/4/2018



Yichun
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Moo Jhong
Rhee

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OFFICE OF DEVICE EVALUATIONDIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES**GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM**

Date	January 14, 2018
To	Florence Aisida Bamidele.Aisida@fda.hhs.gov OMPT/CDER/OPQ/OPRO/DRBPMI/RBPMBI 240-402-2691
Requesting Division	CDER/OPQ
From	Robert Meyer Carolyn Dorgan CDRH/ODE/DAGRID/GHDB Note: This file was transferred to Carolyn Dorgan on January 5, 2018
Through (Team Lead)	Carolyn Dorgan, ICC Team Lead CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CAPT Alan Stevens CDRH/ODE/DAGRID/GHDB
Subject	Consult for NDA 210566 ICCR2017-01410 ICC1700659
Recommendation	CDRH recommends approval of the device constituent of the combination product.

Digital Signature Concurrence Table

Reviewer	Carolyn C.	Digitally signed by Carolyn C. Dorgan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
Team Lead	Dorgan -S	0.9.2342.19200300.100.1.1=2001800814 , cn=Carolyn C. Dorgan -S Date: 2018.01.14 17:55:56 -05'00'
Branch Chief	Alan M. Stevens -S	Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2018.01.16 09:16:26 -05'00'

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR2017-01410
ICCR SharePoint Link	http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/DispForm.aspx?ID=1620
ICC tracking # (Lead)	ICC1700659
Submission Number	NDA 210566
Sponsor	Therapeutics Inc.
Drug/Biologic	Halobetasol Propionate Foam
Indications for Use	Treatment of plaque psoriasis in patients eighteen (18) years of age and older.
Device Constituent	Spray Canister
Related Files	ICC1700455

Table 2. Review Team				
CDER/CBER Lead Review Division	CDER			
Submission RPM	Florence Aisida			
Lead Device Reviewer	Robert Meyer/Carolyn Dorgan			
The CDRH review is being managed under ICC #: ICC1700659				
Below is a list of the Discipline Specific ICCR#, ICC# and CON#.				
Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	ICCR #	ICC #	CON #
N/A	N/A	N/A	N/A	N/A

Table 3. Important Dates	
Interactive Review Goal Dates	N/A
1st round of Information Requests	N/A
2nd Round of Information Requests	N/A
Final Discipline Specific Memos Due	N/A
Final Lead Device Review Memo Due	3/6/18
CMC Pre Mid Cycle	1/9/18
CMC Pre Wrap up	3/6/18
Final Reviews signed by Secondary in panorama	3/12/18

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REVIEWER NOTE:

The original CDRH reviewer for this ICCR was Robert Meyer. He left GHDB and the review of the file was transferred to Carolyn Dorgan on January 5, 2018. Blue text is from Robert’s original review. Black text is new text provided by Carolyn Dorgan.

2. PURPOSE/BACKGROUND

2.1. Scope

CDER requests: “The container closure system of the drug product, which consists a (b) (4) aluminum canister, (b) (4) an actuator, and cover cap, needs to be reviewed by CDRH from a perspective of device.”

Sponsor states [Cover Letter]: “In accordance with Section 505(b) of the Federal Food Drug and Cosmetic Act and Section 314.50 of the United States Code of Federal Regulation, Therapeutics Inc. (TI) is submitting an Original New Drug Application for Halobetasol Propionate Foam, 0.05% for the indication of Plaque Psoriasis in patients 18 years of age and older.

The Sponsor has developed a new topical formulation of Halobetasol propionate to provide patients with a new dosage form for those who prefer a foam over the existing, FDA approved, cream, ointment, and lotion formulations. The dose strength and regimen of the new dosage form is consistent with other formulations of Halobetasol Propionate, 0.05% (i.e., applied twice daily to the affected skin for up to two weeks with a maximum dose of 50 grams per week). In addition, the inactive ingredients in the formulation are present at or below levels found in FDA’s Inactive Ingredient Database (IiD) for approved topical drug products.”

2.2. Prior Interactions

The Sponsor submitted a preNDA briefing package for review under ICC1700455, which included a summary of the design specifications. In response to their questions CDRH provided an outline of information that should be provided within the NDA submission.

2.2.1. Related Files ICC1700455

2.3. Indications for Use

Combination Product	Indications for Use
Halobetasol Propionate	Treatment of plaque psoriasis in patients eighteen (18) years of age and older.
(b) (4) aluminum canister, (b) (4) an actuator, and cover cap	Spray drug product as specified

2.4. Drug Summary

Dosage Forms: Foam

Route of Administration: Topical (dermal)

Strength: 0.05%

Dosing Regimen: Twice daily. Treatment should be limited to two weeks, and amounts greater than 50 grams per week should not be used.

How Supplied: HBP Foam is supplied in pressurized aluminum canister with (b) (4) actuator. HBP Foam is available in cans of:

- 1 × 50 g can (Commercial Configuration)
- 1 × 17 g can (Physician Sample)

Therapeutics Inc. (TI) has developed a new topical formulation, Halobetasol Propionate Foam, 0.05% (HBP Foam), for the treatment of plaque psoriasis in patients 18 years of age and older. The dosing regimen of the new dosage form is consistent with other formulations of HBP, 0.05% (i.e., applied twice daily to the affected skin for up to two weeks with a maximum dose of 50 grams per week).

The foam formulation contains halobetasol propionate, 0.5 mg/g, in a white to off-white hydroethanolic foam vehicle consisting of denatured alcohol, propylene glycol, emulsifying wax, polyoxyl 20 cetostearyl ether, cetostearyl alcohol, benzoic acid, and purified water. The foam is dispensed from an aluminum can pressurized with a hydrocarbon (isobutane and propane) propellant.

3. ADMINISTRATIVE

3.1. Documents Reviewed

Documents Reviewed by Robert Meyer:

Document Title	Location
cover.pdf – (cover letter)	GSR/seq.0001
1-16-risk-mgmt-plans.pdf (risk management)	
uspi-plr-format-201707v1.pdf (labeling)	
container-closure-system-1.pdf (description)	
pharmaceutical-development.pdf	
postapproval-stability.pdf	GSR/seq.0001/3.2.P.8
specifications.pdf	GSR/seq.0001/3.2.P.5.1
tm-100-3-075.pdf	GSR/seq.0001/3.2.P.5.2
i107302-pre-NDA-Briefing-Package.pdf	Via email on 6/2/17
tm-100-3-039.pdf	GSR/seq.0001/3.2.P.5.2

Documents Reviewed by Carolyn Dorgan:

Document Title	Location
Stability Data	SN0001 - 3.2.P.8.3.
Specifications	SN0001 – 3.2.P.5.1.
TI Technical Report	SN0001 – 3.2.A
Analytical Procedures	SN0001 – 3.2.P.5.2
Container Closure System	SN0001 – 3.2.P.7.
Justification for Specifications	SN0001 – 3.2.P.5.6.
Quality Information Amendment 2017.12.15	SN0010 – 1.11.1

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

Figure 1. Exploded view and actual image of the Halobetasol Propionate Foam container closure system.



The following description is included within document “container-closure-system-1.pdf”:

Halobetasol Propionate (HBP) Foam, 0.05% finished drug product is a pressurized aerosol foam, embodying the same fundamental design as is used for common consumer products such as shaving cream and other prescription pharmaceutical products. It is comprised of three major components – the bulk drug (HBP 0.05% in a hydroethanolic solution); the container closure system (consisting of a (b) (4) aluminum canister, (b) (4), an actuator, and cover cap); and (b) (4) hydrocarbon propellant (b) (4)

(b) (4)

(b) (4)

Primary Packaging (Commercial Size)

The primary packaging container closure of the Halobetasol Propionate Foam, 0.05%, (HBP Foam) commercial configurations consists of a 38 mm×106 mm aluminum can with (b) (4) actuator with cover cap. (b) (4)

(b) (4) Container closure components meet FDA food grade requirements for direct contact. A summary of the primary packaging container closure for the commercial size units is provided in Table 5.

Table 5: Summary of the Primary Packaging Container Closure for the HBP Foam Commercial Configuration

Component	Specification and Drawing	Pharmasol Acceptance Test Results
38 mm×106 mm aluminum can (b) (4)	C-011012	Lot 167222 Test Results
(b) (4)	C-05739	Lot 011414 Test Results
Actuator and cover cap	C-13622	Lot LT00000078350 Test Results

The 38 mm×106 mm aluminum can (b) (4)

(b) (4)

(b) (4)

5. CLINICAL DEVELOPMENT

The following summary is extracted from document “i107302-pre-NDA-Briefing-Package.pdf [via email on 06/02/2-17]”.

A series of six nonclinical toxicology studies have been completed with HBP Foam. These include dermal and ocular irritation studies in rabbits, a sensitization study in guinea pigs, a 4-week dermal toxicity study in minipigs, a 4-day dosing feasibility study in rats using vehicle material, and a 13-week dermal toxicity study in rats. FDA has granted a waiver for the dermal carcinogenicity study on 2 March 2016, and a waiver request from conducting a nonclinical phototoxicity study was submitted to the IND on 8 May 2015 (SN-0043) [page 16].

A total of seven clinical studies have been conducted to support the safety and effectiveness of HBP Foam: two Phase 1 (Vasoconstrictor Assay [VCA], combined Cumulative Irritation Test [CIT] and Human Repeat Insult Patch Test

[HRIPT]), two Phase 2 (Pharmacokinetic [PK]/Hypothalamic-Pituitary Adrenal [HPA] axis suppression study, one safety/efficacy supportive study), and three Phase 3 adequate well-controlled studies that were conducted in accordance with the Agreed Special Protocol Assessment (SPA) [page 16]

Two of the Phase 3 clinical studies met their primary endpoint (i.e., IGA “treatment success” at Day 15) and thus, demonstrate pivotal evidence of effectiveness for HBP Foam in the treatment of plaque psoriasis in adults. In these two studies, HBP Foam treated subjects had a greater improvement in their disease than subjects treated with vehicle (VEH) Foam with similar results for the primary and secondary efficacy endpoints. The third Phase 3 clinical study was directionally consistent with the confirmative trials and demonstrated a notable improvement in psoriasis in terms of IGA and the three clinical signs (plaque elevation, scaling, and erythema) assessed, but did not achieve statistical significance for the primary efficacy endpoint [page 16].

It is noted that the three bulk drug product batches for Phase 3 clinical studies, Lots 30217, 30218 and 30224, were filled into six packaged lots, all of which met release specifications [page 87].

6. DESIGN CONTROL REVIEW

6.1. Design Review Summary

The Sponsor adequately demonstrates the aerosol spray canister device has been evaluated by a thorough research and development process to ensure the final foam product is delivered as intended. The methods included various test determine the optimal can (size, and function), (b) (4) and propellant pressure. The final choice was evaluated in a clinical study, and the container was ultimately chosen for market.

The Sponsor provides adequate information to demonstrate the selected aerosol can functions per specifications; the verification includes analysis of design output specifications of the finished foam product, as well as verification of the cans after interaction with the contents. In addition to the analysis the Sponsor is proposing to apply similar design verification techniques to marketed products up to 36 months.

The Sponsor provides engineering drawings which control the aerosol canister physical requirements adequately. The requirements are considered acceptable, because they were controlled during the production of the evaluated products which functioned acceptably. The Sponsor provides Lot Release requirements which verify essential design characteristics, and functions; the requirements align with requirements previously verified.

Via email on December 13, 2017 Yichun Sun from CDER states “Evaluation of biocompatibility of the canister is not deemed necessary as the device (canister) does not contact patients’ skin during application of the drug product.” The Sponsor noted throughout documentation that he finished product is manufactured using food grade equivalent materials.

The Sponsor states they have worked with CDER and concluded a post market risk evaluation and mitigation is acceptable.

6.1.1. Design Control Documentation Check

Design Control Requirement*	Signed/Dated Document Present		Submission Location
	Yes	No	
Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	X		GSR/seq.0001/3.2.P.5.1
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	X		GSR/seq.0001/3.2.P.5.2
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	X		GSR/0001/3.2.P.7
Validation Data <ul style="list-style-type: none"> • Human factors • Clinical data 	X		GSR/seq.0001/5.3
	X		
Traceability Documentation	X		See Information Request 1; GSR SN0010/1.11.1. Quality Amendment

6.1.2. Design Control Review

Reviewer Comments:

The design controls are adequate, see review of Information Request 1 in Section 13 of this memo.

7. DESIGN VERIFICATION AND VALIDATION REVIEW

7.1. Summary of Design V&V Attributes

Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial	X		
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		

Discipline -Specific Design Verification / Validation adequately addressed*						
	Consult needed			Consultant Name	Attributes Acceptable	
	Yes	No	N/A		Yes	No
Engineering (Materials, Mechanical, General)		X		-	X	
Biocompatibility		X		-	X	

Sterility			X	-	-	
Software / Cybersecurity			X	-	-	
Electrical Safety / EMC			X	-	-	
Human Factors			X	-	-	

7.2. Design Validation Review

Design Validation Attributes	Yes	No	N/A
Phase I/II/III Study utilized the to-be-marketed device	X		
Bioequivalence Study utilized to-be-marketed device			X
Simulated Actual Use Study utilized to-be-marketed device			X

The to be marketed product was used in two Phase 3 studies, and the Sponsor notes clinical endpoints were met.

7.3. Design Verification Review

The following excerpts are extracted from various documents and summarize the canister device development, specifications, and verification provided.



[Product Specifications \[document - specifications.pdf\]](#)

8. DISCIPLINE SPECIFIC SUB-CONSULTED REVIEW

N/A - No discipline specific consults were requested

9. RISK ANALYSIS

9.1. Risk Analysis Attributes

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product			X
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)			X
Mitigations are adequate to reduce risk to health			X

Version history demonstrates risk management throughout design / development activities			X
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9.2. Summary of Risk Analysis

Document “1-16-risk-mgmt-plans.pdf” states “Reference is made to the pre-NDA meeting between FDA and the Applicant. As noted in the minutes for this meeting, FDA has agreed with the Applicant’s plan for postmarket risk evaluation and mitigation, which would include routine pharmacovigilance and the product label (i.e., prescribing and patient information). Thus, a formal Risk Evaluation and Mitigation Strategy (REMS) is not needed for this product. This is supported by the extensive marketing experience with other halobetasol propionate, 0.05% drug products (Ultravate Cream, Ointment, Lotion, and numerous generics) and the 680 subject exposures during the clinical development of HBP Foam. Further, the types of adverse reactions experienced over the course of the HBP Foam development program were similar to the other marketed formulations of halobetasol propionate, 0.05% and present no new risks that would require a formal risk management measure such as REMS.”

10. LABELING

INSTRUCTIONS FOR USE
Halobetasol Propionate (b) (4)

Read the Patient Information and Instructions for Use before you use Halobetasol Propionate (b) (4)

Important information: For skin use only. (b) (4) Do not get Halobetasol Propionate (b) (4) in your mouth, eyes, or vagina. (b) (4)

Parts of Halobetasol Propionate (b) (4)

(b) (4)

(b) (4)



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Halobetasol Propionate (b) (4) safely and effectively. See full prescribing information for Halobetasol Propionate (b) (4)

(b) (4)
Initial U.S. Approval: 1990

INDICATIONS AND USAGE

Halobetasol Propionate (b) (4) is a corticosteroid indicated for the topical treatment of plaque psoriasis in patients eighteen (18) years of age and older. (1)

DOSAGE AND ADMINISTRATION

- Shake before use. (2)
- Apply Halobetasol Propionate (b) (4) as a thin uniform film to the affected skin twice daily for up to two weeks. Rub in gently. (2)
- Do not use more than 50 grams/week. (2)
- Discontinue Halobetasol Propionate (b) (4) when control is achieved. (2)
- If no improvement is seen within 2 weeks, reassess diagnosis. (2)
- Treatment beyond 2 consecutive weeks is not recommended. (2)
- Do not use with occlusive dressings unless directed by a physician. (2)
- Avoid use on the face, groin, or axillae. (2)
- Halobetasol Propionate (b) (4) is not for ophthalmic, oral, or intravaginal use.

DOSAGE FORMS AND STRENGTHS

(b) (4) 0.05% (0.5 mg/g). (3)

CONTRAINDICATIONS

None.

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
 2 DOSAGE AND ADMINISTRATION
 3 DOSAGE FORMS AND STRENGTHS
 4 CONTRAINDICATIONS
 5 WARNINGS AND PRECAUTIONS
 (b) (4)
 5.2 Local Adverse Reactions
 5.3 Concomitant Skin Infections
 5.4 Allergic Contact Dermatitis
 5.5 Flammability
 6 ADVERSE REACTIONS
 6.1 Clinical Trials Experience
 8 USE IN SPECIFIC POPULATIONS
 8.1 Pregnancy
 8.2 Lactation
 8.4 Pediatric Use
 8.5 Geriatric Use
 10 OVERDOSAGE

WARNINGS AND PRECAUTIONS

- Reversible hypothalamic-pituitary-adrenal (HPA) axis suppression may occur, with the potential for glucocorticosteroid insufficiency during or after treatment. (5.1)
- Systemic effects following prolonged exposure of topical corticosteroids may also include Cushing's syndrome, hyperglycemia, and glucosuria. (5.1)
- Use of potent corticosteroids on large areas, for prolonged durations, under occlusive dressings, or on an altered skin barrier may increase systemic exposure. (5.1)
- Children may be more susceptible to systemic toxicity when treated with topical corticosteroids. (5, 8.4)
- Local adverse reactions with topical steroids may include atrophy, striae, irritation, acneiform eruptions, hypopigmentation, and allergic contact dermatitis. Adverse reactions may be more likely to occur with occlusive use or more potent corticosteroids. (5.2)
- Initiate appropriate therapy if concomitant skin infections develop. (5.3)
- Flammable contents. Avoid heat, flame, or smoking during and immediately following application. (5.5)

ADVERSE REACTIONS

The most commonly reported adverse reactions (b) (4)
(b) (4)

To report SUSPECTED ADVERSE REACTIONS, contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: (b) (4)

11 DESCRIPTION
 12 CLINICAL PHARMACOLOGY
 12.1 Mechanism of Action
 12.2 Pharmacodynamics
 12.3 Pharmacokinetics
 13 NONCLINICAL TOXICOLOGY
 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
 14 CLINICAL STUDIES
 16 HOW SUPPLIED/STORAGE AND HANDLING
 16.1 How Supplied
 16.2 Storage
 16.3 Handling
 17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

The labeling is acceptable to CDRH, but review of the final labeling is deferred to CDER.

11. DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

The following excerpts are extracted from “i107302-pre-NDA-Briefing-Package.pdf” document.



ICC1700659

NDA 210566, Halobetasol Propionate Foam,
Spray Canister, Therapeutics Inc.

(b) (4)



(b) (4)



12. POST APPROVAL COMMITMENT

Document “[postapproval-stability.pdf](#)” states

“Pharmasol Corporation (Pharmasol) commits to completing the ongoing pivotal stability protocol for the three (3) registration batches of Halobetasol Propionate Foam, 0.05%, (HBP Foam). The expiration dating will be extended as warranted based on the data generated during the controlled room temperature stability testing.

Pharmasol commits to initiate stability testing with the first three (3) marketed (validation) lots of each configuration (physician sample canisters and commercial canisters) of HBP Foam and to initiate stability testing with one lot of each configuration yearly thereafter. The post-approval stability protocol may be terminated prior to 36 months based on the expiration dating.

Post-approval stability storage will occur in the inverted orientation at $25\pm 2^{\circ}\text{C}/60\pm 5\%$ relative humidity (RH). The post-approval stability protocol is presented in Table 1.”

Table 1: Post-Approval Marketed Product Stability Protocol for HBP Foam at Controlled Room Temperature (25±2°C/60±5% RH)



(b) (4)

Reviewer Comment

The post approval commitment is acceptable.

13.INTERACTIVE REVIEW

[Information Request # \(sent on 12/15/17\)](#) - **ADEQUATE**

You provide various documents necessary for review which support the safety and efficacy of the to-be-marketed aerosol canister, including a specifications document, verification method documents, and clinical study reports; however a traceability document is not included. To ensure all design inputs and requirements align with design outputs please provide a traceability report which identifies all design input and relates each do design output documentation. CDRH recommends the table list all aspects of the design which you consider essential for functionality, and next to each a clear reference is provided (preferably hyperlinked to documents). An example is provided below:

Design Traceability				
Functional Specifications	Method	Acceptance Criteria	Test Results Summary	Test Report
Foam Collapse	Name or summary and include document	...	Qty. Pass/ Qty. Fail	Provide reference and document
Foam Stiffness
Delivered Amount
Can Pressure
Leak Rate
Minimum Fill
Delivery Rate
Etc.
Biocompatibility Verification	Ex: Per ISO 10993-1	All biocompatibility Reports should be provided, and endpoints should be clearly identified
Validation	Human Factors or Clinical	A summary of all validation should be provided

Sponsor Response (received on 12/27/2017)

The request for a traceability matrix was first discussed at the pre-NDA meeting on June 14, 2017. At that time we agreed to provide a summary report within the NDA that describes the container closure system and identifies the design features that we consider essential for product functionality. The summary report (TI Report Number 122-0551-013) was provided in Module 3.2.A of the NDA submission and accessible via a hyperlink in Section 3.2.P.7 Container Closure System. The report includes a traceability matrix that lists the functional requirements of the container closure system, provides the key design elements and specifications for each, the verification of the key design elements and specifications, and the control for each.

While we view our summary report as adequate to characterize the key product features, we acknowledge that certain Centers within FDA may be more accustomed to other formats, such as the example provided in your IR. Therefore, we have converted our existing summary to align with the requested format; see Table 1 and Table 2 below.

We believe Biocompatibility Verification and design Validation are not relevant given the product is used topically and product performance (effectiveness) was demonstrated clinically. Physical/chemical compatibility of the container closure was evaluated during the pivotal stability study and by a controlled extraction study in accordance with the plan agreed to by FDA at the End of Phase 2 meeting (held on August 21, 2013). This information was provided in Section 3.2.P.7.1.3 and 3.2.A, TI Report 122-0551-011 of the NDA submission.

Lastly, we would like to emphasize our understanding of the product package type as an aerosol “canister” (as defined under CDER’s Data Standards Manual for Package Types), a component of the drug product that is similar in design to other CDER-regulated topical aerosol foam drug products such as ECOZA® (econazole nitrate) foam, OLUX® (clobetasol propionate) Foam, and ENSTILAR® (calcipotriene and betamethasone dipropionate) Foam.

Table 1: Traceability Matrix in CDRH Format, Commercial Canister

Functional Specification ^a	Method ^b	Acceptance Criteria	Test Results Summary	Test Report
Foam Stiffness	100-3-075	(b) (4)	3.2.P.5.6	3.2.P.8.3
Foam Collapse	100-3-075		3.2.P.5.6	3.2.P.8.3
Can Pressure	100-3-115, USP<603>		3.2.P.5.6	3.2.P.8.3
Delivery Rate	100-3-115, USP<603>		3.2.P.5.6	3.2.P.8.3
Delivered Amount	100-3-115, USP<603>		3.2.P.5.6	3.2.P.8.3
Minimum Fill	USP<755>		3.2.P.5.6	3.2.P.8.3
Leak Rate	USP<604>		3.2.P.5.6	3.2.P.8.3

^a Applicable NDA sections include: 3.2.P.5.1 Specifications.

^b Test Method descriptions are included in NDA section: 3.2.P.5.2 Analytical Procedures.

Table 2: Traceability Matrix in CDRH Format, Physician Sample Canister

Functional Specification ^a	Method ^b	Acceptance Criteria	Test Results Summary	Test Report
Foam Stiffness	100-3-075	(b) (4)	3.2.P.5.6	3.2.P.8.3
Foam Collapse	100-3-075		3.2.P.5.6	3.2.P.8.3
Can Pressure	100-3-115, USP<603>		3.2.P.5.6	3.2.P.8.3
Delivery Rate	100-3-115, USP<603>		3.2.P.5.6	3.2.P.8.3
Delivered Amount	100-3-115, USP<603>		3.2.P.5.6	3.2.P.8.3
Minimum Fill	USP<755>		3.2.P.5.6	3.2.P.8.3
Leak Rate	USP<604>		3.2.P.5.6	3.2.P.8.3

^a Applicable NDA sections include: 3.2.P.5.1 Specifications.

^b Test Method descriptions are included in NDA section: 3.2.P.5.2 Analytical Procedures.

A more comprehensive summary of the container closure system is detailed within the aforementioned TI Report Number 122-0551-013.

Reviewer Comments

The Sponsor provided a traceability matrix outlining the specifications followed by the verification and validation thereof for the commercial canister and the physician sample canister.

Robert reviewed the methods and test results to determine them to be acceptable.

ICC1700659

NDA 210566, Halobetasol Propionate Foam,
Spray Canister, Therapeutics Inc.

Carolyn reviewed the test summary and test reports located in 3.2.P.5.6. and 3.2.P.8.3. respectively and found the tests to evaluate the correlated specifications. Based on the results, all the samples met the acceptance criteria without deviations.

The CDRH reviewer concurs with the Sponsor in that biocompatibility verification is not required [REDACTED] (b) (4)

The Sponsor has adequately addressed the information request and CDRH does not have any further requests.

14. OUTSTANDING DEFICIENCIES

None

15. RECOMMENDATION

CDRH recommends approval of the device constituent of the combination product.

LABEL FOR NDA 210566

I. PI

1. Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Halobetasol Propionate (b) (4) safely and effectively. See full prescribing information for Halobetasol Propionate (b) (4)

(b) (4)
Initial U.S. Approval: 1990

INDICATIONS AND USAGE

Halobetasol Propionate (b) (4) is a corticosteroid indicated for the topical treatment of plaque psoriasis in patients eighteen (18) years of age and older. (1)

DOSAGE AND ADMINISTRATION

- Shake before use. (2)
- Apply Halobetasol Propionate (b) (4) as a thin uniform film to the affected skin twice daily for up to two weeks. Rub in gently. (2)
- Do not use more than 50 grams/week. (2)
- Discontinue Halobetasol Propionate (b) (4) when control is achieved. (2)
- If no improvement is seen within 2 weeks, reassess diagnosis. (2)
- Treatment beyond 2 consecutive weeks is not recommended. (2)
- Do not use with occlusive dressings unless directed by a physician. (2)
- Avoid use on the face, groin, or axillae. (2)
- Halobetasol Propionate (b) (4) is not for ophthalmic, oral, or intravaginal use.

DOSAGE FORMS AND STRENGTHS

(b) (4) 0.05% (0.5 mg/g). (3)

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

- Reversible hypothalamic-pituitary-adrenal (HPA) axis suppression may occur, with the potential for glucocorticosteroid insufficiency during or after treatment. (5.1)
- Systemic effects following prolonged exposure of topical corticosteroids may also include Cushing's syndrome, hyperglycemia, and glucosuria. (5.1)
- Use of potent corticosteroids on large areas, for prolonged durations, under occlusive dressings, or on an altered skin barrier may increase systemic exposure. (5.1)
- Children may be more susceptible to systemic toxicity when treated with topical corticosteroids. (5, 8.4)
- Local adverse reactions with topical steroids may include atrophy, striae, irritation, acneiform eruptions, hypopigmentation, and allergic contact dermatitis. Adverse reactions may be more likely to occur with occlusive use or more potent corticosteroids. (5.2)
- Initiate appropriate therapy if concomitant skin infections develop. (5.3)
- Flammable contents. Avoid heat, flame, or smoking during and immediately following application. (5.5)

ADVERSE REACTIONS

The most commonly reported adverse reactions (b) (4) (b) (4)

To report SUSPECTED ADVERSE REACTIONS, contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised (b) (4)

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)	Tradename is pending. The established name is halobetasol propionate Adequate
Dosage form, route of administration	foam, 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	Foam: 0.05% (0.5 mg/g).	Adequate

This section is adequate

2. Section 2 Dosage and Administration

Shake can prior to use. Apply Halobetasol Propionate (b) (4) as a thin uniform film to the affected skin twice daily for up to two weeks. Rub in gently. Wash hands after applying the product.

Discontinue therapy when control is achieved. If no improvement is seen within two weeks, reassessment of the diagnosis may be necessary.

Treatment beyond two weeks is not recommended and the total dosage should not exceed 50 grams (one can) per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis [see *Warnings and Precautions (5.1)*]. Do not use with occlusive dressings unless directed by a physician.

Halobetasol Propionate (b) (4) is for topical use only.

Avoid use on the face, groin, or axillae.

Halobetasol Propionate (b) (4) is not for ophthalmic, oral, 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)	Shake can prior to use. Wash hands after use. Halobetasol Propionate (b) (4) is for topical use only.	Adequate

3. Section 3 Dosage Forms and Strengths

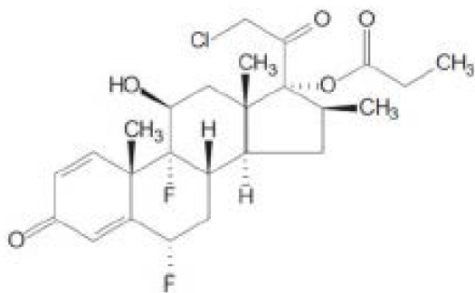
Halobetasol Propionate (b) (4) is a white to off-white Foam. Each gram of Halobetasol Propionate (b) (4) 0.05% contains 0.5 mg of halobetasol propionate.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))		
Available dosage forms	Halobetasol Propionate (b) (4)	Adequate
Strengths: in metric system	0.05%. Each gram of Halobetasol Propionate (b) (4) 0.05% contains 0.5 mg of halobetasol propionate	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 Foam	Adequate

This section is adequate.

4. Section 11 Description

Halobetasol Propionate (b) (4) for topical use is a hydroethanolic aerosol foam that 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 Halobetasol Propionate (b) (4) contains 0.5 mg of halobetasol propionate in a white to off-white foam base consisting of Alcohol, (b) (4) (specially denatured alcohol [SDA]); purified water, (b) (4) propylene glycol, (b) (4) emulsifying wax (b) (4); cetostearyl alcohol, (b) (4) polyoxyyl 20 cetostearyl ether, (b) (4) and benzoic acid, (b) (4).

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)	should be revised to Tradename (halobetasol propionate) foam Not Adequate
Dosage form and route of administration	Foam, for topical use	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>)	Each gram of TRADENAME contains 0.5 mg of halobetasol propionate in a white to off-white foam base consisting of Alcohol, (b) (4) (specially denatured alcohol [SDA]); purified water, (b) (4) propylene glycol, (b) (4) emulsifying wax, (b) (4) cetostearyl alcohol, (b) (4) polyoxyl 20 cetostearyl ether, (b) (4) and benzoic acid, (b) (4).	1) (b) (4) The excipients should be included as: alcohol (denatured), benzoic acid, cetostearyl alcohol, emulsified wax, polyoxyl 20 cetostearyl ether, propylene glycol, purified water 2) Include a description of propellant reading as: Tradename is dispensed from an aluminum can pressurized with a propellant containing isobutane and propane Not Adequate
Statement of being sterile (if applicable)	N/A	Adequate
Pharmacological/ therapeutic class	a 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 practically insoluble in water and freely soluble in dichloromethane and in acetone.	Adequate
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This section is not adequate. The following revision should be made:

- 1) The Proprietary name and established name should be written as Tradename (halobetasol propionate) foam in the beginning of the paragraph
- 2) ^{(b) (4)} The excipients should be included as: alcohol (specifically denatured alcohol [SDA]), benzoic acid, cetostearyl alcohol, emulsified wax, polyoxyl 20 cetostearyl ether, propylene glycol, purified water
- 3) Include a description of the propellant reading as: Tradename is dispensed from an aluminum can pressurized with a hydrocarbon (isobutane and propane) propellant

5. Section 16 How Supplied/Storage and Handling

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Halobetasol Propionate ^{(b) (4)} is a white to off-white foam. It is supplied in aluminum cans of:

50 grams (NDC XXXXX-XXX-XX)

^{(b) (4)}

16.2 Storage


Store at 20°-25°C (68°-77°F); excursions permitted to 15°C and 30°C (59°F to 86°F). Contents under pressure. Do not puncture or incinerate. Do not expose to heat or store at temperatures above 120°F (49°C). Do not freeze.

16.3 Handling

Halobetasol Propionate ^{(b) (4)} is flammable; avoid heat, flame or smoking when using this product.

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	<p>The "TRADENAME is a white to off-white foam. It is supplied in aluminum cans of" should be revised to the following: TRADENAME (halobetasol propionate) foam, 0.05% is a white to off-white foam. It is supplied in aluminum cans of:</p> <p>Not Adequate</p>
Available units (e.g., bottles of 100 tablets)	50 grams (NDC XXXXX-XXX-XX) (b) (4)	(b) (4) Not Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	white to off-white foam	Adequate
Special handling (e.g., Dispense in tight and light resistant container as defined in USP)	TRADENAME is flammable; avoid heat, flame or smoking when using this product.	Adequate
Storage conditions	Store at 20°-25°C (68°-77°F); excursions permitted to 15°C and 30°C (59°F to 86°F). Contents under pressure. Do not puncture or incinerate. Do not expose to heat or store at temperatures above 120°F (49°C). Do not freeze.	Adequate
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for (b) (4) By: Pharnasol Corporation, Easton, MA 02375 Provided after section 17 Patient Counseling Information	Adequate

This section is not adequate. The following revision should be made:

1. The “TRADENAME is a white to off-white foam.” should be revised to: TRADENAME (halobetasol propionate) foam, 0.05% is a white to off-white foam.
2.  (b) (4)

II. Labels:

1. Immediate Container Label



Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2)))	<p>[TRADEMARK]</p> <p>(halobetasol propionate) Topical Foam, 0.05%</p>	<p>“Topical” should be removed from dosage form</p> <p>Not Adequate</p>
Dosage strength Active moiety expression of strength with equivalence statement (if applicable), if space is available	0.05%	Adequate
Net contents	50 g (17 g for physician sample)	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 that “see bottom of the can for Lot No./Exp. Date”	Adequate
Storage conditions Special handling, e.g., “Dispense in tight and light resistant container as defined in USP”.	<p>Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). Protect from freezing.</p> <p>Warning: Flammable. Avoid fire, flame, or smoking during and immediately following application. Contents under pressure. Do not puncture or incinerate container. Do not expose to heat or store at temperatures above 120°F (49°C).</p>	Adequate
Bar code (21CFR 201.25)	Not provided	Not Adequate
Name of manufacturer/distributor	Provided	Adequate

<p>And others, if space is available</p>	<p>Shake well before each application and invert can to dispense. USUAL DOSAGE: Apply twice daily to affected skin areas or as directed by physician. Rub in gently. (b) (4)</p> <p>(b) (4)</p> <p>Each gram contains: Active: halobetasol propionate 0.5 mg. Inactive: Alcohol (b) (4), specially denatured alcohol [SDA]; purified water, (b) (4) propylene glycol, (b) (4) emulsifying wax, (b) (4) cetostearyl alcohol, (b) (4) polyoxyl 20 cetostearyl ether, (b) (4) and benzoic acid, (b) (4)</p>	<p>For the ingredients section:</p> <p>1) Add “a hydrocarbon propellant containing isobutane and propane”</p> <p>2) (b) (4)</p> <p>(b) (4)</p> <p>Remove (b) (4) for the inactive ingredients.</p> <p>Not Adequate</p>
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This section is not adequate. The following revision should be made:

1. Include bar code on the container labels
2. For the ingredients section displayed:
 - 1) Add “a hydrocarbon (isobutane and propane) propellant”
 - 2) (b) (4) Remove (b) (4) for the inactive ingredients.

2. Carton Label

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	[TRADEMARK] (halobetasol propionate) (b) (4), 0.05%	Adequate
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	0.05%	Adequate
Net quantity of dosage form	50 g	Adequate
"Rx only" displayed prominently on the main panel	provided	Adequate
Lot number and expiration date	See Lot number and expiration date on the bottom flap of this carton. Lot No.: ##### Exp.: MM/YYYY	Adequate
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Warning: Flammable. Avoid fire, flame, or smoking during and immediately following application. Contents under pressure. Do not puncture or incinerate container. Do not expose to heat or store at temperatures above 120°F (49°C). Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). Protect from freezing.	Adequate
Bar code (21CFR 201.25)	Space for barcode is provided	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Provided	Adequate
Manufacturer/distributor's name	Manufactured for (b) (4) (b) by Pharnasol Corporation (Easton, MA 02375)	Adequate

Quantitative ingredient information (injectables)	Each gram contains: Active: halobetasol propionate 0.5mg. Inactive: Alcohol, (b) (4) (specially denatured alcohol [SDA]); purified water, (b) (4) propylene glycol, (b) (4) emulsifying wax, (b) (4) cetostearyl alcohol, (b) (4) polyoxyl 20 cetostearyl ether, (b) (4) and benzoic acid, (b) (4)	For the ingredients section displayed: 1) Add “a hydrocarbon propellant containing isobutane and propane” 2) (b) (4). Remove (b) (4) for the inactive ingredients. Not Adequate
Statement of being sterile (if applicable)	N/A	Adequate
“See package insert for dosage information”	Usual Dosage: Apply twice daily to affected skin areas or as directed by physician. Rub in gently. (b) (4) (b) (4) See (b) (4) package insert for (b) (4) prescribing information (b) (4) and instructions for use. (b) (4)	Adequate
“Keep out of reach of children” (Required for OTC in CFR. Optional for Rx drugs)	Provided	Adequate

This section is not adequate. The following revision should be made:

1. For the ingredients section displayed:
 - 1) (b) (4) Remove (b) (4) for the inactive ingredients.
 - 2) Add “a hydrocarbon (isobutane and propane) propellant”
2. Provide carton mock up for physician samples

List of Deficiencies:

For the Labeling insert

1. The section 11 should be revised to:
 - 1) The Proprietary name and established name should be written as Tradename (halobetasol propionate) foam in the beginning of the paragraph
 - 2) (b) (4) The excipients should be included as: alcohol (specifically denatured alcohol [SDA]), benzoic acid, cetostearyl alcohol, emulsified wax, polyoxyl 20 cetostearyl ether, propylene glycol, purified water

- 3) Include a description of the propellant reading as: Tradename is dispensed from an aluminum can pressurized with a hydrocarbon (isobutane and propane) propellant
2. The section 16 should be revised to:
 - 1) The “TRADENAME is a white to off-white foam.” should be revised to: TRADENAME (halobetasol propionate) foam, 0.05% is a white to off-white foam.
 - 2) [REDACTED] (b) (4)

For the Container Labels:

1. “Topical” should be removed from dosage form.
2. Include bar code on the container labels
3. For the ingredients section:
 - 1) [REDACTED] (b) (4) Remove [REDACTED] (b) (4) for the inactive ingredients.
 - 2) The excipients should be included in alphabetical order.
 - 3) Add “a hydrocarbon (isobutane and propane) propellant”

For the Carton Labels:

1. For the ingredients section:
 - 1) [REDACTED] (b) (4) Remove [REDACTED] (b) (4) for the inactive ingredients.
 - 2) The excipients should be included in alphabetical order.
 - 3) Add “a hydrocarbon (isobutane and propane) propellant”
2. Provide carton mock up for physician samples

Overall Assessment and Recommendation:

The labels and labeling are not acceptable for approval of this application until the above deficiencies are adequately addressed.

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 concur with Dr. Ge’s assessment and her recommendation that this application is not ready for approval in its present form from the labeling perspective per 21 CFR 314.125(b)(6) until the deficiencies in the **List of Deficiencies** are satisfactorily resolved.

Moo-Jhong Rhee, Ph. D.

Branch Chief, BRANCH V/DIVISION II
OFFICE OF NEW DRUG PRODUCT



Zhengfang
Ge

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Date: 2/16/2018 10:32:09AM
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Moo Jhong
Rhee

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Date: 2/16/2018 12:58:56PM
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BIOPHARMACEUTICS***Product Background:*****NDA:** 210566 ORIG-1**Drug Product Name / Strength:** Halobetasol Propionate Foam, 0.05%**Route of Administration:** Topical**Applicant Name:** Therapeutics, Inc.

There are three marketed formulations of Halobetasol Propionate (HBP), ULTRAVATE® Cream, Ointment, and Lotion, each containing 0.05% HBP as the active ingredient and several generic cream and ointment formulations currently available in the United States. This NDA submission for HBP is to be marketed as immediate release foam in one concentration/strength. The proposed drug product is a topical aerosol foam (hydro-ethanolic foam) which contains 0.05% w/w halobetasol propionate as the active ingredient in a solution of ethanol and water with (b) (4) % propylene glycol proposed for the treatment of psoriasis. The proposed dosing regimen (i.e., twice daily topical for two weeks) and maximum recommended dose (i.e., up to (b) (4) 50 grams per week) are consistent with those of the currently marketed HBP topical formulations. Seven clinical studies were conducted with HBP Foam: two Phase 1, two Phase 2, and three Phase 3 studies.

Review Summary:

The Applicant is seeking approval of Halobetasol Propionate Foam, 0.05% for the treatment of psoriasis. This 505b drug product relies on PK and pivotal Phase 3 studies to support its approval. There were no major changes implemented to the clinical trial formulation. The phase 3 clinical and to-be-marketed (TBM) HBP Foam Formulation is 338-13-6, is very similar to the one used in the vasoconstriction study (Formulation (b) (4)). (b) (4)

The manufacturing site for the clinical and commercial product is Pharmasol Corporation, in Massachusetts, USA. The drug product is a hydroethanolic foam where the API is in solution. Therefore, the assurance of the quality of the drug product relies on drug product

specifications (other than in vitro release testing) and in process controls characteristic of topical aerosol foam formulations.

List Submissions being reviewed (table):

SUBMISSION(S) DATE	SEQUENCE NO.
7/28/17	0000

Highlight Key Outstanding Issues from Last Cycle: NONE

Concise Description Outstanding Issues Remaining: NONE

The following comments were conveyed to the CMC reviewers during the review cycle:

1.

(b) (4)

Response received via email on 2/16/18 by Drs. Youmin Wang and Yichun Sun

(b) (4)



(b) (4)

From Biopharmaceutics perspective, NDA 210566 for Halobetasol Propionate Foam, 0.05% is recommended for Approval.

Primary Biopharmaceutics Reviewer Name and Date:

Sandra Suarez Sharp, Ph.D. (Branch 2DB\ONDP\OPQ), 3/19/18

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

Vidula Kolhatkar, Ph.D., Acting Team Lead (Branch 2\DB\ONDP\OPQ), 3/20/18



Sandra
Suarez

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Vidula
Kolhatkar

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MICROBIOLOGY

Product Background:

NDA/ANDA/BLA: 210566

Drug Product Name / Strength: Halobetasol Propionate Foam, 0.05%

Route of Administration: topical

Applicant Name: (b) (4)

Manufacturing Site: Pharmasol Corporation One Norfolk Ave South Easton, MA 02375

Method of Sterilization: Not applicable (non-sterile)

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

Review Summary: This is a non-sterile foam supplied in 35 × 70 mm aluminum cans as physician samples and 38 × 106 mm aluminum cans in the commercial configuration.

List Submissions being reviewed: 07/28/2017, 10/16/2017, 12/01/17

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: N/A

Supporting/Related Documents: N/A

Remarks Section: N/A

S Drug Substance – Not applicable

P.1 Description of the Composition of the Drug Product

(Section 3.2.P.1, Description and Composition of the Drug Product.pdf)

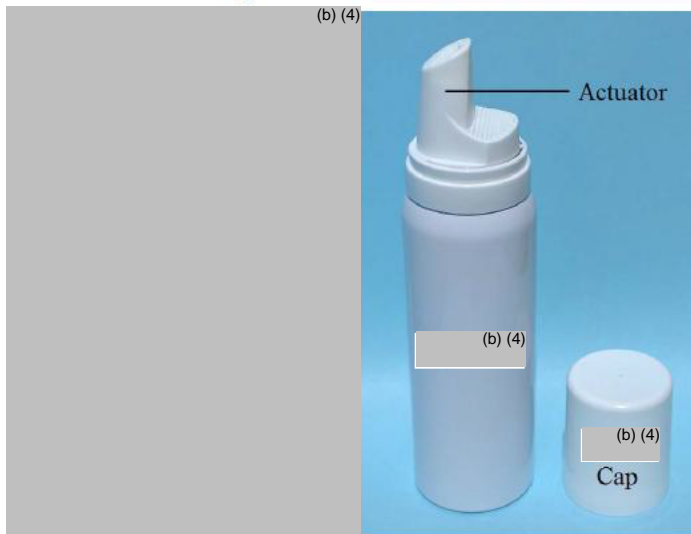
- **Description of drug product** – Halobetasol Propionate Foam, 0.05% is a topical aerosol foam that contains drug product in a solution of ethanol and water with (b) (4)% propylene glycol. (b) (4)
- **Drug product composition** –

Ingredient	Function	Quantity (% w/w)

Halobetasol Propionate, USP	API	0..05
Alcohol, denatured, USP	(b) (4)	
Propylene Glycol, USP		
Emulsifying Wax, NF		
Polyoxyl 20 Cetostearyl Ether, NF		
Cetostearyl Alcohol, NF		
Purified water, USP		
Benzoic Acid, USP		

- Description of container closure system –**

Plain, white glossy aluminum can with (b) (4) actuator with cover/cap.



Reviewer's Assessment: ADEQUATE

The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity – Not applicable.

Antimicrobial Effectiveness Testing

(3.2.A tm-100-4-273.pdf)

Antimicrobial effectiveness testing was performed according to USP <51>.

Preservative: (b) (4)

This is a category 2 product (topical made with aqueous base) therefore the following acceptance criteria should be met.

- Product should have NLT 2.0 log reduction from initial count at 14 days, and no increase from the 14 days' count at 28 days for bacteria.
- No increase from the initial calculated count at 14 and 28 days.

The applicant tested (b) (4)

Below is a summary of the (b) (4) tests results:

Organism	Log Reduction	
	Day 14	Day 28
<i>A. brasiliensis</i> (ATCC 16404)	1.9	5.3
<i>C. albicans</i> (ATCC 10231)	5.7	5.7
<i>E. coli</i> (ATCC 8739)	5.9	5.9
<i>S. aureus</i> (ATCC 6538)	5.8	5.8
<i>P. aeruginosa</i> (ATCC 9027)	5.7	5.7

Results meet acceptance criteria for category 2 product (b) (4)

Reviewer's Assessment: **ADEQUATE**

Testing meets acceptance criteria of USP <51>.

P.3 Manufacture

P.3.1 Manufacturers

(3.2.P.3.1, Manufacturers.pdf)

Pharmasol Corporation One Norfolk Ave South Easton, MA 02375

(b) (4)

Reviewer's Assessment: **ADEQUATE**

The drug product manufacturer has been adequately identified by the applicant.

P. 3.3 Description of the Manufacturing Process and Process Controls

Overall Manufacturing Operation

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P.7 Container Closure

Summary table of the container closure system proposed – Not Applicable

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(Section 3.2.P.8.1, Stability Summary and Conclusions.pdf)

Microbiological testing (USP <61> and <62>) is performed at  (b) (4)

Proposed Expiry:  (b) (4)

Deficiency (Submitted 10/6/17): Provide a commitment to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability

batch at the end of the proposed shelf life (reference ICH Q1A Stability Testing of New Drug Substances and Products for new drug products).

Response (Received 10/26/17): The applicant states that the AET testing completed on (b) (4) and is therefore a worst case for the product. In addition, the BCC testing was completed on a drug product lot that was manufactured 31 months prior and this is also worse case. However, this does not exempt the applicant from including Antimicrobial Effectiveness Testing on at least on primary stability batch at the end of proposed shelf life. This is not included in the submission. (b) (4)

Response (Received 12/01/17): The stability protocol is updated to include AET at 36 months for the inverted position at $25 \pm 2^\circ\text{C}$ and $60 \pm 5\%$ R.H. Section 3.2.P.8.1 is updated with this information.

Reviewer’s Assessment: ADEQUATE

The stability protocol is adequate.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

The stability specification requires a TAMC of NMT (b) (4) cfu/gm, TYMC of NMT (b) (4) cfu/gm, and the absence/mL of *S. aureus* and *P. aeruginosa*. USP <61> and <62> methods will be used for microbial limits testing. (b) (4)

The testing schedule in the post-approval protocol for microbial limits testing is as follows:

Stability storage conditions: $25^\circ\text{C} \pm 2^\circ\text{C}$, $60\% \text{ RH} \pm 5\% \text{ RH}$ Upright and Inverted

Orientation	Time (Months)							
	0	3	6	9	12	18	24	36
Upright	X		X		X	X	X	X
Inverted	X		X		X	X	X	X

Post Approval Stability Commitment

The applicant commits to placing the first three marketed lots in each configuration of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot of each configuration will be added to the stability program.

Reviewer’s Assessment: ADEQUATE

The stability protocol and commitment for stability are adequate.

P.8.3 Stability Data

(Section 3.2.P.8.3, Stability Data)

Stability data was provided for lot numbers 25452 for (b) (4) can clinical size and lot numbers 30217, 30218, and 30224 for the physician sample size and commercial size. All lots met the stability acceptance criteria for TAMC, TYMC, absence of specified organisms under long term conditions ($25\pm 2^{\circ}\text{C}$, %R.H. $60\pm 5\%$) at 6, 12, 18 and 24 months.

Reviewer's Assessment: ADEQUATE

The stability data provided by the applicant supports the maintenance of microbiological quality during storage.

A Appendices

A.2 Adventitious Agents Safety Evaluation

Reviewer's Assessment: Not applicable

A.2.1 Materials of Biological Origin

Reviewer's Assessment: Not applicable

A.2.2 Testing at Appropriate Stages of Production

Reviewer's Assessment: Not applicable

A.2.3. Viral Testing of Unprocessed Bulk

Reviewer's Assessment: Not applicable

A. 2.4 Viral Clearance Studies

Reviewer's Assessment: Not applicable

R Regional Information

Executed Batch Records

The executed batch records provided do not provide information concerning manufacturing processes used to maintain the microbiological quality of the subject drug product.

Reviewer's Assessment: Not applicable.

Comparability Protocols – No CP was included in the application.

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

2.A. Package Insert

(1.14.1.3, HBP Foam, 0.05% Package Insert (Draft).pdf)

The proposed storage conditions for the drug product include a storage temperature of $20 - 25^{\circ}\text{C}$ with excursions permitted to $15 - 30^{\circ}\text{C}$ and an expiry period of (b) (4). Shake canister prior to use and apply a thin film of product to affected skin twice daily for up to 2 weeks. Treatment should not exceed two weeks and dosage should not exceed one can per week. The product is labeled for topical use only.



QUALITY ASSESSMENT



Reviewer's Assessment: ADEQUATE

The instructions for use and storage conditions are adequate.

Post-Approval Commitments: N/A

Lifecycle Management Considerations

Reviewer's Assessment: Changes to the post-approval stability protocol would require review.

List of Deficiencies:

Primary Microbiology Reviewer Name and Date: Jennifer N. Patro, Ph.D., 12/14/2017

Secondary Reviewer Name and Date: Erika Pfeiler, Ph.D. 12/14/2017



Jennifer
Patro

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Erika
Pfeiler

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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: May 21, 2018

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 210566

Subject: Final labeling/labels

The Labeling review #1 has noted the following pending issues:

For the Labeling insert

1. The section 11 should be revised to:
 - 1) The Proprietary name and established name should be written as Tradename (halobetasol propionate) foam in the beginning of the paragraph
 - 2) [REDACTED] (b) (4) The excipients should be included as: alcohol (specifically denatured alcohol [SDA]), benzoic acid, cetostearyl alcohol, emulsified wax, polyoxyl 20 cetostearyl ether, propylene glycol, purified water
 - 3) Include a description of the propellant reading as: Tradename is dispensed from an aluminum can pressurized with a hydrocarbon (isobutane and propane) propellant
2. The section 16 should be revised to:
 - 1) The "TRADENAME is a white to off-white foam." should be revised to: TRADENAME (halobetasol propionate) foam, 0.05% is a white to off-white foam.
 - 2) [REDACTED] (b) (4)

For the Container Labels:

1. "Topical" should be removed from dosage form.
2. Include bar code on the container labels
3. For the ingredients section:

- 1) (b) (4) Remove (b) (4) for the inactive ingredients.
- 2) The excipients should be included in alphabetical order.
- 3) Add “a hydrocarbon (isobutane and propane) propellant”

For the Carton Labels:

1. For the ingredients section:
 - 1) (b) (4) Remove (b) (4) for the inactive ingredients.
 - 2) The excipients should be included in alphabetical order.
 - 3) Add “a hydrocarbon (isobutane and propane) propellant”
2. Provide carton mock up for physician samples

And because of these deficiencies, in the Labeling Review #1, this NDA was not recommended for approval from the labeling perspective.

The above requests have been implemented in the revised labeling. Based on the recently published Agency’s draft product title guidance, a dosage form of “topical foam” should be used in place of (b) (4) that was previously used. Therefore, (b) (4) has been changed to “topical foam” in labeling/labels.

On May 11, 2018, the applicant informed the Agency that the company may not have the right to use the proposed proprietary name. Therefore, the company has proposed to revise the drug product name, dosage form and strength as “Halobetasol Propionate topical foam, 0.05%”. The change is acceptable from CMC perspective. The revised carton/container labels are provided in the **Attachment**.

Recommendation:

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



Zhengfang
Ge

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Moo Jhong
Rhee

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