

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208079Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

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

Date: January 22, 2016
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 208079

Subject: Final Approval Recommendation for NDA 208079

At the time when the CMC review #1 was written, the NDA was recommended for approval from the ONDP's perspective. However, minor changes have been made to the package insert, and container and carton labels regarding the manufacturer and distributor.

Label/Labeling

The container carton labels were revised and submitted on December 23, 2015 by the NDA applicant. The package insert was updated on January 20, 2016. The CMC sections of the final package insert, and mock-up container and carton labels have been reviewed by Dr. Hamid Shafiei and found acceptable according to Dr. Hamid Shafiei's emails dated January 6, 2016 and January 21, 2016, respectively. The CMC sections of the final package insert, and mock up container and carton labels are attached (**Attachment - 1**).

Recommendation:

The revised package insert, and mock-up container and carton labels are acceptable from the quality perspective, and therefore, the previous **Approval** recommendation for this application remains valid. An expiration dating period of **24 months** is granted for the drug product of NDA 208079.

Application Technical Lead's Assessment and Signature

The NDA is recommended for approval from quality perspective.

Yichun Sun, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
1/22/2016

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

1. Package Insert

(a) "Highlights" Section

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SERNIVO™ Spray safely and effectively. See full prescribing information for SERNIVO™ Spray.

SERNIVO™ (betamethasone dipropionate) Spray, 0.05% for topical use

Initial U.S. Approval: 1975

————— DOSAGE FORMS AND STRENGTHS —————

Spray: 0.05% (equivalent to 0.5 mg betamethasone/g) (3)

(b) "Full Prescription Information" Section

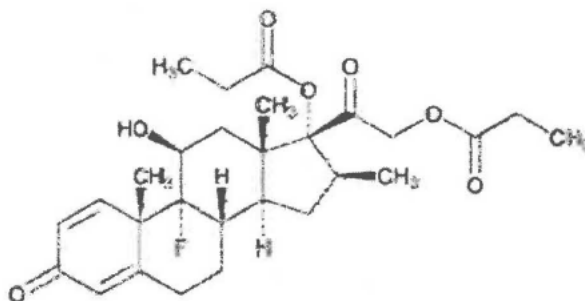
3 DOSAGE FORMS AND STRENGTHS

Spray, 0.05% for topical use. Each gram of SERNIVO Spray contains 0.643 mg betamethasone dipropionate USP (equivalent to 0.5 mg betamethasone) in a slightly thickened, white to off-white oil-in-water emulsion.

11 DESCRIPTION

SERNIVO Spray contains 0.0643% betamethasone dipropionate (equivalent to 0.05% betamethasone), a synthetic, fluorinated corticosteroid.

The chemical name for betamethasone dipropionate is 9-fluoro-11 β , 17, 21-trihydroxy-16 β -methylpregna-1,4-diene-3,20-dione-17,21-dipropionate. The empirical formula is C₂₈H₃₇F₂O₇ and the molecular weight is 504.6. The structural formula is shown below.



Each gram of SERNIVO Spray contains 0.643 mg of betamethasone dipropionate USP (equivalent to 0.5 mg betamethasone) in a slightly thickened, white to off-white, oil-in-water, non-sterile emulsion with the following inactive ingredients: butylated hydroxytoluene, cetostearyl alcohol, hydroxyethyl cellulose, methylparaben, mineral oil, oleyl alcohol, polyoxyl 20 cetostearyl ether, propylparaben, purified water, and sorbitan monostearate. SERNIVO Spray is co-packaged with a manual spray pump for installation by the pharmacist prior to dispensing to patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied/Storage

SERNIVO Spray is a slightly thickened, white to off-white, non-sterile emulsion supplied in high density polyethylene bottles with a heat induction seal lined polypropylene cap. The drug is supplied in the following volumes:

- 60 mL (NDC 67857-808-17)
- 120 mL (NDC 67857-808-04)

Store at controlled room temperature of 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

Each unit is co-packaged with a manual spray pump for installation by the pharmacist prior to dispensing.

16.2 Handling/Instructions for the Pharmacist

1. Remove the spray pump from the wrapper.
2. Remove and discard the cap from the bottle.
3. Keeping the bottle upright, insert the spray pump into the bottle and turn clockwise until it is closed tightly.
4. Dispense the bottle with the spray pump inserted.
5. Include the date dispensed in the space provided on the carton.

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



QUALITY ASSESSMENT



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

NDA 208079 Review #1

Drug Name/Dosage Form	SERNIVO® (Betamethasone Dipropionate) Spray
Strength	0.05%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Promius Pharma, LLC
US agent, if applicable	Hari Nagaradona, Ph.D.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	4/6/2015	N/A
Amendment	6/24/2015	Drug product and drug product process
Amendment	7/15/2015	Drug substance, drug product, biopharmaceutics, quality microbiology
Amendment	9/16/2015	Drug product process and quality microbiology
Amendment	9/29/2015	Quality microbiology
Amendment	10/14/2015	Drug product process
Amendment	11/6/2015	Quality microbiology
Amendment	11/10/2015	Drug product
Amendment	12/9/2015	Drug product
Amendment	12/10/2015	Biopharmaceutics

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sukhamaya (Sam) Bain	Branch II/Division of New Drug API
Drug Product	Hamid Shafiei	Branch V/Division of New Drug Products II
Process	Yaodong (Tony) Huang	Branch VIII/Division of Process Assessment III
Microbiology	Erika Pfeiler	Branch I/Division of Microbiology Assessment
Facility	Tony Wilson	Branch III/Division of Inspection Assessment
Biopharmaceutics	Vidula Kolhatkar	Branch II/Division of Biopharmaceutics
Regulatory Business Process Manager	Maria Cowan	Branch I/Division of Regulatory and Business Process



CHEMISTRY REVIEW



		Management
Application Technical Lead	Yichun Sun	Branch V/Division of New Drug Products II
ORA Lead	Paul Perdue, Jr	Division of Medical Products & Tobacco Operations
Environmental Assessment (EA)	Hamid Shafiei	Branch V/Division of New Drug Products II



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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)	Betamethasone dipropionate	Adequate	03-SEP-2015	N/A
	Type III (if applicable)		(b) (4)	N/A	N/A	N/A
	Type III			N/A	N/A	N/A
	Type III			N/A	N/A	N/A
	Type III			N/A	N/A	N/A
	Type III			N/A	N/A	N/A
	Type III			N/A	N/A	N/A
	Type III			N/A	N/A	N/A

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

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Pre-NDA meeting minutes	IND 104853	Discussion of the planned 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

A. Recommendation and Conclusion on Approvability

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

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

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

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

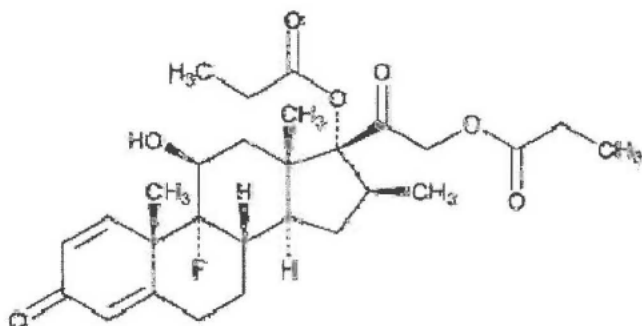
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

The drug substance/active pharmaceutical ingredient (API) used in the drug product, (betamethasone dipropionate spray), is betamethasone dipropionate. The drug substance is chemically produced. The chemical name of betamethasone dipropionate is: [2-[(8S,9R,10S,11S,13S,14S,16S,17R)-9-fluoro-11-hydroxy-10,13,16-trimethyl-3-oxo-17-propanoyloxy-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-17-yl]-2-oxoethyl] propionate. It has the following structural formula:



Betamethasone dipropionate is a white to cream-white, odorless powder with a molecular weight of 504.60 and a molecular formula of $C_{28}H_{37}FO_7$. It is insoluble in water; freely soluble in acetone; freely soluble in chloroform; and freely soluble in dichloromethane and in acetone. Betamethasone dipropionate is packaged in (b) (4). Detailed CMC information for betamethasone dipropionate is referred to DMF # (b) (4). The DMF has been

reviewed and found adequate in supporting the use of the drug substance in the NDA. The recommended retest period for betamethasone dipropionate is (b) (4) months when stored at room temperature in the proposed container closure system based on the DMF review # 6 conducted by Dr. Richard Chang. However, the NDA applicant indicated that the applicant intends to retest the drug substance (b) (4).

B. Drug Product [Established Name] Quality Summary

The drug product, SERNIVO (betamethasone dipropionate) Spray, is a slightly thickened oil-in-water emulsion containing 0.05% (w/w) betamethasone dipropionate (potency expressed as betamethasone, 0.643 mg betamethasone dipropionate equivalent to 0.5 mg of betamethasone). Betamethasone dipropionate is a corticosteroid indicated for the topical treatment of moderate plaque psoriasis in patients 18 years of age or older. The drug product is a white to off-white lotion. Each gram of SERNIVO lotion contains 0.643 mg betamethasone dipropionate, (equivalent to 0.5 mg betamethasone) in a lotion vehicle consisting of butylated hydroxytoluene, cetostearyl alcohol, hydroxyethyl cellulose, methylparaben, mineral oil, oleyl alcohol, polyoxyl 20 cetostearyl ether, propylparaben, purified water, and sorbitan monostearate. Betamethasone dipropionate Spray, 0.05%, is packaged in a high density polyethylene (HDPE) bottle with a heat induction seal and a polypropylene cap. A spray pump is also co-packaged with the bottle in each carton. When the product is assembled, the cap will be removed and replaced with the spray pump which will be tightly affixed on to the bottle prior to use. The assembled spray pump is designed to deliver approximately 0.16 ml per actuation.

The lotion is prepared by

(b) (4)

(b) (4)

The in-process controls and tests implemented during the drug product manufacturing process include the following:

(b) (4)

The identity, strength, purity including microbial limits, and quality of the drug product are deemed assured by the drug product specification. (b) (4)

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

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Sernivo
Non Proprietary Name of the Drug Product	Betamethasone dipropionate spray
Non Proprietary Name of the Drug Substance	Betamethasone dipropionate
Proposed Indication(s) including Intended Patient Population	Betamethasone dipropionate spray is indicated for the treatment of moderate plaque psoriasis in patients 18 years of age or older.
Duration of Treatment	For up to 4 weeks of treatment
Maximum Daily Dose	Spray to the affected skin areas twice daily
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Classification:

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

2. Biowaivers/Biostudies

- Biowaiver Requests: N/A
- PK studies: N/A
- IVIVC: N/A
- IVRT: The IVRT is not mandatorily required for the drug product. The lack of IVRT information does not affect approvability of this NDA. However, as recommended by the Biopharm review team, the applicant will develop an IVRT method for the drug product. The IVRT method development and validation are in progress and the acceptance criterion of IVRT will be established based on data generated during testing of the marketed drug product.

E. Novel Approaches

N/A

F. Any Special Product Quality Labeling Recommendations

Shake well and avoid freezing.

G. Life Cycle Knowledge Information (see Attachment A)



QUALITY ASSESSMENT



OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

The NDA is recommended for approval from quality perspective.

Yichun Sun, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
12/16/2015

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ASSESSMENT OF THE BIOPHARMACEUTICS

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

In the June 16, 2015 74-day letter, the Agency recommended that the applicant develop an in vitro release test (IVRT) methodology and propose in vitro release acceptance criteria (range) for the proposed drug product to be used at release and during stability as a quality control parameter.

Applicant's Response:

On July 15, 2015 the applicant provided the following response for the request:



However, the applicant indicated that they will initiate development of an in vitro release test (IVRT) method and establish acceptance criterion for the drug product.

To date, the applicant has not submitted IVRT method or acceptance criterion. This is not an approvability issue.

The following Information Requests (IRs) were communicated to the applicant on December 08 and December 09, 2015:

In response to the 74-day letter, you indicated that you will initiate development of an in vitro release test (IVRT) method per amendment received on July, 15, 2015. We have not received any IVRT information to date.

Please provide your IVRT method development plan and update the status of your IVRT method development.

Please submit your response to our Information Request by December 10. We only ask that you **confirm your plan** to develop an IVRT method.

Please note we will not review any IVRT information at this point. Therefore, we are not requesting a submission of the IVRT method development and validation report this late in the review cycle.

The applicant provided the following update on December 10, 2015:

- The method development and validation is ongoing in accordance with the guidance from the Agency in 74-day letter.
- The method development technical report has been finalized.
- Going forward, IVRT acceptance criterion for the drug product will be established based on data generated during testing of the marketed drug product.

Reviewer's Assessment: The applicant indicated that they will initiate development of an in vitro release test (IVRT) method but have not submitted any IVRT information to date. Although the lack of IVRT information does not affect approvability of this NDA, the applicant was requested to confirm their plan to develop an IVRT method per their response in the July 15, 2015 amendment. The applicant's confirmation that method development and validation work is in progress is acceptable.

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

No bridging studies are needed. After initial formulation development studies, subsequent clinical trials were conducted with the final to-be-marketed formulation including the two Phase 3 studies, the HPA axis suppression study with PK sampling, and the Phase 1 dermal safety studies. This was confirmed with the Clinical Pharmacology reviewer Dr. Doanh Tran and the Clinical reviewer Dr. Hon Sum Ko.

Applicant's Response: N/A

Reviewer's Assessment: No bridging studies are needed.



QUALITY ASSESSMENT



OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature: There is no biopharmaceutics information to review in this application. As recommended by Division of Biopharmaceutics, the applicant indicated that they will initiate development of an in vitro release test (IVRT) method, but have not submitted any report to date. Although the lack of IVRT information does not affect approvability of this NDA, the applicant was asked to confirm their plan to develop an IVRT method. The applicant's confirmation that the method development and validation work is in progress and IVRT acceptance criterion will be established based on data generated during testing of the marketed drug product is acceptable.

Reviewer's Signature

Vidula Kolhatkar, Ph.D.

Branch II

Division of Biopharmaceutics/ONDP

12/10/2015

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Secondary Review Comments and Concurrence:

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

Supervisor's Signature

Kelly Kitchens, Ph.D.

Acting Quality Assessment Lead, Branch II

Division of Biopharmaceutics/ONDP

12/10/2015

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ASSESSMENT OF MICROBIOLOGY

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

Applicant's Response: Betamethasone Dipropionate Spray 0.05% is for topical administration. The product is intended for multiple uses and contains (b) (4) propylparaben and (b) (4) methylparaben (b) (4).

The drug product is tested for microbial limits at (b) (4) using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The microbial limits acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use). This chapter recommends that products for cutaneous use contain NMT 10^2 CFU/mL total aerobic microbial count, NMT 10^1 CFU/mL total combined yeasts/molds count, and that *Staphylococcus aureus* and *Pseudomonas aeruginosa* be absent in 1 ml. Additionally, the release specification for the drug product states that *Escherichia coli*, *Salmonella* species, *Candida albicans*, *Burkholderia cepacia*, and bile tolerant gram negative bacteria should be absent. The microbial limits test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapters <61> and <62>. (See the final paragraph in this review for information on the proposed *Burkholderia cepacia* testing method).

Since this product is intended for multiple uses, antimicrobial effectiveness testing was performed using methods described in USP <51> (Antimicrobial Effectiveness Testing). Testing was performed on product formulations containing 75%, 100%, and 125% of the stated preservative strength. All formulations achieved the acceptance criteria described in USP <51> for category 2 products.

Methylparaben and propylparaben content is tested (b) (4) with acceptance criteria (b) (4).

(b) (4)

The following information requests were submitted to the applicant over the course of the review, and a summary of responses is documented below.

16 June 2015 Information Request

Non-sterile aqueous drug products may potentially be contaminated with organisms in the *Burkholderia cepacia* complex (BCC). BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, BCC strains can survive and even proliferate in product during storage. For a recent review of FDA's perspective on BCC please see *PDA J Pharm Sci Tech* 2011; 65(5): 535-43.

In order to control for the presence of BCC in the proposed drug product, please consider the following:

- A. Identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.
- B. Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC. The test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g., temperature) before testing.

As there are currently no compendial methods for detection of BCC, we have provided suggestions for a potential validation approach and some points to consider when designing validation studies. However, any validated method capable of detecting BCC organisms would be adequate. It is currently sufficient to precondition representative strain(s) of BCC in water and/or the drug product without preservatives to demonstrate that the proposed method is capable of detecting small numbers of BCC. The submission should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to insure that the proposed recovery methods are adequate to recover organisms potentially present in the environment.

For more information, please refer to *Envir Microbiol* 2011; 13(1):1-12 and *J. Appl Microbiol* 1997; 83(3):322-6.

15 July 2015 Response

The applicant committed to performing a BCC risk assessment and establishing product testing if necessary.

02 September 2015 Information Request

The 15 July 2015 Information Request response is acknowledged. This response states that a product-specific risk assessment will be performed for the presence of *Burkholderia cepacia* (BCC) in raw materials and in the finished drug product, and that testing will be implemented based on the outcome of the risk assessment. More information is needed. Please address the following points:

- a. A description of the BCC risk assessment and its outcome is necessary for review. Please provide this information.
- b. If the outcome of the risk assessment results in the addition of a BCC specification for raw materials or finished product, this information should be submitted for review. This information should include a description of validation studies performed to ensure the appropriateness of the selected test method.
- c. Please note that the "Assessment for the recovery of *Burkholderia cepacia* in non-selective culture media" is not adequate to demonstrate the effectiveness of the use of this test method with the drug product or raw materials, as the sampling method described demonstrates recovery of BCC from water. Please refer to the original information request (Dated 16 June 2015) regarding the Agency's expectations and suggestions for validation study parameters.

16 September 2015 Response

The applicant provided a summary of risk assessment, and stated that BCC testing validation studies were ongoing. The information regarding the risk assessment was incorporated into the text of the review.

29 September 2015 Response

The applicant provided results from BCC testing validation studies performed with *B. cepacia* (b) (4) (b) (4). The results of these studies were incorporated into the review. The applicant also provided a commitment to performing this test on *B. cepacia* (b) (4); however, noted that this strain is on backorder until December, and stated that results of the testing would be provided following its receipt.

27 October Information Request

The list of specifications provided on 16 September 2015 state that *Burkholderia cepacia* testing is performed according to methods described in DPT-SOP-02946; however, a validation testing report submitted on 29 September 2015 implies that testing will be performed using method (b) (4) (the method used for identification of *Staphylococcus aureus* and *Pseudomonas aeruginosa* from the drug product.) Please clarify the *B. cepacia* testing method used in routine product testing.

06 November 2015 Response

The applicant provided a clarification on the method used in routine testing, and also provided results of validation testing performed using *B. cepacia* (b) (4).

Reviewer's Assessment:

The proposed specification is adequate to ensure the microbiological quality of the drug product. The applicant has performed method validation test with two *Burkholderia cepacia* strains to account for phenotypic variation in this complex, and

therefore information from the backordered strain (b) (4) will not be requested.

The microbial limits specification for Betamethasone Dipropionate Spray 0.05% is acceptable from a product quality microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

2.3.P.7 Container/Closure System

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

Applicant's Response: N/A

Reviewer's Assessment: N/A

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

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

Applicant's Response: N/A

Reviewer's Assessment: N/A

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

Applicant's Response: N/A



QUALITY ASSESSMENT



Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Recommended for approval on the basis of product quality microbiology.

Reviewer's Signature

Erika Pfeiler, Ph.D.

Branch I

Division of Microbiology Assessment/OPF

11/23/15

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Secondary Review Comments and Concurrence: I concur.

Supervisor's Signature

John Arigo, Ph.D.

Chief, Branch I

Division of Microbiology Assessment/OPF

12/16/2015

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QUALITY ASSESSMENT



ASSESSMENT OF ENVIRONMENTAL ANALYSIS

28. Is the applicant's claim for categorical exclusion acceptable?

The applicant, Promius Pharma, LLC. has requested Categorical Exclusion from the environmental assessment analysis under 21 CFR § 25.31(b). Based on the estimated (b)(4) maximum number 60mL bottles intended for marketing per year and that each bottle contains (b)(4) of the active moiety, betamethasone, applicant has estimated that (b)(4) kg/year of this active moiety can be potentially introduced into aquatic environment assuming the entire amount active moiety is excreted unchanged. Based on this estimated maximum amount active moiety marketed per year, the estimated EIC is (b)(4) ppb/day which is below 1ppb threshold for preparing an Environmental Assessment under 21 CFR § 25.31(b). It is also expressed that to the applicant's knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment.

29. Is the applicant's Environmental Assessment adequate for approval of the application?

Not applicable.

Reviewer's Assessment:

Based on the estimated annual (b)(4) kg production of the active moiety that is needed to support the maximum potential marketing need for this drug product, the calculated EIC is far below 1ppb. Therefore, the applicant's request for the categorical exclusion from the environmental assessment analysis is appropriate and is granted according to 21 CFR § 25.31(b).

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:

Categorical exclusion from the environmental assessment analysis is **granted**.

Reviewer's Signature

Hamid Shafiei, Ph.D.

Branch V

Division of New Drug Products II/ONDP

12/10/2015

Hamid
Shafiei -S

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Secondary Review Comments and Concurrence:

I concur.

Supervisor's Signature

Moo-Jhong Rhee, Ph.D.

Chief, Branch V

Division of New Drug Products II/ONDP

12/15/2015

Moojhong
Rhee -S

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

Labeling & Package Insert**1. Package Insert****(a) “Highlights” Section (21CFR 201.57(a))**

SERNIVO (betamethasone dipropionate) Spray, 0.05% for topical use
Initial U.S. Approval: 1975

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	SERNIVO (betamethasone dipropionate)	Proprietary name provided. Established name not provided Satisfactory
Dosage form, route of administration	Spray, 0.05% for topical use	Dosage form and route of administration are provided. Satisfactory
Controlled drug substance symbol (if applicable)	Not applicable	Not applicable
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Spray, 0.05%	The dosage forms and strengths are described correctly. Satisfactory

Conclusion:

The Highlights Section of the PI is **Adequate**.

(b) "Full Prescribing Information" Section

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

Spray, 0.05% for topical use. Each gram of SERNIVO Spray contains 0.643 mg betamethasone dipropionate USP (equivalent to 0.5 mg betamethasone) in a slightly thickened, white to off- white, emulsion

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Spray	Provided Satisfactory
Strengths: in metric system	0.05%	Provided Satisfactory
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	A slightly thickened, white to off-white, emulsion	Appropriately described Satisfactory

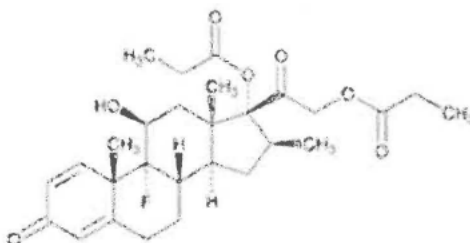
Conclusion:

The Dosage Forms and Strengths Section of the PI is Adequate.

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

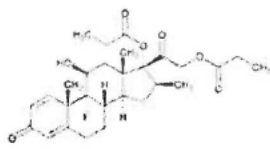
SERNIVO Spray for topical administration contains 0.0643% betamethasone dipropionate (equivalent to 0.05% betamethasone), a synthetic, fluorinated corticosteroid.

The chemical name for betamethasone dipropionate is 9-fluoro-11(β), 17, 21-trihydroxy-16(β)-methylpregna-1,4-diene-3,20-dione-17,21-dipropionate. The empirical formula is C₂₈H₃₇FO₇ and the molecular weight is 504.6. The structural formula is shown below.



Each gram of SERNIVO Spray contains 0.643 mg of betamethasone dipropionate USP (equivalent to 0.5 mg betamethasone) in a slightly thickened,

white to off- white emulsion with the following inactive ingredients: butylated hydroxytoluene, cetostearyl alcohol, hydroxyethyl cellulose, methylparaben, mineral oil, oleyl alcohol, polyoxyl 20 cetostearyl ether, propylparaben, purified water, and sorbitan monostearate. SERNIVO spray is co-packaged with a manual spray pump for installation by the pharmacist prior to dispensing to patients.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	SERNIVO Spray contains 0.0643% betamethasone dipropionate (equivalent to 0.05% betamethasone), a synthetic, fluorinated corticosteroid.	Proprietary name and established name is described correctly. Satisfactory
Dosage form and route of administration	Spray contains 0.05%	Route of administration provided. Satisfactory
Active moiety expression of strength with equivalence statement for salt (if applicable)	0.643 mg of betamethasone dipropionate USP (equivalent to 0.5 mg betamethasone)	Satisfactory
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	A slightly thickened, white to off-white emulsion with the following inactive ingredients: butylated hydroxytoluene, cetostearyl alcohol, hydroxyethyl cellulose, methylparaben, mineral oil, oleyl alcohol, polyoxyl 20 cetostearyl ether, propylparaben, purified water, and sorbitan monostearate.	Inactive ingredients of capsules and tablets are appropriately provided. Satisfactory
Statement of being sterile (if applicable)	Not applicable	Not applicable
Pharmacological/ therapeutic class	a synthetic, fluorinated corticosteroid	Satisfactory
Chemical name, structural formula, molecular weight	Chemical Name: 9-fluoro-11(β), 17, 21-trihydroxy-16(β)-methylpregna-1,4-diene-3,20-dione-17,21-dipropionate Structural formula:  Molecular weight: 504.6 Empirical formula: C ₂₈ H ₃₇ FO ₇	All necessary information provided. Satisfactory
If radioactive, statement of important nuclear characteristics.	Not applicable	Not applicable
Other important chemical or physical properties (such as pKa, solubility, or pH)	Not applicable	N/A Satisfactory

Conclusion:

The Description Section of the PI is Adequate.

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

SERNIVO Spray, 0.05% is a slightly thickened, white to off- white non-sterile emulsion supplied in high density polyethylene bottles with a heat induction seal lined polypropylene cap. The drug is supplied in the following volumes:

- 60 mL (NDC 67857-808-17)
- 120 mL (NDC 67857-808-04)

Store at controlled room temperature of 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature].

Each unit is co-packaged with a manual spray pump for installation by the pharmacist prior to dispensing.

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

Conclusion:

The information provided in sections 16 and 17 of the PI is **adequate**.

2. Container and Carton Labeling

1) Immediate Container Label

Reviewer's Assessment:

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2)))	Proprietary name, established name are provided with appropriate font size and prominence that satisfies 21 CFR 201.10(g)(2).	Satisfactory
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	0.05%	Provided Satisfactory
Net contents (21 CFR 201.51(a))	(b) (4) 60mL 120mL	Provided Satisfactory
Lot number per 21 CFR 201.18	The location on the immediate container label where the lot number will be displayed is provided. Satisfies 21 CFR 201.18.	Provided Satisfactory
Expiration date per 21 CFR 201.17	The location on the immediate container label where the expiration date will be displayed is provided. Satisfies 21 CFR 201.17.	Provided Satisfactory
"Rx only" statement per 21 CFR 201.100(b)(1)	"Rx only" is displayed. Satisfies 21 CFR 201.100(b)(1).	Displayed Satisfactory
Storage (not required)	Storage condition displayed for 60-mL and 120-mL bottles (commercial product)	Displayed Satisfactory
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR	Provided.	Displayed Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	The location on the immediate container label where the barcode will be displayed on 60-mL and 120-mL bottles (commercial product) provided.	Provided Satisfactory
Name of manufacturer/distributor	Name of manufacturer/distributor is appropriately displayed.	Displayed Satisfactory
Others	Discard the product 28 day after dispensing by pharmacist.	Satisfactory



QUALITY ASSESSMENT



* [REDACTED] (b) (4)

**For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label

**Not required for Physician’s samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion:

The proposed immediate container (bottles) label for the commercial product is **satisfactory.**

2) Carton Labeling

Reviewer's Assessment:

(b) (4)

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

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Proprietary name, established name are provided with appropriate font size and prominence that satisfies FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2).	Satisfactory
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	0.05%	Satisfactory
Net contents (21 CFR 201.51(a))	(b) (4) 60mL 120mL	Satisfactory
Lot number per 21 CFR 201.18	The location on the carton where the lot number will be displayed is provided. Satisfies 21 CFR 201.18.	Satisfactory
Expiration date per 21 CFR 201.17	The location on the carton where the expiration date will be displayed is provided. Satisfies 21 CFR 201.17.	Satisfactory
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	The inactive ingredients are listed. Inactive ingredients: purified water, mineral oil, oleyl alcohol, sorbitan monostearate, polyoxyl 20 cetostearyl ether, cetostearyl alcohol, propylparaben, methylparaben, butylated hydroxytoluene, hydroxyethyl cellulose	Satisfactory
Sterility Information (if applicable)	Non-sterile drug product. Not applicable	N/A
"Rx only" statement per 21 CFR 201.100(b)(1)	Appropriately displayed. Satisfies 21 CFR 201.100(b)(1).	Satisfactory
Storage Conditions	Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).	Satisfactory
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR	Appropriately displayed. Satisfies 21 CFR 201.2.	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	The location on the carton where the barcode will be displayed is provided. Satisfies 21 CFR 201.25(c)(2).	Satisfactory

Name of manufacturer/distributor	Manufactured by: DPT Laboratories Ltd. San Antonio, TX 78215 Distributed by: Promius Pharma, LLC Princeton, NJ 08540	Satisfactory
"See package insert for dosage information" (21 CFR 201.55)	See insert for full prescribing information is provided. Satisfies 21 CFR 201.55.	Satisfactory
"Keep out of reach of children" (optional for Rx, required for OTC)	KEEP THIS AND ALL MEDICATION OUT OF REACH OF CHILDREN is displayed.	Satisfactory
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	For Topical Use Only is displayed	Satisfactory

Conclusion:

The proposed carton labels for the commercial product are **satisfactory**.

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

The package insert, immediate container labels, and carton labels are **adequate** from the CMC perspective. Therefore, all label and labeling for the drug product, SERNIVO (betamethasone dipropionate) Spray, 0.05% are deemed **satisfactory**.

Reviewer's Signature

Hamid Shafiei, Ph.D.

Branch V

Division of New Drug Products II/ONDP

12/10/2015

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Shafiei -S

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Secondary Review Comments and Concurrence:

I concur with Dr. Shafiei's evaluation on the labeling and labels.

Supervisor's Signature

Moo-Jhong Rhee, Ph.D.

Chief, Branch V

Division of New Drug Products II/ONDP

12/15/2015

Moojhong Rhee
-S

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I. List of Deficiencies To Be Communicated

Drug Substance: None

Drug Product: None

Process: None

Facility: None

Biopharmaceutics: None

Microbiology: None

Environmental: None

Label/Labeling: None

II. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay for betamethasone dipropionate	• Formulation • Raw materials • Process parameters	Low = 32	Formulation well developed. Raw material is controlled according to compendial requirements. Assay is tested using a validated analytical method.	Acceptable (risk is re-rank lower to 10)	Review of the 24-month real time stability data for potential loss of strength.
Impurities of betamethasone dipropionate	• Formulation • Raw materials • Process parameters	Low = 32	Excipient compatibility is well established. Drug substance is well controlled. Raw material is controlled according to compendial requirements. Impurities are determined using validated analytical methods.	Acceptable (risk is re-rank lower to 10)	Review of the 24-month real time stability data for the increase in impurity (b) (4)
(b) (4)	• Control of amount added • Degradation during storage	Low = 24	The addition (b) (4) is well controlled.	Acceptable (risk is re-rank lower to 15)	Review of the 24-month real time stability data for the

			(b) (4) content in the drug product is routinely tested at (b) (4) program.		potential loss of (b) (4)
(b) (4)	- Control of amount added - Degradation during storage	Low = 24	The addition of (b) (4) is well controlled. (b) (4) contents in the drug product are routinely tested at (b) (4) program.	Acceptable (risk is re-rank lower to 15)	Review of the 24-month real time stability data for the potential loss of (b) (4)
Active Content Uniformity (B/M/E)	- Formulation - Raw materials - Process parameters - Scale/equipment	Low = 32	The content uniformity is routinely tested (USP <3>).	Acceptable (risk is re-rank lower to 10)	None
Minimum Fill	- Process parameters - Scale/equipment - Site	Low = 32	The minimum fill is routinely tested (USP <755>).	Acceptable (risk is re-rank lower to 6)	None

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OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 208079 **Submission Type:** NDA

Established/Proper Name:
betamethasone dipropionate

Applicant: Promius
Pharma, LLC

Letter Date: 4/6/15

Dosage Form: Spray

Chemical Type: Type
3, New formulation

Stamp Date: 4/6/15

Strength: 0.05%

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.		X	N/A
3.	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?	X		Comments and information requests to be forwarded to the applicant are listed at the end of the filing review.

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity ¹	☐	☒	
2.	Botanical ¹	☐	☒	
3.	Naturally-derived Product	☐	☒	
4.	Narrow Therapeutic Index Drug	☐	☒	
5.	PET Drug	☐	☒	
6.	PEPFAR Drug	☐	☒	
7.	Sterile Drug Product	☐	☒	
8.	Transdermal ¹	☐	☒	
9.	Pediatric form/dose ¹	☐	☒	
10.	Locally acting drug ¹	☒	☐	
11.	Lyophilized product ¹	☐	☒	
12.	First generic ¹	☐	☒	
13.	Solid dispersion product ¹	☐	☒	
14.	Oral disintegrating tablet ¹	☐	☒	
15.	Modified release product ¹	☐	☒	
16.	Liposome product ¹	☐	☒	
17.	Biosimilar product ¹	☐	☒	
18.	Combination Product	☐	☒	

OFFICE OF PHARMACEUTICAL QUALITY
FILING REVIEW

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
19.	Other	☐	☐	

Regulatory Considerations				
20.	USAN Name Assigned		☒	☐
21.	End of Phase II/Pre-NDA Agreements		☒	☐
22.	SPOTS (Special Products On-line Tracking System)		☐	☒
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		☐	☒
24.	Comparability Protocol(s) ²		☐	☒
25.	Other		☐	☐
Quality Considerations				
26.	Drug Substance Overage		☐	☒
27.	Design Space	Formulation	☐	☒
28.		Process	☐	☒
29.		Analytical Methods	☐	☒
30.		Other	☐	☐
31.	Real Time Release Testing (RTRT)		☐	☒
32.	Parametric Release in lieu of Sterility Testing		☐	☒
33.	Alternative Microbiological Test Methods		☐	☒
34.	Process Analytical Technology ¹		☐	☒
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	☒	☐
36.		Excipients	☐	☒
37.		Microbial	☐	☒
38.	Unique analytical methodology ¹		☐	☒
39.	Excipients of Human or Animal Origin		☐	☒
40.	Novel Excipients		☐	☒
41.	Nanomaterials ¹		☐	☒
42.	Hold Times Exceeding 30 Days		☒	☐
43.	Genotoxic Impurities or Structural Alerts		☐	☒
44.	Continuous Manufacturing		☐	☒
45.	Other unique manufacturing process ¹		☐	☐
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		☐	☒
47.	New delivery system or dosage form ¹		☐	☒
48.	Novel BE study designs		☐	☒
49.	New product design ¹		☐	☒
50.	Other		☐	☐

¹Contact Office of Testing and Research for review team considerations

²Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ☐ Drug Substance ☐ Drug Product ☐ Appendices ☐ Facilities and Equipment ☐ Adventitious Agents Safety Evaluation ☐ Novel Excipients ☐ Regional Information ☐ Executed Batch Records ☐ Method Validation Package ☐ Comparability Protocols	☒	☐	☐	The section of Facilities and Equipment is not included in the Appendices. No comparability protocols are provided.
FACILITY INFORMATION					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ☐ Name of facility, ☐ Full address of facility including street, city, state, country ☐ FEI number for facility (if previously registered with FDA) ☐ Full name and title, telephone, fax number and email for on-site contact person. ☐ Is the manufacturing responsibility and function identified for each facility, and ☐ DMF number (if applicable)	☒	☐	☐	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ☐ Is a manufacturing schedule provided? ☐ Is the schedule feasible to conduct an inspection within the review cycle?	☒	☐	☐	
DRUG SUBSTANCE INFORMATION					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☒	☐	☐	
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient	☐	☐	☒	CMC information related to the drug substance is referred to DMF # (b) (4)

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS

information in the following sections to conduct a review? ☐ general information ☐ manufacture ○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only ○ Includes complete description of product lots and their uses during development – BLA only ☐ characterization of drug substance ☐ control of drug substance ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ☐ reference standards or materials ☐ container closure system ☐ stability ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment				
DRUG PRODUCT INFORMATION				
7. Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ☐ Description and Composition of the Drug Product ☐ Pharmaceutical Development ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots ○ Includes complete description of product lots and their uses during development ☐ Manufacture ○ If sterile, are sterilization validation studies submitted? For aseptic processes, are	☒	☐	☐	Summary of changes in the composition and manufacturing process from clinical to commercial production lots is not provided in the Pharmaceutical Development Report. Summary of product lots and their uses during development is not included in the Pharmaceutical Development Report. The drug product specification needs to be updated to include all the tests proposed for commercial batches.

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	bacterial challenge studies submitted to support the proposed filter? ☐ Control of Excipients ☐ Control of Drug Product - Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) - Includes data to demonstrate process consistency (i.e. data on process validation lots) - Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) - Analytical validation package for release test procedures, including dissolution ☐ Reference Standards or Materials ☐ Container Closure System - Include data outlined in container closure guidance document ☐ Stability - Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ☐ APPENDICES ☐ REGIONAL INFORMATION				
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: - Does the application contain the complete BA/BE data? - Are the PK files in the correct format? - Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☐	☒	There are no BA or BE studies.
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i>	☐	☐	☐	No bridging studies are needed, after initial formulation development studies, subsequent clinical trials were conducted with the final to-be-marketed formulation including the two Phase 3 studies, the HPA axis suppression study with PK sampling, and the Phase 1 dermal safety studies. This was confirmed with Clinical Pharmacology reviewer Dr. Doanh Tran and Clinical reviewer Dr. Hon Sum Ko.

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS				
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☐	☒	☐
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☒
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	☒
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☐	☒
REGIONAL INFORMATION AND APPENDICES				
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☐	☒	☐
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☒	☐	☐
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ☐ facilities and equipment - o manufacturing flow; adjacent areas - o other products in facility - o equipment dedication, preparation, sterilization and storage - o procedures and design features to prevent contamination and cross-contamination ☐ adventitious agents safety evaluation (viral and non-viral) e.g.: - o avoidance and control procedures - o cell line qualification - o other materials of biological origin - o viral testing of unprocessed bulk - o viral clearance studies - o testing at appropriate stages of production ☐ novel excipients	☐	☐	☒
17.	Are the following information available for Biotech Products: ☐ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: - o LAL instead of rabbit pyrogen - o Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples	☐	☐	☒

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Biopharmaceutics Quality Assessment Comments for 74-Day Letter

- We recommend that you develop an *in vitro* release test (IVRT) methodology and propose *in vitro* release acceptance criteria (range) for your drug product to be used systemically at release and during stability as a quality control parameter. Your proposed acceptance criteria should be based on generated data for the final to-be-marketed batches. Submit all the generated data in electronic format.
- Also, along with the proposed *in vitro* release specification, include the IVRT method development and validation report. The IVRT method development report should contain (but is not limited to) justification for the selection of the following methodology components:
 - a. Diffusion apparatus
 - b. Receptor medium selection
 - c. Membrane selection
 - d. Sampling time points
 - e. Temperature
- The IVRT method validation report should contain (but is not limited to) the following validation components:
 - a. Linearity and Range
 - b. Accuracy/Precision and Reproducibility
 - c. Mass Balance
 - d. Sensitivity and Specificity
 - e. Selectivity
 - f. Robustness
 - g. Membrane Inertness
 - h. Receptor Solution Solubility/Stability
- The IVRT method's sensitivity, specificity, selectivity and robustness need to be performed with altered product lots that contain 50% and 150% of the label claim of active pharmaceutical ingredient (API) in the reference product, with the test evaluating a minimum of one run of 6 diffusion cells each per product concentration, including the reference.

Microbiology Quality Information Request for 74-Day Letter

Non-sterile aqueous drug products may potentially be contaminated with organisms in the *Burkholderia cepacia* complex (BCC). BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, BCC strains can survive and even proliferate in product during storage. For a recent review of FDA's perspective on BCC please see PDA J Pharm Sci Tech 2011; 65(5): 535-43.

In order to control for the presence of BCC in the proposed drug product, please consider the following:

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- A. Identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.
- B. Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC. The test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g., temperature) before testing.

As there are currently no compendial methods for detection of BCC, we have provided suggestions for a potential validation approach and some points to consider when designing validation studies. However, any validated method capable of detecting BCC organisms would be adequate. It is currently sufficient to precondition representative strain(s) of BCC in water and/or the drug product without preservatives to demonstrate that the proposed method is capable of detecting small numbers of BCC. The submission should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to insure that the proposed recovery methods are adequate to recover organisms potentially present in the environment.

For more information, please refer to *Envir Microbiol* 2011; 13(1):1-12 and *J. Appl Microbiol* 1997; 83(3):322-6.

Drug Substance Information Request for 74-Day Letter

- The drug substance is insoluble in water, and you have proposed to use it in an emulsified, aqueous, topical spray formulation. Please include a multi-point particle size distribution test in the drug substance specification.

Drug Product Information Requests for 74-Day Letter

- Provide a comparison regarding the composition and manufacturing process between the commercial and the pivotal clinical batches of the drug product.
- Provide a table to summarize drug product lots and their uses during development.

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- The drug product specification needs to be updated to include all the tests proposed for commercial batches. Future and ongoing stability studies should be performed according to the updated drug product specification.

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