CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209022Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

CDRH EIR Review Memo

Establishment Inspection Report Review

DATE: June 26, 2017

FROM: Bella Pelina, Consumer Safety Officer,
CDRH/OC/DMQ/POND, WO66 Rm 3453,
Arabella.Pelina@fda.hhs.gov

THROUGH: For: Kenneth Chen, Acting Branch Chief, CDRH/OC/DMQ/POND,
Kenneth.Chen@fda.hhs.gov

Katelyn Bittleman -S
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TO: Cassandra Abellard, CDER/OPQ/OPF/DIA/IABIII, off-site,
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Craig Bertha, CDER/OPQ/ONDP/DNDPII/NDPBIV, WO21 Rm 2548, Craig.Bertha@fda.hhs.gov

Julia Pinto, CDER/OPQ/ONDP/DNDPII/NDPBIV, WO21 Rm 2675, Julia.Pinto@fda.hhs.gov

Office of Combination Products, combination@fda.gov

RPM: Steven Kinsley, CDER/OPQ/OPRO/DRBPMI/RBPMBI, WO75 Rm 4668, Steven.Kinsley@fda.hhs.gov

Bamidele (Florence) Aisida,
CDER/OPQ/OPRO/DRBPMI/RBPMBI, WO75 Rm 4509,
Bamidele.Aisida@fda.hhs.gov

SUBJECT:	Review of NDA-Related Establishment Inspection Report (EIR) and Exhibits Inspection Dates: 03/27/2017 – 03/31/2017 Application #: NDA 209022 Product Name: OptiNose Fluticasone, OPN-375
	Applicant: OptiNose US, Inc. 10101 Stony Hill Road, Suite 375 Yardley, PA 19067
	Inspection Site: Contract Pharmaceuticals Ltd. 7600 East Danbro Cres Mississauga, Canada L5N 6L6 FEI: 3001581899
Inspection Purpose:	Pre-Approval Inspection for NDA 209022
Inspection Type:	Abbreviated cGMP surveillance inspection (Management Responsibility, Purchasing Controls, CAPA, Final Acceptance Activities, and Design Controls)
Device Covered:	OptiNose Fluticasone, OPN-375
Investigator:	Sangeeta M. Khurana, IOG
ORA Recommendation:	NAI
SITE COMPLIANCE DECISION:	NAI – Facility Clearance
CDRH RECOMMENDATION:	**APPROVAL**

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1. Background Information

- Contract Pharmaceuticals Ltd. (CPL) is a privately-held company which was founded in 1991 by Peter Wege, Allan MacFarlane, and Anne Hustis. In 2000, the Wege family acquired

shares from the other two founders and it became a US company with a Canadian subsidiary (Contract Pharmaceuticals Limited Canada).

- CPL has two locations in Mississauga, the Danbro campus manufacturing facility (FEI: 3001581899) and Meadowpine campus control laboratory (FEI: 3011158222).
- CPL develops and produces pharmaceutical products, specializing in liquid and semi-solid products. The Liquid products may be Suspensions and Solutions such as Nasal Sprays, Oral Suspensions and solutions and topical sprays. The Semi-Solid products may be Lotions, Creams, Ointments and Gels for example Hormone products, Wound care and Anti-infectives and Corticosteroids.
- The firm continues to operate as a contract manufacturer. They do not own any of the Rx or OTC products made for distribution in the US. The Rx and OTC drug products are owned by this firm's clients who contract with them to manufacture the drug products. This firm ships finished product to distribution centers designated by the client and the client directs the distribution of the drug product into the US market.

2. Regulatory History

- **04/07/2014 – 04/11/2014**
  - Conducted by: IOG
  - Part 820 violations found: 820.100
  - Classification: VAI
  - Regulatory Action: none
- **02/21/2012 – 02/24/2012**
  - Conducted by: IOG
  - Part 820 violations found: 820.40, 820.100
  - Classification: VAI
  - Regulatory Action: none

3. Quality System Review

The review of the EIR and exhibits for compliance with the QS regulation has been completed. The results of the evaluation did not disclose any QS regulation violations or objectionable conditions that justify further FDA action.

- **Nonsupportable FDA 483 Quality System Observations**

There are no non-supportable FDA 483 observations.

4. Observations Pertaining To Other Regulations

There are no observations pertaining to other regulations.

5. Compliance Decision

Based on the review of the documentation provided, the Division of Manufacturing and Quality has determined that this inspection meets the criteria of a Situation II, in Compliance Program, CP 7383.001, Part V, dated March 5, 2012.

Situation II was met because the deficiencies do not qualify as major at this time and the inspection is being classified as NAI.

From the particular product and manufacturing processes involved, the inspection documents QS deficiencies of a quantity and/or type which appear to have minimal probability of producing nonconforming devices and/or defective finished devices.

6. Inspection Classification

The Division of Manufacturing and Quality concurs with the NAI classification of the EIR dated 03/27/2017 – 03/31/2017 and recommends approval of NDA 209022.

U.S. FOOD & DRUG ADMINISTRATION

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/s/

PHUONG N TON
09/06/2017
Administratively checked into DARRTS by Project Manager on behalf of the reviewer

U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

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2017.08.01 15:44:09 -04'00'

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Bamidele (Florence) Aisida,
CDER/OPQ/OPRO/DRBPMI/RBPMBI, WO75 Rm 4509,
Bamidele.Aisida@fda.hhs.gov

SUBJECT:	Review of NDA-Related Establishment Inspection Report (EIR) Inspection Dates: 5/11/2017 – 5/16/2017 Application #: NDA 209022 Product Name: OptiNose Fluticasone, OPN-375
	Applicant: OptiNose US, Inc. 10101 Stony Hill Road, Suite 375 Yardley, PA 19067
	Inspection Site: Ximedica, LLC 55 Dupont Drive Providence, RI 02907 FEI: 3006463947
Inspection Purpose:	PMA Pre-Approval Inspection for P130023/S002
Inspection Type:	Comprehensive Baseline Level 2
Device Covered:	(b) (4)
Investigator:	Maryam Tabatabaie, NWE-DO
ORA Recommendation:	NAI
SITE COMPLIANCE DECISION:	NAI – Facility Clearance
CDRH	
RECOMMENDATION:	**APPROVAL**

On June 12, 2017, the Office of Compliance at CDRH received an email from CDER regarding a consult to complete an EIR Review of a recent medical device inspection conducted at Ximedica LLC to be leveraged in lieu of a preapproval inspection for approval of NDA 209022.

Mary Wen of the Abdominal and Surgical Devices Branch of the Division of Manufacturing and

Quality completed the EIR Review for the inspection conducted at Ximedica LLC conducted on May 11-16, 2017. Her review memo is attached and indicates concurrence with the NAI classification.

As the pre-approval inspections for the facilities involved in the manufacture of the device constituent of OPN-375, the subject combination device under application NDA 209022 have a NAI classification, CDRH recommends approval of NDA 209022.

FDA U.S. FOOD & DRUG ADMINISTRATION

Arabella Pelina -S
2017.06.26
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Bella Pelina

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/s/

PHUONG N TON
09/06/2017
Administratively checked into DARRTS by Project Manager on behalf of the reviewer

Recommendation: Approval

NDA 209022
Review #1

Drug Name/Dosage Form	XHANCE™ (fluticasone propionate) Nasal Spray
Strength	93 mcg/actuation
Route of Administration	Nasal inhalation
Rx/OTC Dispensed	Rx
Applicant	OptiNose US, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	*18-NOV-2016*	*all*
Amendment	*22-FEB-2017*	*facilities, process*
Amendment	*14-JUN-2017*	*drug product*

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Jeffrey Medwid	NDBII/DNDAPI
Drug Product	Caroline Strasinger	NDPBIV/DNDPII
Process	Joanne Wang	PABIV/DPAII
Microbiology	Joanne Wang	PABIV/DPAII
Facility	Cassandra Abellard	IABII/DIA
Biopharmaceutics	Min Li	BBIII/DB
Regulatory Business Process Manager	Florence Aisida	RBPMBI/DRBPMI
Application Technical Lead	Craig M. Bertha	NDPBIV/DNDPII
Laboratory (OTR)		
ORA Lead		
Environmental Analysis (EA)		

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II		(b) (4)	Adequate	28-APR-2017	
	III			Adequate	23-JUN-2017	Also includes sufficient information on the (b) (4) (b) (4)
	III			Adequate	23-JUN-2017	
	III			Adequate	07-JUN-2016	No quality amendments have been submitted since last review; (b) (4)
	III			Adequate	14-JUN-2011	Used in (b) (4)
	III			N/A Sufficient information provided in application		Used as a (b) (4)
	III			N/A Sufficient information provided in application		Used (b) (4)
	III			N/A Sufficient information provided in application		Used in (b) (4)

(b) (4)		(b) (4)			
	III		N/A Sufficient information provided in application		(b) (4)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	110089	Fluticasone propionate nasal spray

2. CONSULTS

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

Executive Summary

I. Recommendations and Conclusion on Approvability

Based on the reviews and recommendations from the drug substance, drug product, process, and facilities teams outlined in the review below, an overall recommendation of **approval** is forwarded to the clinical Division (DPARP).

II. Summary of Quality Assessments

A. Product Overview

The current application seeks approval for a nasal spray of fluticasone propionate for the treatment of nasal (b) (4) in patients 18 years or older.

Proposed Indication(s) including Intended Patient Population	Nasal (b) (4)
Duration of Treatment	Chronic
Maximum Daily Dose	744 mcg (8 actuations)/day
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

OptiNose US, Inc. has developed OPN-375 as a novel nasal drug delivery system with the intention to improve the performance of fluticasone propionate in the treatment of serious diseases characterized by chronic nasal inflammation. The product is intended to facilitate deposition of a topically-acting steroid in anatomic regions affected by local inflammation. The majority of the information and data supporting the drug substance is provided by reference to DMF (b) (4) which has been reviewed recently (see review dated 28-APR-2017) and found adequate.

The drug product formulation is a white milky suspension of compendial excipients common to nasal and inhalation products and (b) (4)% (w/w) fluticasone propionate. The fill volume is 16 mL equating to a reliable delivery of 120 sprays after initial priming. The combination product cannot be refilled or reused after doses are dispensed. The finished product utilizes an intranasal drug delivery system for the nominal dose of 93 mcg of fluticasone propionate suspension per actuation. The drug delivery system is comprised of the primary container closure (a standard (b) (4) amber glass vial, crimp-sealed with a standard metering spray pump and applicator) enclosed within injection-

molded parts referred to as the liquid delivery subassembly. The use of the device is novel and a user must insert the nosepiece into the nostril and coordinate their exhalation into the flexible mouthpiece while actuating the unit by pressing up on the bottle. By blowing into the mouthpiece, the soft palate rises separating the nose and throat, and enabling the user's breath to aid in propelling the formulation to the sight of action for local delivery. Overall, the information submitted to support the proposed drug product, Fluticasone Propionate Nasal Spray, is deemed adequate for assuring the identity, strength, purity, and quality of the drug product, and therefore, this application is recommended for approval from the ONDP perspective with an expiration dating period of 24 months.

The application is recommended for approval from a process perspective. The manufacturing process for the drug product formulation involves (b) (4) , and packaging. There is (b) (4) from the submission to the commercial batch. A substantial amount of manufacturing development data are provided. Critical process parameters and in-process tests and acceptance criteria are established based on data collected from development and submission batches. Overall this is a medium risk, but straightforward process. The applicant has mitigated the risk by adopting tight process parameter control, and also in-process controls for all critical quality attributes (CQAs).

From the facilities perspective, a review of the application and inspectional documents of the facilities responsible for manufacturing Flucticasone Propionate nasal spray per NDA 209022 has determined that there are no significant outstanding issues with the firms involved in the manufacturing of the product. Note that a CDRH consult was requested and recommended two pre-approval inspections. An inspection of the Drug product manufacturer (Contract Pharmaceuticals Limited Canada, FEI: 3011158222) was performed and classified NAI. An inspection of the sub assembly manufacturer was performed and classified NAI as well (Ximedica, LLC, FEI: 300646397). Note the Ximedica inspection was not PAI specific. Refer to final CDRH memos for evaluation of the facilities requiring CFR 820 compliance and final recommendations. Final review by CDRH found all pertinent facilities acceptable for manufacturing of this product.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

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LABELING

R. Regional Information

1.14 Labeling

I. Package Insert

The below label was provided on 18-NOV-2016

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

1) Title

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use (b) (4) XHANCE™ safely and effectively. See full prescribing information for (b) (4) XHANCE™.

(b) (4) XHANCE™ (fluticasone propionate) Nasal Spray, (b) (4) (b) (4) (b) (4)

Initial U.S. Approval: 1994

2) DOSAGE FORMS AND STRENGTHS

(b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: XHANCE Established Name: fluticasone propionate	INADEQUATE (refer to edits above)
Dosage form, route of administration	Dosage: Nasal Spray Route: nasal	INADEQUATE (refer to edits above)
Controlled drug substance symbol (if applicable)		NA
Dosage Forms and Strengths (201.57(a)(8))		
Summary of dosage form and strength	Nasal Spray: 93 mcg fluticasone propionate	INADEQUATE (refer to edits above)

Reviewer Assessment: The above changes were recommended to OND on 25-JUL-2017.

2. "FULL PRESCRIBING INFORMATION

1) #3: DOSAGE FORM AND STRENGTHS

(b) (4)

[redacted]

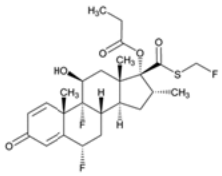
Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Available dosage forms	Nasal Spray	Adequate
Strengths: in metric system	93 mcg	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Spray, 120 metered sprays per unit	Adequate **Information is adequate however for clarity the above recommendations are made.**

Reviewer Assessment: The above changes were recommended to OND on 25-JUL-2017.

2) #11: DESCRIPTION

11 DESCRIPTION

The active component of [(b) (4)] XHANCE is fluticasone propionate, a corticosteroid, having the chemical name *S*-(fluoromethyl) 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate and the following chemical structure:



Fluticasone propionate is a white powder with a molecular weight of 500.57, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethylformamide, sparingly soluble in acetone and dichloromethane, and slightly soluble in 96% ethanol.

[(b) (4)] XHANCE (fluticasone propionate) Nasal Spray, 93 mcg, for intranasal administration, [(b) (4)] [(b) (4)] exhalation delivery system that delivers an aqueous suspension of microfine fluticasone propionate having a particle size distribution [(b) (4)] in the range of 0 to 5 microns for topical intranasal administration by means of a metering, atomizing spray pump and exhaled breath. [(b) (4)] XHANCE also contains microcrystalline cellulose and carboxymethylcellulose sodium, dextrose, benzalkonium chloride, polysorbate 80, edetate disodium dihydrate, and purified water, and has a pH between 5 and 7.

Before initial use, p[Prime] [(b) (4)] XHANCE [(b) (4)] by [(b) (4)] gently shaking [(b) (4)] nd [(b) (4)] [(b) (4)] hen pressing the amber glass bottle 7 times or until a fine mist appears. Once primed, [(b) (4)] XHANCE contains 120 metered sprays. When [(b) (4)] XHANCE has not been used for ≥ 7 days, prime again by releasing 2 sprays into the air, away from the face [*see Dosage and Administration (2.2) and patient Instructions for Use*].

After [(b) (4)] priming, each [(b) (4)] spray delivers 93 mcg of fluticasone propionate in 106 mg of aqueous suspension through the cone-shaped nosepiece [(b) (4)] [(b) (4)] The system also has a flexible mouthpiece [(b) (4)] [(b) (4)] Within the device is a non-removable amber glass bottle with a metering spray pump and applicator. A removable orange cap covers both the nosepiece and mouthpiece.

[(b) (4)]

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name	[(b) (4)] XHANCE (fluticasone propionate) Nasal Spray	INADEQUATE; remove [(b) (4)]
Dosage form and route of administration	For intranasal administration	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	93 mcg in 106 mg of aqueous suspension	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	microcrystalline cellulose and carboxymethylcellulose sodium, dextrose, benzalkonium chloride, polysorbate 80, edetate disodium dihydrate, and purified water	Adequate ([(b) (4)] not required to be listed
Statement of being sterile (if	Not Applicable	Adequate

applicable)		
Pharmacological/ therapeutic class	corticosteroid	Adequate
Chemical name, structural formula, molecular weight	All Provided	Adequate
If radioactive, statement of important nuclear characteristics.	NA	Adequate
Other important chemical or physical properties (such as pKa or pH)	White powder, solubility; particle size distribution	Adequate

Reviewer Assessment: For clarity of the section and to remove promotional material, the above changes were recommended to OND on 25-JUL-2017.

3) #16: HOW SUPPLIED/STORAGE AND HANDLING

16 HOW SUPPLIED/STORAGE AND HANDLING

(b) (4) XHANCE (fluticasone propionate) Nasal Spray, (b) (4), is supplied as a non-removable amber glass bottle fitted with a metered-dose manual spray pump unit inside the white XHANCE device with a nasal applicator, valve mechanism, asymmetrical cone-shaped nosepiece, flexible mouthpiece, and orange cap in a box of 1 (NDC XXX-XXX-XX) with FDA-approved Patient Labeling [for proper use, see patient *Instructions for Use*].

Each bottle contains a net fill content of 16 mL, and after priming will provide 120 metered sprays. Each metered spray delivers 93 mcg of fluticasone propionate in 106 mg of aqueous suspension through the cone-shaped nosepiece. The correct amount of medication in each metered spray cannot be assured after 120 metered sprays even though the bottle is not completely empty. The bottle should be discarded when the labeled number of metered sprays has been used.

Store (b) (4) and 25°C (b) (4) and 77°F), excursions permitted (b) (4) 15°C to 30°C (59°F to 86°F). (b) (4). Shake (b) (4) XHANCE (b) (4) before each use.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Item	**Information Provided in**	**Reviewer's Assessment**
Strength of dosage form	93 mcg in 106 mg aqueous suspension	Adequate
Available units (e.g., bottles of 100 tablets)	Box of 1;	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	amber vial with white XHANCE device with nasal applicator, valve mechanism, asymmetrical cone-shaped nosepiece, flexible mouthpiece and orange cap; 16 mL	Adequate
Special handling (e.g., Dispense in tight and light resisteant container as defined in USP)	(b) (4); 120 sprays after priming	Adequate
Storage conditions	Store at (b) (4) to 25°C (b) (4) to 77°F); excursions permitted (b) (4) 15° – 30°C (59° – 86°F) (b) (4)	Adequate
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for OptiNose	Adequate

Reviewer Assessment: For clarity of the section, the above changes were recommended to OND on 25-JUL-2017.

II. Labels

1. IMMEDIATE CONTAINER LABEL

The below container labels were provided on June 19, 2017

(b) (4)

	NDA	
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	XHANCE (fluticasone propionate)	Adequate
Dosage strength Active moiety expression of strength with equivalence statement (if applicable), if space is available	93 mcg/spray	Adequate
Net contents	Not provided	Adequate: Size restriction
"Rx only" displayed prominently on the main panel	Rx only	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Present	Adequate
Lot number and expiration date (21 CFR 201.17)	Location present	adequate
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Not provided	Adequate: Size restriction
Bar code (21CFR 201.25)	Not provided	Adequate: Size restriction
Name of manufacturer/distributor	OptiNose	Adequate
And others, if space is available		

Reviewer Assessment: ADEQUATE. For the immediate container, size limits the amount of information that can be provided.

2. CARTON LABELS:

(b) (4)

[redacted]

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	XHANCE (fluticasone propionate) nasal spray	Inadequate Text is italicized and difficult to read
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	93 mcg	Adequate
Net quantity of dosage form	16 mL/120 metered sprays front panel 1 prefilled (b) (4)	INADEQUATE change "1 prefilled (b) (4) to "1 prefilled unit"
"Rx only" displayed prominently on the main panel	Rx only	Adequate
Lot number and expiration date	Present	Adequate
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	(b) (4) between (b) (4) -25°C (b) (4) -77°F). (b) (4) . Shake (b) (4) before each use.	INADEQUATE (b) (4) should be changed to "Store"
Bar code (21CFR 201.25)	Side panel	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Front and side panel	Adequate
Manufacturer/distributor's name	Back panel	Adequate
Quantitative ingredient information (injectables)	Qualitative ingredients presented	Adequate
Statement of being sterile (if applicable)	Not Applicable	Adequate
"See package insert for dosage information"	Side Panel reads "see prescribing information"	Adequate
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Not present	Adequate

Reviewer Assessment: INADEQUATE.

- Font of name difficult to read; covered by DMEPA review
- Typo in Storage information on side panel: Change (b) (4) to "Store"
- On the side panel change "1 prefilled (b) (4) to "1 prefilled unit"
- Change (b) (4)" to "For Intranasal Use Only" on the front panel to be consistent with the PI

III. LIST OF DEFICIENCIES:

As of the date of this review, all deficiencies regarding the PI were communicated to OND on 07/25/2017. Comments on the Carton have not yet been communicated.

Regarding PI

a) Highlight Section

1) Title

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use (b) (4) XHANCE™ safely and effectively. See full prescribing information for (b) (4) XHANCE™.

(b) (4) XHANCE™ (fluticasone propionate) Nasal Spray (b) (4)
(b) (4) (b) (4)
Initial U.S. Approval: 1994

2) DOSAGE FORMS AND STRENGTHS

(b) (4)

b) Full Prescribing Information

#3: Dosage Forms and Strengths

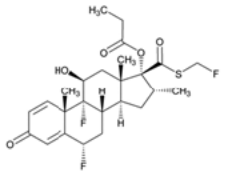
#3: DOSAGE FORM AND STRENGTHS

(b) (4)

#11: Description

11 DESCRIPTION

The active component of (b) (4) XHANCE is fluticasone propionate, a corticosteroid, having the chemical name *S*-(fluoromethyl) 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate and the following chemical structure:



Fluticasone propionate is a white powder with a molecular weight of 500.57, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethylformamide, sparingly soluble in acetone and dichloromethane, and slightly soluble in 96% ethanol.

(b) (4) XHANCE (fluticasone propionate) Nasal Spray, 93 mcg, for intranasal administration, (b) (4) (b) (4) exhalation delivery system that delivers an aqueous suspension of microfine fluticasone propionate having a particle size distribution (b) (4) in the range of 0 to 5 microns for topical intranasal administration by means of a metering, atomizing spray pump and exhaled breath. (b) (4) XHANCE also contains microcrystalline cellulose and carboxymethylcellulose sodium, dextrose, benzalkonium chloride, polysorbate 80, edetate disodium dihydrate, and purified water, and has a pH between 5 and 7.

Before initial use, pPrime (b) (4) XHANCE (b) (4) by (b) (4) gently shaking (b) (4) nd (b) (4) (b) (4) hen pressing the amber glass bottle 7 times or until a fine mist appears. Once primed, (b) (4) XHANCE contains 120 metered sprays. When (b) (4) XHANCE has not been used for ≥ 7 days, prime again by releasing 2 sprays into the air, away from the face [*see Dosage and Administration (2.2) and patient Instructions for Use*].

After (b) (4) priming, each (b) (4) spray delivers 93 mcg of fluticasone propionate in 106 mg of aqueous suspension through the cone-shaped nosepiece (b) (4) (b) (4) The system also has a flexible mouthpiece (b) (4) (b) (4) Within the device is a non-removable amber glass bottle with a metering spray pump and applicator. A removable orange cap covers both the nosepiece and mouthpiece.

(b) (4)

#16: How Supplied/Storage and Handling

16 HOW SUPPLIED/STORAGE AND HANDLING

(b) (4) XHANCE (fluticasone propionate) Nasal Spray (b) (4) is supplied as a non-removable amber glass bottle fitted with a metered-dose manual spray pump unit inside the white XHANCE device with a nasal applicator, valve mechanism, asymmetrical cone-shaped nosepiece, flexible mouthpiece, and orange cap in a box of 1 (NDC XXX-XXX-XX) with FDA-approved Patient Labeling [for proper use, see patient *Instructions for Use*].

Each bottle contains a net fill content of 16 mL, and after priming will provide 120 metered sprays. Each metered spray delivers 93 mcg of fluticasone propionate in 106 mg of aqueous suspension through the cone-shaped nosepiece. The correct amount of medication in each metered spray cannot be assured after 120 metered sprays even though the bottle is not completely empty. The bottle should be discarded when the labeled number of metered sprays has been used.

Store (b) (4) and 25°C (b) (4) nd 77°F), excursions permitted (b) 5°C to 30°C (59°F to 86°F). (b) (4) Shake (b) (4) XHANCE (b) (4) before each use.

A. Regarding of the Carton Labels:

- Font of name difficult to read due to italics; covered by DMEPA review

- Change [redacted] (b) (4) to "For Intranasal Use Only" on the front panel to be consistent with the PI
- Typo in Storage information on side panel: Change "[redacted] (b) (4) to "Store"
- On the side panel change "1 prefilled [redacted] (b) (4) to [redacted] (b) (4)

IV. OVERALL ASSESSMENT AND RECOMMENDATION:

Recommendation: This application is ready for approval upon concurrence from the Applicant of the above listed labeling deficiencies of the PI and Carton.

Primary Labeling Reviewer Name and Date:

Caroline Strasinger, PhD 25-JUL-2017
OPQ, ONDP, DNDP II, BV

Caroline Strasinger

Digitally signed by Caroline Strasinger
Date: 7/28/2017 02:07:40PM
GUID: 5051dfdd000013b995075b4d54108ed8

Craig Bertha

Digitally signed by Craig Bertha
Date: 7/28/2017 02:17:49PM
GUID: 50841a65000098a9383c817879a6a84d

OFFICE OF PHARMACEUTICAL QUALITY

Attachment – Final Risk Assessment

(b) (4)

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Craig Bertha

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Date: 8/15/2017 10:19:40AM
GUID: 50841a65000098a9383c817879a6a84d

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality
Physical Medicine, Orthopedic, Neurology, and Dental Devices Branch

Date: January 4, 2017

To: Craig M. Bertha, CDER/OPQ/ONDP/DNDPII/NDPBIV, WO21 Rm 2548, Craig.Bertha@fda.hhs.gov

Julia Pinto, CDER/OPQ/ONDP/DNDPII/NDPBIV, WO21 Rm 2675, Julia.Pinto@fda.hhs.gov

Office of Combination Products at combination@fda.gov

RPM: Steven Kinsley, CDER/OPQ/OPRO/DRBPMI/RBPMBI, WO75 Rm 4668, Steven.Kinsley@fda.hhs.gov

Bamidele (Florence) Aisida, CDER/OPQ/OPRO/DRBPMI/RBPMBI, WO75 Rm 4509, Bamidele.Aisida@fda.hhs.gov

Through: Vesa Vuniqi, Acting Branch Chief, CDRH/OC/DMQ/POND, Vesa.Vuniqi@fda.hhs.gov

Vesa Vuniqi -S
Vesa Vuniqi -S
2017.02.07 13:28:37
-05'00'

From: Bella Pelina, CDRH/OC/DMQ/POND, Arabella.Pelina@fda.hhs.gov

Applicant: OptiNose US, Inc.
1010 Stony Hill Road, Suite 375
Yardley, PA 19067

Application # NDA 209022

Consult # ICC1600847

Product Name: OptiNose Fluticasone, OPN-375

Pre-Approval Inspection: Yes

Documentation Review: Additional Information Required

Final Recommendation: **DELAY**

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of NDA 209022.

PRODUCT DESCRIPTION

OPN-375 is a nasal spray drug product containing fluticasone propionate as the therapeutically-active ingredient, delivered as a metered dose from a multi-dose non-pressurized container closure system. It is intended for the treatment of nasal (b) (4) in patients 18 years of age and older.

During product development, the product has been referred to as OPTINOSE™ FLUTICASONE, OPN-375 (fluticasone propionate) (b) (4)

The container closure system comprises the components of the exhalation delivery system: a metering nasal spray pump with (b) (4), an amber glass vial, and the liquid delivery subassembly component.

The liquid delivery subassembly is a critical component of the fully assembled exhalation delivery system, and includes the shaped nosepiece, flexible mouthpiece, and housing with applicator, valving mechanism, and (b) (4)

(b) (4)

OPN-375 Container Closure Components

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You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm

RECOMMENDATION

The approvability of application NDA 209022 for OptiNose Fluticasone, OPN-375 should be delayed for the following reasons:

(1) Deficiencies were identified during the documentation review. Additional information from the firm is needed to complete the documentation review.

(2) A pre-approval inspection is recommended for the following facilities:

a. **Ximedica**
55 Dupont Drive
Providence, RI 02907
FEI: 3006463947

b. **Contract Pharmaceuticals Limited (CPL)**
7600 Danbro Crescent
Mississauga, Ontario
L5N 6L6, Canada
FEI: 3001581899

FDA U.S. FOOD & DRUG ADMINISTRATION
Arabella Pelina -S
2017.02.07
06:30:11 -05'00'

Bella Pelina

Prepared: APelina: 01/4/2017
Reviewed:

CTS: ICC1600847
NDA 209022

INSPECTIONAL GUIDANCE

Firms to be inspected:

a. **Ximedica**
55 Dupont Drive
Providence, RI 02907
FEI: 3006463947

b. **Contract Pharmaceuticals Limited (CPL)**
7600 Danbro Crescent
Mississauga, Ontario
L5N 6L6, Canada
FEI: 3001581899

CDRH recommends the inspection under the applicable Medical Device Regulations of the two aforementioned facilities.

A limited inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30) for the OptiNose Fluticasone, OPN-375 (NDA 209022).

Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Detailed inspection guidance will be provided upon request.

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Bella Pelina
Consumer Safety Officer
Physical Medicine, Orthopedic, Neurology, and Dental Devices Branch
Division of Manufacturing and Quality
Office of Compliance, WO66 Rm 3453
Phone: 240-402-6010

Secondary Contacts (if Primary is unavailable and a timely answer is required)

Vesa Vuniqi
Acting Branch Chief
Physical Medicine, Orthopedic, Neurology, and Dental Devices Branch
Division of Manufacturing and Quality
Office of Compliance, WO66 Rm 3438
Phone: 301-796-6614

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PHUONG N TON
09/12/2017
Administratively checked into DARRTS by Project Manager on behalf of the reviewer

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 209022[1]	**Submission Type: 505(b)(2)**	**Established/Proper Name: fluticasone propionate (FP)**
Applicant: OptiNose US, Inc.	**Letter Date: 18-NOV-2016**	**Dosage Form: nasal spray**
Chemical Type: 5	**Stamp Date: 18-NOV-2016**	**Strengths: 93 mcg/actuation**

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.			N/A
3	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?		X	N/A

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

[1] Reviewers should be aware that although this is considered to be a nasal spray drug product, the device and method of administration is distinct from that of typical nasal spray drug products approved in the past. Refer to the draft patient instructions for use in attachment 1 of this filing review.

[2] Contact Office of Testing and Research for review team considerations

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
16.	Liposome product[2]	☐	☒	
17.	Biosimiliar product[2]	☐	☒	
18.	Combination Product _____	☐	☒	Although drug product consists of a device and associated formulation, by the strict definition of 21 CFR 3.2(e)(1), this does not seem to be a true combination product because neither the device nor the formulation alone would be regulated separately for use without the other.
19.	Other_____	☒	☐	See footnote 1 above.; Fifty-four percent of complaint returned drug product units had broken bottles from dropping (0.16% of total clinical units of drug product distributed; refer to attachment 3 for device drawings)

Regulatory Considerations					
20.	USAN Name Assigned			☒	☐	
21.	End of Phase II/Pre-NDA Agreements			☒	☐	See IND 110089 Pre-NDA Meeting of 18-NOV-2015; no substantive issues or agreements were discussed (refer also to Written Response Only comments sent 21-JUL-2015, for CMC-specific issues)
22.	SPOTS (Special Products On-line Tracking System)			☐	☒	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application			☐	☐	Unknown
24.	Comparability Protocol(s)[3]			☐	☒	
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			☐	☒	Drug product is not sterile
33.	Alternative Microbiological Test Methods			☐	☐	To be determined by process review team
34.	Process Analytical Technology[2]			☐	☒	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product		☒	☐	
36.		Excipients		☐	☒	
37.		Microbial		☐	☒	USP <61> and <62> followed for the drug product
38.	Unique analytical methodology[2]			☐	☒	
39.	Excipients of Human or Animal Origin			☐	☒	
40.	Novel Excipients			☐	☒	
41.	Nanomaterials[2]			☐	☒	
42.	Hold Times Exceeding 30 Days			☐	☒	
43.	Genotoxic Impurities or Structural Alerts					(b) (4)

[3] Contact Post Marketing Assessment staff for review team considerations

				with typically (b) (4)) is a leachable from the CCS components into the formulation; note the API and related impurities (b) (4) (unlikely an issue as FP is a USP monographed API)
44.	Continuous Manufacturing	☐	☒	
45.	Other unique manufacturing process[2]	☐	☒	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).	☐	☐	N/A – drug is for topical application and action
47.	New delivery system or dosage form[2]	☒	☐	The device is a unique design relative to other nasal spray devices that the Agency has approved (refer to footnote 1)
48.	Novel BE study designs	☐	☐	To be evaluated by the clinical pharmacology group; note a BE study was done versus Flonase Nasal Spray
49.	New product design[2]	☒	☐	See footnote 1
50.	Other_____	☐	☐	

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	Applicant requests a categorical exclusion as per 21 CFR 25.31(e)
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	☒	☐	☐	• Much of the information provided to support the drug substance is provided by reference tc (b) (4) DMF (b) (4) (retest period is said to be (b) (4)) • The application provides 18-24 months of long-term stability data for the drug product, yet only a 24 month expiry period is proposed (see table 3.2.P.8.1-1) • Two executed batch records (from CPL (b) (4)) are provided along with associated certificates of analyses for the components of the formulations • A separate methods validation package is not included, but there is a list of available samples that can be provided to the Agency laboratory if method assessment is deemed necessary during review
FACILITY INFORMATION					

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
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)	☒	☐	☐	(b) (4) sites listed on 356h: (b) (4) • Contract Pharmaceuticals Ltd. (FEI 3001581899) • Contract Pharmaceuticals Ltd. (FEI0 3011158222) (b) (4)
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?	☒	☐	☐	There is one DMF for the (b) (4), DMF (b) (4)
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ general information ❑ manufacture o Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only o Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance	☒	☐	☐	Most information for the API is provided by reference to (b) (4) DMF (b) (4) (electronic file reviewed recently for an (b) (4) application and found to be "adequate with information request."

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FILING REVIEW

C. FILING CONSIDERATIONS					
	○ 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 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	☒	☐	☐	• Note that as part of the clinical program, there was a BE study performed (relative to an RLD, Flonase Nasal Spray) in support of this NDA • See P.2 for (one-time) drug product characterization study results as per Agency guidance recommendations for nasal sprays • See P.5.4 for CoAs for clinical and registration batches • P.2.4 outlines "minor" modifications that were made to the CCS *after* clinical phase III (in the (b) (4) of 15-JUL-2015, we recommended that the sponsor use the final to-be-marketed version of the device in important clinical and other supportive studies) • The process reviewer will need to evaluate the microbiology attributes in P.2.5.2 • Excipients are all compendial grade and tested with compendial methodology (no novel excipients) • "Registration batches" were produced at (b) (4), which has discontinued manufacture of (b) (4) thus the new drug product manufacturer is (b) (4) Note that the applicant does provide stability data (up to 18 months long term) for drug product manufactured at the intended (b) (4) commercial site;

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FILING REVIEW

C. FILING CONSIDERATIONS					
	❑ 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				**Only (b) (4) drug product batches were used in clinical studies, so a comparison of the CMC information/data for the (b) (4) versus the (b) (4) drug product (intended for commercial marketing) will be important to demonstrate comparability: differences that may have clinical impact will need to be brought to the attention of the clinical, clinical pharmacology, and biopharmaceutics teams** • See box 2 above re: the methods validation package and executed batch records • The applicant obtains an FP reference standard from the USP and (b) (4) provides FP-related impurities for testing of the finished drug product
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?	☐	☒	☐	The BA/BE studies will be reviewed by clinical pharmacology reviewers
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? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*	☐	☒	☐	The manufacturer for registration and commercial batches is (b) (4) while all the clinical batches were produced by (b) (4). The two manufacturing sites (b) (4) but different locations. In addition, there is a (b) (4) from the clinical batches ((b) (4)) to commercial batches ((b) (4)). The manufacturing site bridging information cannot be located in the current submission. It was claimed that the overall batch formula, control strategy for the commercial to-be-marketed product is essentially the same as that used for the manufacture of clinical trials supplies and registration stability batches of OPN-375.

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
					The in-process controls, and controls on input materials, container closure system and drug product remain principally the same for commercial production at the (b) (4) and (b) (4) However, minor differences in the execution of specific tests or testing have been made over the course of the product development. (Module 2.3.P Page 55). Depending on the extent of changes in formulation, process and assembling system and the potential impact on the product quality and in vivo performance associated with the manufacturing site change, in vitro and/or in vivo data may be needed to ensure that the to-be-marketed product is comparable to the pivotal clinical batch. It is noted that the batch release and stability data for clinical or registration batches from (b) (4) are provided in the submission (Module 3.2.P.5.4 and 3.2.P.8.3) but whether the data is adequate to show the equivalence of products manufactured at the two sites could be a review issue. The evaluation and comments from product quality and process reviewers regarding the manufacturing site change will be needed for the evaluating the manufacturing site change from biopharmaceutics perspective.
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?	☒	☐	☐	See box 2 above

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
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 Attachment 1 – Draft Instructions for Use

Start of Applicant Material

(b) (4)

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW Attachment 1 – Draft Instructions for Use

(b) (4)

End of Applicant Material

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW Attachment 2 – Risk Assessment

(b) (4)

[redacted]

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FILING REVIEW Attachment 3 – Device – "Exploded" View

Start of Applicant Material

Figure 3.2.P.7-1. Exploded View of the Constituent Parts

End of Applicant Material

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW - Signatures

Craig M. Bertha, ATL (DNDPII, CMC Lead for DPARP)

Min Li, Biopharmaceutics Reviewer

Craig Bertha

Digitally signed by Craig Bertha
Date: 1/03/2017 09:02:50AM
GUID: 50841a65000098a9383c817879a6a84d

Min Li

Digitally signed by Min Li
Date: 1/03/2017 09:12:17AM
GUID: 5390b860000014ac1413f0693cdb1440
Comments: I made some minor changes on biopharm comments