CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209022Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 209022 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Xhance Established/Proper Name: Fluticasone propionate Dosage Form: Nasal Spray 93 mcg		Applicant: OptiNose US, Inc. Agent for Applicant (if applicable):
RPM: Nina Ton		Division: DPARP

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: 9/15/17

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is September 18, 2017	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval September 18, 2017
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Letters Granted 9/6/2017, Ack 6/28/2017, Ack 4/10/2017, Granted 3/21/2017, Ack 1/3/2017, Advice 12/16/2016 Reviews 8/28/2017, 3/20/2017
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 1/26/2017 DMEPA: ☐ None 8/14/2017 DMPP/PLT: ☐ None 8/10/2017 OPDP: ☐ None 8/9/2017 SEALD: ☒ None CSS: ☒ None Product Quality ☐ None See CMC review dated 8/15/2017 Other: ☐ None DPMH 7/24/2017
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	1/26/2017 ☐ Not a (b)(2) 9/15/2017
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 8/16/17 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	9/12/2017, 9/7/2017, 8/31/2017, 8/1/2017, 7/27/2017, 5/31/2017 (CMC), 3/6/2017, 2/8/2017 (CMC), 1/30/2017, 1/6/2017, 1/5/2017 (CMC), 12/5/2016
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	PeRC meeting minutes 8/30/2017
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 11/18/2015 under IND 110089
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None Combined CDTL/Summary Review 9/18/2017
PMR/PMC Development Templates *(indicate total number)*	☐ None 1
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	8/14/2017, 1/6/2017
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See page 16 of the clinical review dated 8/14/2017
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 6/2/2017
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None 8/14/2017, 1/9/2017

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 8/14/2017, 1/17/2017
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☐ No separate review 8/15/2017
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 8/14/2017, 7/28/2017, 1/4/2017
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None 8/15/2017, 1/3/2017
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☐ None CDRH OC 8/1/2017(2), 2/7/2017
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	8/15/2017
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable ☐ Withhold recommendation ☐ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☐ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	
❖ Take Action Package (if in paper) down to Document Room for scanning within **two business days**	

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/s/

PHUONG N TON
09/18/2017

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: September 12, 2017

To: Alan Traettino Vice President, Regulatory Affairs	**From:** Nina Ton, PharmD Senior Regulatory Project Manager
Applicant: OptiNose US, Inc. 1020 Stony Hill Road, Suite 300 Yardley, PA 19067	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 267-395-2119	**Fax number:** 301-796-9728
Phone number: 267-364-3559	**Phone number:** 301-796-1648

Subject: NDA 209022 Xhance Labeling Comments #3

Total no. of pages including cover and signature page 19

Comments: Please acknowledge receipt and respond by September 13, 2017

Document to be emailed to: alan.traettino@optinose.com

NDA 209022
Xhance
OptiNose US, Inc.

Dear Mr. Traettino:

We are currently reviewing your submission dated November 18, 2016. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are underlined, deletions are in strike-out, and comments are included adjacent to the labeling text. Please be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

In order to facilitate the review of your submission, provide the requested information no later than September 13, 2017. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your NDA.

If you have any questions, please contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

NDA 209022
Xhance
OptiNose US, Inc.

Drafted by:	NTon 9/12/17
Cleared by:	CMcGuire 9/12/17
	TDurmowicz 9/12/17
	LJafari 9/12/17
Finalized by:	NTon 9/12/17

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

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/s/

PHUONG N TON
09/12/2017

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: September 7, 2017

To: Alan Traettino Vice President, Regulatory Affairs	**From:** Nina Ton, PharmD Senior Regulatory Project Manager
Applicant: OptiNose US, Inc. 1020 Stony Hill Road, Suite 300 Yardley, PA 19067	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 267-395-2119	**Fax number:** 301-796-9728
Phone number: 267-364-3559	**Phone number:** 301-796-1648

Subject: NDA 209022 Xhance Information Request

Total no. of pages including cover and signature page 3

Comments: Please acknowledge receipt and respond by noon tomorrow, September 8, 2017

Document to be emailed to: alan.traettino@optinose.com

NDA 209022
Xhance
OptiNose US, Inc.

Dear Mr. Traettino:

We are currently reviewing your submission dated November 18, 2016, and have the following request for information.

Provide your commitment to conduct the following pediatric study and provide the final protocol submission date, study completion date and the final report submission date for the study listed below.

PMR-1: Conduct a randomized, double-blind, placebo controlled, parallel group clinical study in children and adolescents 6 to 17 years of age with bilateral nasal polyps associated with nasal congestion to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of OPN-375 (tradename Xhance) in improving symptoms of nasal congestion and degree of nasal obstruction.

Final Protocol Submission:	MM /YYYY
Study Completion:	MM /YYYY
Final Report Submission:	MM/YYYY

In order to facilitate the review of your submission, provide the requested information no later than noon tomorrow, September 8, 2017. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your NDA.

If you have any questions, please contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

NDA 209022
Xhance
OptiNose US, Inc.

Drafted by:	NTon 9/7/17
Cleared by:	CMcGuire 9/7/17
	TDurmowicz 9/7/17
	LJafari 9/7/17
Finalized by:	NTon 9/7/17

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/s/

PHUONG N TON
09/07/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209022

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

OptiNose US, Inc.
1020 Stony Hill Rd
Ste 300
Yardley, PA 19067

ATTENTION: Alan Traettino
Vice President, Regulatory Affairs

Dear Mr. Traettino:

Please refer to your New Drug Application (NDA) dated June 16, 2017, received June 16, 2017, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Fluticasone Propionate Nasal Spray, 93 mcg per spray.

We also refer to:

- Your correspondence, dated and received June 16, 2017, requesting withdrawal of your request for a review of the proposed proprietary name, [redacted] (b) (4), and requesting review of your proposed proprietary name, Xhance.
- Your amendment to the Request for Proprietary Name Review, dated and received July 13, 2017.

We have completed our review of the proposed proprietary name, Xhance and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your June 16, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,

(http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Michael Sinks, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact Phuong N. Ton, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
09/06/2017

NDA 209022
Xhance
OptiNose US, Inc.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: August 31, 2017

To: Alan Traettino Vice President, Regulatory Affairs	**From:** Nina Ton, PharmD Senior Regulatory Project Manager
Applicant: OptiNose US, Inc. 1020 Stony Hill Road, Suite 300 Yardley, PA 19067	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 267-395-2119	**Fax number:** 301-796-9728
Phone number: 267-364-3559	**Phone number:** 301-796-1648

Subject: NDA 209022 Xhance Labeling Comments #2

Total no. of pages including cover and signature page 29

Comments: Please acknowledge receipt and respond by September 7, 2017

Document to be emailed to: alan.traettino@optinose.com

NDA 209022
Xhance
OptiNose US, Inc.

Dear Mr. Traettino:

We are currently reviewing your submission dated November 18, 2016. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are underlined, deletions are in strike-out, and comments are included adjacent to the labeling text. Please be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

In addition, we have the following comments:

1. Carton Labeling

a. In order to increase the readability of the proprietary name, do not use graphic font for any part of the proprietary name. The entire proprietary name must be presented in the same font.

b. The proposed carton labeling includes the following claims:

- (b) (4)
-

These claims are promotional and may misleadingly imply that the Xhance nasal spray device is superior to other nasal spray devices when this is not the case. Delete these claims.

c. The proposed carton includes a graphic of (b) (4) . Delete this graphic or revise to include the full approved indication, complete administration instructions, and sufficient disclosure of the most serious and most common risks associated with the drug in depth and in detail to balance this presentation.

d. The proposed (b) (4) labeling includes the following claim:

- (b) (4)

This claim is promotional and may misleadingly imply that the Xhance nasal spray device is superior to other nasal spray devices when this is not the case. Delete this claim.

e. The term "(b) (4) has not been used in the PI. Revise "(b) (4) to "device" or "XHANCE device" where applicable.

f. On the side carton, the word "(b) (4) should be changed to "store."

g. The container/carton label should be consistent with the PI. The words (b) (4)" should be changed to "for intranasal use"

2. Instructions For Use

a. Your human factors study results indicated that one participant placed his fingers over the mouthpiece while priming and shaking the device during both dose administrations. To further address this, add the statement 'Do Not place your finger above or over the Flexible Mouthpiece.' to the beginning of the IFU after the warning 'Do Not block (b) (4) second nostril while blowing.' to increase the prominence of this warning.

In order to facilitate the review of your submission, provide the requested information no later than September 7, 2017. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your NDA.

If you have any questions, please contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

Drafted by: NTon 8/31/17
Cleared by: CMcGuire 8/31/17
TDurmowicz 8/31/17
LJafari 8/31/17
Finalized by: NTon 8/31/17

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

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/s/

PHUONG N TON
08/31/2017

PeRC Meeting Minutes
August 16, 2017

PeRC Members Attending:
Lynne Yao
John Alexander
Skip Nelson
Meshaun Payne
Jacquline Yancy
Gettie Audain
Hari Cheryl Sachs
Wiley Chambers
Tom Smith
Gil Burkhart
Lily Mulugeta
James Travis
Mark Rothmann
Raquel Tapia
Victor Baum
Greg Reamann
Kevin Krudys
Barbara Buch
Adrienne Hornatko-Munoz
Dionna Green
Julia Pinto
Jingjing Ye

Agenda

NON-RESPONSIVE

9:00					
9:45					
10:05					
10:15					
10:30					
10:45					
11:05	NDA 209022	Fluticasone Propionate Nasal Spray ((b) (4) Waiver/Deferral/Plan) with Agreed iPSP	DPARP	Nina Phuong Top	Treatment of nasal polyps

NON-RESPONSIVE

2 Page(s) has been Withheld in Full as NON-RESPONSIVE immediately following this page

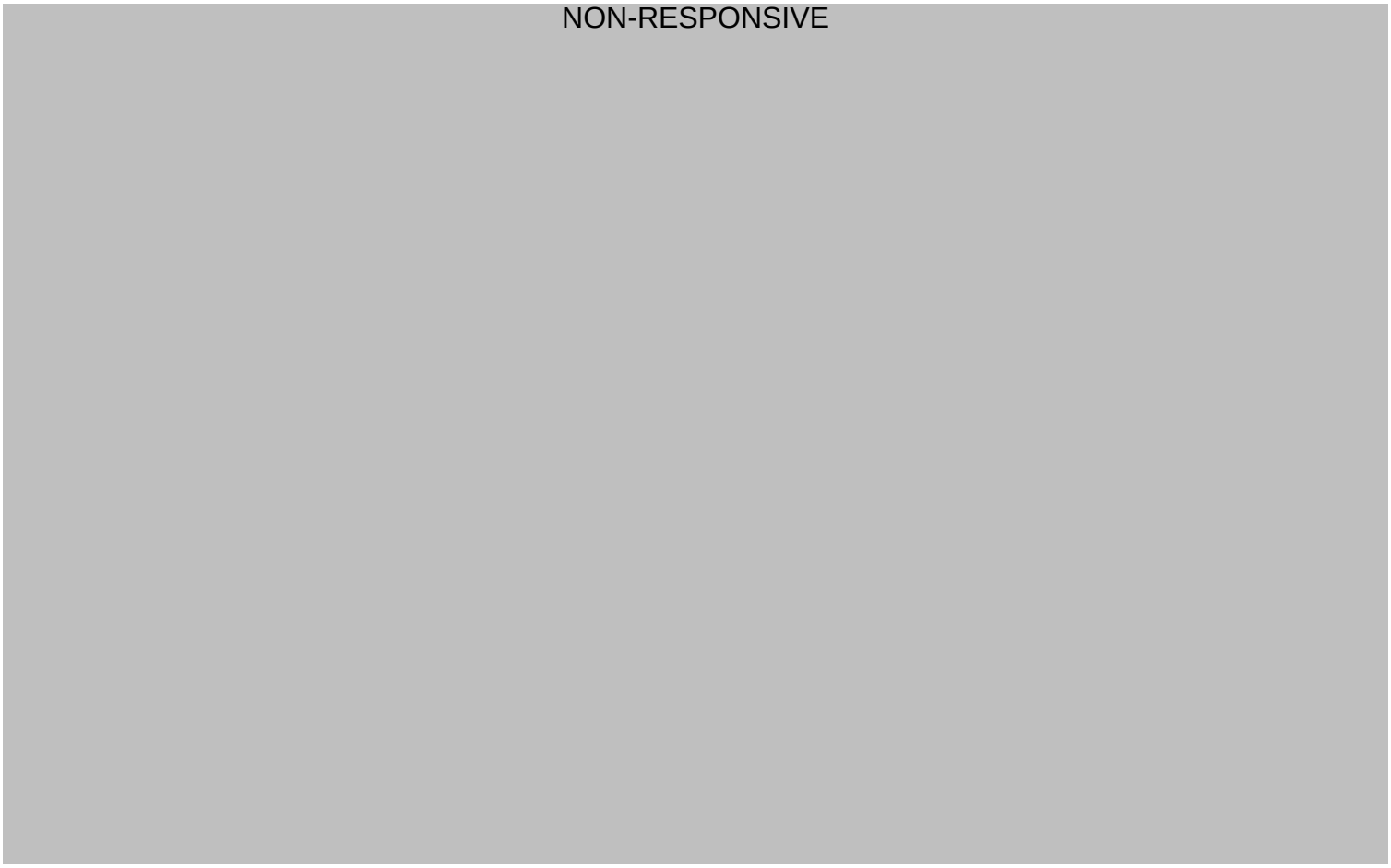
NON-RESPONSIVE

Fluticasone Propionate Nasal Spray ((b) (4) Waiver/Deferral/Plan) with Agreed iPSP

- Approved Indication: Treatment of nasal polyps
- This application has a PDUFA goal date of September 30, 2017.
- This application triggers PREA as a new indication and new dosing regimen.
- The sponsor requests a (b) (4) waiver of pediatrics less than 6 years as studies are impossible or highly impracticable. The division states that pending an evaluation on the usability of the device in children 6-11 years of age, a (b) (4) waiver may be extended to children < 12 years of age.
- The sponsor requests a deferral in pediatrics 6 to less than 17 years.

- PeRC Recommendations:
  - The PeRC agrees to a (b) (4) waiver of pediatrics less than 6 years as studies are impossible or highly impracticable. The PeRC agrees to deferral in pediatrics 6 to less than 17 years.

NON-RESPONSIVE


NON-RESPONSIVE

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/s/

JACQULINE A YANCY
08/30/2017

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: August 1, 2017

To: Alan Traettino Vice President, Regulatory Affairs	**From:** Nina Ton, PharmD Senior Regulatory Project Manager
Applicant: OptiNose US, Inc. 1020 Stony Hill Road, Suite 300 Yardley, PA 19067	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 267-395-2119	**Fax number:** 301-796-9728
Phone number: 267-364-3559	**Phone number:** 301-796-1648

Subject: NDA 209022 Fluticasone Propionate NS Labeling Comments #1

Total no. of pages including cover and signature page: 29

Comments: Please acknowledge receipt and respond by August 8, 2017

Document to be emailed to: alan.traettino@optinose.com

NDA 209022
Fluticasone Propionate NS
OptiNose US, Inc.

Dear Mr. Traettino:

We are currently reviewing your submission dated November 18, 2016, and your proposed labeling submitted on March 16, 2017. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are underlined, deletions are in strike-out, and comments are included adjacent to the labeling text. Please be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

In order to facilitate the review of your submission, provide the requested information no later than August 8, 2017. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your NDA.

If you have any questions, please contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

Drafted by: NTon 8/1/17
Cleared by: CMcGuire 8/1/17
TDurmowicz 8/1/17
Finalized by: NTon 8/1/17

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

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/s/

PHUONG N TON
08/01/2017

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: July 27, 2017

To: Alan Traettino Vice President, Regulatory Affairs	**From:** Nina Ton, PharmD Senior Regulatory Project Manager
Applicant: OptiNose US, Inc. 1020 Stony Hill Road, Suite 300 Yardley, PA 19067	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 267-395-2119	**Fax number:** 301-796-9728
Phone number: 267-364-3559	**Phone number:** 301-796-1648
Subject: NDA 209022 Fluticasone Propionate NS Information Request	
Total no. of pages including cover and signature page 3	
Comments: Please acknowledge receipt and respond by August 1, 2017	

Document to be emailed to: alan.traettino@optinose.com

NDA 209022
Fluticasone Propionate NS
OptiNose US, Inc.

Dear Mr. Traettino:

We are currently reviewing your submission dated November 18, 2016, and have the following request for information.

Submit an updated timeline of the pediatric development program (i.e. updated Table 10.1 from the Agreed Initial Pediatric Study Plan).

In order to facilitate the review of your submission, provide the requested information no later than August 1, 2017. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your NDA.

If you have any questions, please contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

NDA 209022
Fluticasone Propionate NS
OptiNose US, Inc.

Drafted by:	NTon 7/27/17
Cleared by:	CMcGuire 7/27/17
	TDurmowicz 7/26/17
	LJafari 7/27/17
Finalized by:	NTon 7/27/17

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/s/

PHUONG N TON
07/27/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209022

PROPRIETARY NAME ACKNOWLEDGEMENT

OptiNose US, Inc.
1020 Stony Hill Rd, Ste 300
Yardley, PA 19067

ATTENTION: Ramona Lloyd, PhD, RAC
Vice President, Regulatory Affairs and Quality

Dear Dr. Lloyd:

Please refer to your New Drug Application (NDA) dated and received November 18, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Fluticasone Propionate Nasal Spray, 93 mcg per spray.

We acknowledge receipt of your correspondence, dated and received June, 16, 2017, requesting a review of your proposed proprietary name, Xhance.

The user fee goal date is September 14, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Michael Sinks, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact Phuong N. Ton, Regulatory Project Manager, in the Office of New Drugs at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Michael Sinks, PharmD
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

MICHAEL A SINKS
06/28/2017

Ton, Phuong Nina

From: Aisida, Bamidele (Florence)
Sent: Wednesday, May 31, 2017 2:35 PM
To: 'Ramona Lloyd'
Cc: Ton, Phuong Nina
Subject: NDA 209022 IR 5-31-17

Follow Up Flag: Follow up
Flag Status: Flagged

Hi Ramona,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Wednesday, June 15,,2017.

1) It is unclear what kind of failure in the first stage of testing would result in stage two testing for Pump Delivery in the drug product specification. The acceptance criterion for stage 1 does not contain a limit of sample failures required to trigger stage 2 testing (e.g. Not More than One of Ten Determinations). Clarify the acceptance criterion for Pump Delivery.
2) Provide updated (if available) long term and accelerated stability data collected to date for all registration, site specific and (b) (4) stability batches.

Please confirm receipt of this email.

Florence

Florence Aisida, Pharm.D,BCPS
Regulatory Business Process Manager, Office of Program and Regulatory Operations (OPRO)
Office of Pharmaceutical Quality/CDER/FDA. T: 240.402.2691

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209022

PROPRIETARY NAME REQUEST ACKNOWLEDGEMENT/WITHDRAWAL

OptiNose US, Inc.
1020 Stony Hill Road, Suite 300
Yardley, PA 19067

ATTENTION: Ramona M. Lloyd, PhD, RAC
Vice President, Regulatory Affairs and Quality

Dear Dr. Lloyd:

Please refer to your New Drug Application (NDA) dated and received November 18, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Fluticasone Propionate Nasal Spray, 93 mcg per spray.

We also refer to your correspondence, dated and received on March 29, 2017, notifying us that you are withdrawing your request for a review of the proposed proprietary name, (b) (4) . Therefore, (b) (4) is considered withdrawn as of March 29, 2017.

Finally, we refer to your correspondence, dated and received March 29, 2017, requesting review of your proposed proprietary name, (b) (4) . Upon preliminary review of your submission, we have determined that it is a complete submission as described in the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names,* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf.

Therefore, the user fee goal date is June 27, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Michael Sinks, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact Nina Ton, Regulatory Project Manager, in the Office of New Drugs at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Neil Vora, PharmD, MBA, PMP
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

NEIL VORA
04/10/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209022

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

OptiNose US, Inc.
1020 Stony Hill Road, Suite 300
Yardley, PA 19067

ATTENTION: Ramona M. Lloyd, PhD, RAC
Vice President, Regulatory Affairs and Quality

Dear Dr. Lloyd:

Please refer to your New Drug Application (NDA) dated and received November 18, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Fluticasone Propionate Nasal Spray, 93 mcg per spray.

We also refer to your correspondence, dated and received December 22, 2016, requesting review of your proposed proprietary name, (b) (4)

We have completed our review of the proposed proprietary name, (b) (4) and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Michael Sinks, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact Nina Ton, Regulatory Project Manager, in the Office of New Drugs at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
03/21/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209022

INFORMATION REQUEST
PATENT CERTIFICATION OR VERIFICATION

OptiNose US, Inc.
1020 Stony Hill Road, Suite 300
Yardley, PA 19067

Attention: Ramona M. Lloyd, PhD, RAC
Vice President, Regulatory Affairs and Quality

Dear Dr. Lloyd:

Please refer to your New Drug Application (NDA) dated November 18, 2016, received November 18, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Fluticasone Propionate Nasal Spray, 93 mcg.

We also refer to your amendment dated January 12, 2017. This amendment does not comply with 21 CFR 314.60(f), which was added by the final rule on Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule, 81 FR 69580 (October 6, 2016). The final rule became effective on December 5, 2016.

Section 314.60(f) requires that an amendment to an unapproved 505(b)(2) application contain an appropriate patent certification or statement described in 21 CFR 314.50(i), or a "recertification" for a previously submitted paragraph IV certification, if approval is sought for changes described in any of the following types of amendments:

- To add a new indication or other condition of use;
- To add a new strength;
- To make other than minor changes in product formulation; or
- To change the physical form or crystalline structure of the active ingredient.

If an amendment to the 505(b)(2) application does not contain a patent certification (or recertification) or statement, the applicant must verify that the proposed change described in the amendment is not one of the types of amendments described above.

We recommend that the cover letter for your response to this information request and for future amendments to your unapproved 505(b)(2) application either:

1) states that the amendment contains a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or

2) verifies that the proposed change described in the amendment is not one of the types of amendments described in 21 CFR 314.60(f)(1), as appropriate.

Your response to this information request must clearly reference your amendment dated January 12, 2017.

If you have any questions, contact me at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Nina Ton, PharmD
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PHUONG N TON
03/06/2017

From: Aisida, Bamidele (Florence)
To: "Ramona Lloyd"
Cc: Ton, Phuong Nina
Subject: NDA 209022 IR
Date: Wednesday, February 08, 2017 8:43:55 AM

Hello Ms. Lloyd,

The following deficiencies have been identified while conducting the documentation review of application NDA 209022 for OptiNose Fluticasone, OPN-375, in reference to applicable 21 CFR820 regulations and manufacturing of the finished combination product:

1. Please provide a summary of the firm's management structure with executive responsibility who manage, perform, and assess work affecting quality of the product and related controls to ensure that the firm's quality policies are appropriately implemented and followed, and the product appropriately designed and manufactured in conformance with CGMP requirements, including quality system requirements met as per 21 CFR820.20.

2. Please provide a summary of information pertaining to the Purchasing Control as per 21 CFR820.50 to demonstrate controls and documentation for components, products, or services (example sterilization) received at the sponsor's facility for use in the manufacture of the combination product. The summary should include the applicant's evaluation process of their suppliers that meet the manufacturing acceptance criteria of the combination product specifications. Notification of changes by the suppliers should be considered in the firm's Purchasing/Supplier agreement as changes to incoming specification can impact the safety and effectiveness of the final combination product.

3. Please provide a summary of information related to Corrective and Preventive Actions (CAPA) as per the requirement of 21 CFR820.100. CAPA procedures are used to determine the cause of problems and non-conformances, and the appropriate measures used to correct and prevent such problems and non-conformances from recurring. The CAPA system must account for investigations into failures in the device constituent. CAPA activities for the analysis of sources of quality data to identify existing and potential cause of nonconformances, related investigations, and actions considered to correct and prevent recurrences of problems and non-conformances, including the verification or validation of the actions should be documented under the firm's CAPA System as described in 21 CFR820.100.

4. Please provide a summary of the procedure(s) for environmental and contamination controls of the facility where the final manufacturing of the finished combination product occurs, if such conditions could adversely affect the combination product.

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

Please confirm receipt of this email and respond to the IR with a submission to your NDA by Thursday, February 22, 2017.

Florence Aisida, Pharm.D,BCPS

Regulatory Business Process Manager
HHS | FDA | CDER
Office of Pharmaceutical Quality
Office of Program and Regulatory Operations
Bamidele.aisida@fda.hhs.gov | 240.402.2691

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209022

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

OptiNose US, Inc.
1020 Stony Hill Road, Suite 300
Yardley, PA 19067

Attention: Ramona M. Lloyd, PhD, RAC
Vice President, Regulatory Affairs and Quality

Dear Dr. Lloyd:

Please refer to your New Drug Application (NDA) dated November 18, 2016, received November 18, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Fluticasone Propionate Nasal Spray, 93 mcg.

We also refer to your amendment dated January 12, 2017.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **September 18, 2017.**

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by August 21, 2017.

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Pulmonary, Allergy, and Rheumatology Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your requests for a (b) (4) waiver and a (b) (4) deferral of pediatric studies for this application. Once we have reviewed your requests, we will notify you if the (b) (4) waiver and the (b) (4) deferral requests are denied.

If you have any questions, call Nina Ton, Senior Regulatory Project Manager, at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Lydia Gilbert-McClain, MD
Deputy Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

LYDIA I GILBERT MCCLAIN
01/30/2017

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

ELECTRONIC CORRESPONDENCE

Date: January 6, 2017

To: Ramona M. Lloyd, PhD, RAC Vice President, Regulatory Affairs and Quality	**From:** Nina Ton, PharmD Senior Regulatory Project Manager
Applicant: OptiNose US, Inc. 1020 Stony Hill Road, Suite 300 Yardley, PA 19067	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 267-395-2119	**Fax number:** 301-796-9728
Phone number: 267-364-3519	**Phone number:** 301-796-1648
Subject: NDA 209022 Fluticasone Propionate NS Information Request	
Total no. of pages including cover and signature page 3	
Comments: Please acknowledge receipt and respond by January 12, 2017	

Document to be emailed to: ramona.lloyd@optinose.com

Dear Dr. Lloyd:

We are currently reviewing your submission dated November 18, 2016, and have the following requests for information.

1. Clarify if the fluticasone propionate nasal spray drug product tested in Study OPN-FLU-1102 is the same as the to-be-marketed fluticasone propionate nasal spray drug product.

2. Clarify if you used the US approved and marketed reference fluticasone propionate nasal spray (Flonase) and fluticasone propionate metered inhalation aerosol (Flovent HFA) drug products to conduct Study OPN-FLU-1102.

In order to facilitate the review of your submission, provide the requested information no later than January 12, 2017. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your NDA.

If you have any questions, please contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

NDA 209022
Fluticasone Propionate NS
OptiNose US, Inc.

Drafted by: NTon 1-5-2017
Cleared by: LJafari 1-5-2017
AAbsar 1-6-2017
Finalized by: NTon 1-6-2017

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/s/

PHUONG N TON
01/06/2017

From: Ramona Lloyd
To: Aisida, Bamidele (Florence)
Cc: Ton, Phuong Nina
Subject: RE: NDA 209022 IR Sample Request
Date: Thursday, January 05, 2017 2:15:14 PM
Attachments: emfalert.txt

Good afternoon Dr Aisida,

OptiNose can provide samples of the proposed commercial product filled with placebo. The placebo currently available is unlabeled, fully assembled product (the proposed commercial presentation) without any secondary packaging. Please let me know if this is acceptable, and I can have the units sent to your attention at the address below. I will need to request these from the manufacturing site and therefore delivery may take a week or so.

Kind regards,
Ramona

Ramona M Lloyd, PhD, RAC
Regulatory Affairs and Quality
OptiNose US Inc
1020 Stony Hill Road, Ste 300
Yardley, PA 19067
Office: 267 364 3519 | Fax: 267 395 2119 | ramona.lloyd@optinose.com
www.optinose.com

From: Aisida, Bamidele (Florence) [mailto:Bamidele.Aisida@fda.hhs.gov]
Sent: Thursday, January 05, 2017 9:52 AM
To: Ramona Lloyd
Cc: Ton, Phuong Nina
Subject: NDA 209022 IR Sample Request

Hello Ms. Lloyd,

To aid in review of the NDA, provide 10 placebo samples of the combination product that includes the proposed commercial device. If placebos are unavailable, 10 active samples may be provided. The units may be sent to the attention of:

Florence Aisida, Pharm D, BCPS
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 75, Room: 4509
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code 20903 if shipping via United States Postal Service (USPS).
Use zip code 20993 if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).

Please confirm receipt of this email.

Thanks,

Florence Aisida, Pharm.D,BCPS
Regulatory Business Process Manager
HHS | FDA | CDER
Office of Pharmaceutical Quality
Office of Program and Regulatory Operations
Bamidele.aisida@fda.hhs.gov | 240.402.2691

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209022

PROPRIETARY NAME ACKNOWLEDGEMENT

OptiNose US, Inc.
1020 Stony Hill Road, Suite 300
Yardley, PA 19067

ATTENTION: Ramona M. Lloyd, PhD, RAC
Vice President, Regulatory Affairs and Quality

Dear Dr. Lloyd:

Please refer to your New Drug Application (NDA) dated and received December 22, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Fluticasone Propionate Nasal Spray, 93 mcg per metered spray.

We acknowledge receipt of your correspondence, dated and received December 22, 2016, requesting a review of your proposed proprietary name, (b) (4)

If the application is filed, the user fee goal date will be March 22, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Michael Sinks, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact Nina Ton, Regulatory Project Manager, in the Office of New Drugs at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Neil Vora, PharmD, MBA
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

NEIL VORA
01/03/2017

Rashid, Nichelle E

From: Rashid, Nichelle E
Sent: Friday, December 16, 2016 2:59 PM
To: ramona.lloyd@optinose.com
Cc: Sinks, Michael; Rashid, Nichelle E
Subject: Request for Proprietary Name Review/ NDA 209022/ Fluticasone Propionate

Good Afternoon Ms. Lloyd,

Please refer to:

- Your New Drug Application (NDA 209022), dated and received on November 18, 2016, for Fluticasone Propionate
- Your Request for Proprietary Name Review under Investigational New Drug Application (IND 110089), dated and received on December 11, 2015, for (b) (4).

Since you are requesting a different Proprietary Name to be reviewed for your application than the one that was found conditionally acceptable under IND 110089, please withdraw the name, "(b) (4)" from the IND.

Please resubmit the request for Proprietary Name Review for "(b) (4) and include the following information:

- Cover Letter for proposed proprietary name reviews, include the statement "**REQUEST FOR PROPRIETARY NAME REVIEW**" in bold, capital letters on the first page of the submission
- Submit all labels and labeling or refer to the date and eCTD sequence where the labels and labeling can be found.

The PNR review clock will start on the date we receive your new submission.

Please refer to the following Guidance for any questions or concerns.
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075068.pdf

If you have any questions regarding any aspects of the proprietary name review process, contact Michael Sinks, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684.

Best regards,

Nichelle E. Rashid
Lead Safety Regulatory Health Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Tel: (301) 796-3904
Fax: (301) 796-9725
nichelle.rashid@fda.hhs.gov

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/s/

NICHELLE E RASHID
12/16/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209022

NDA ACKNOWLEDGMENT

OptiNose US, Inc.
1020 Stony Hill Road, Suite 300
Yardley, PA 19067

Attention: Ramona M. Lloyd, PhD, RAC
Vice President, Regulatory Affairs and Quality

Dear Dr. Lloyd:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Fluticasone Propionate Nasal Spray, 93 mcg

Date of Application: November 18, 2016

Date of Receipt: November 18, 2016

Our Reference Number: NDA 209022

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 17, 2017, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Nina Ton, PharmD
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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
12/05/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110089

MEETING MINUTES

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

Attention: Ramona M. Lloyd, PhD, RAC
Vice President, Regulatory Affairs and Quality

Dear Dr. Lloyd:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for OPN-375 (Fluticasone Propionate).

We also refer to the meeting between representatives of your firm and the FDA on November 18, 2015. The purpose of the meeting was to discuss the submission of a 505(b)(2) NDA for OPN-375 (Fluticasone Propionate) for the treatment of nasal (b) (4)

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Nina Ton, PharmD
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: November 18, 2015; 11:00 – 12:00 PM EST
Meeting Location: White Oak Building 22, Conference Room 1309

Application Number: IND 110089
Product Name: OPN-375 (Fluticasone Propionate)
Indication: Treatment of nasal (b) (4)
Sponsor Name: OptiNose US Inc.

Meeting Chair: Badrul Chowdhury, MD, PhD
Meeting Recorder: Nina Ton, PharmD

FDA ATTENDEES

Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Lydia Gilbert-McClain, MD, Deputy Director, DPARP
Sofia Chaudhry, MD, Clinical Reviewer, DPARP
Marcie Wood, PhD, Pharmacology/Toxicology Supervisor, DPARP
Carol Galvis, PhD, Pharmacology/Toxicology Reviewer, DPARP
Kiya Hamilton, PhD, Biostatistics Reviewer, Division of Biometrics II, Office of Biostatistics (OB)
Julia Pinto, PhD, Branch Chief, Division of New Drug Products II Branch IV, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)
Craig Bertha, PhD, CMC Lead, Division of New Drug Products II Branch IV, ONDP, OPQ
Kendra Worthy, PharmD, Team Leader, Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE)
Lissa Owens, PharmD, Safety Evaluator, DMEPA, OSE
Michael Sinks, PharmD, RPh, Safety Regulatory Project Manager, OSE
Nina Ton, PharmD, Senior Regulatory Project Manager, DPARP

SPONSOR ATTENDEES

In Person
Ramy Mahmoud, MD, MPH, President and Chief Operating Officer, OptiNose
Ramona Lloyd, PhD, RAC, VP Regulatory Affairs and Quality, OptiNose
John Messina, PharmD, VP Clinical Development, OptiNose
Peter Miller, Chief Executive Officer, OptiNose

By Phone
Colin Sheldrake, BEng, DPhil, Head of Device Development, OptiNose
Tony Flint, BSc, PhD,Head of Quality Assurance and Regulatory, OptiNose
Per Gisle Djupesland, MD, PhD, Chief Scientific Officer, OptiNose

1. BACKGROUND

OptiNose submitted a meeting request dated August 28, 2015, to the Division of Pulmonary, Allergy, and Rheumatology Products. The purpose of the meeting is to discuss the submission of a 505(b)(2) NDA for OPN-375 (Fluticasone Propionate) for the treatment of nasal (b) (4) (b) (4). The Division provided preliminary comments to the Sponsor's questions in the briefing package via electronic correspondence dated November 13, 2015. Ramona Lloyd, Vice President, Regulatory Affairs and Quality, OptiNose, communicated to the Division via email dated November 17, 2015, that OptiNose requested to focus the meeting discussion on Questions 13, 18, 20, 24, 26, and the Additional Comment. OptiNose also provided written responses to the FDA's preliminary comments which are incorporated under the corresponding FDA response. The Sponsor's questions and responses are in *italics*, FDA's responses are in normal font, and the meeting discussion is in **bold**.

2. DISCUSSION

Question 1
Does the Agency agree that the planned liquid delivery subassembly (the device, without the vial and metering pump) supporting documentation and its inclusion in Section 3.2.P.2.4 and Section 3.2.P.7, Container Closure System, of the NDA is adequate for review leading to approval?

FDA Response
The container closure system (CCS) section of P.2 can include one-time characterization studies; however, the final controls for the CCS should be included in P.7 section of the NDA (as per 21 CFR 314.50). The CCS is considered to consist of all components of the device, i.e., the nasal spray pump and (b) (4), amber glass vial, *and* the liquid delivery subassembly components. All of these components that comprise the device, the formulation, and any protective packaging, if applicable, are considered to be parts of the drug product. We consider your drug product to be a nasal spray, thus we refer you to the Agency guidance for the CMC information recommended for support of an application for this type of drug product. The planned NDA presentation of CCS-related information summarized in Table 10 would appear to be appropriate. You may also provide information by reference to supplier drug master files for CCS components.

Meeting Discussion
This question was not discussed.

Question 2
Does the Agency agree with the proposed release specifications for the OPN-375 drug product and the liquid delivery subassembly?

FDA Response
It is premature to comment on the specific proposed acceptance criteria associated with the specifications before our thorough evaluation of the data in your application; regarding the parameters included in the drug product specification, refer to our July 16, 2012, letter.

Regarding the specification for the liquid delivery subassemby device component, the parameters included appear reasonable. Acceptance criteria will be evaluated in conjunction with the associated data during application review.

Meeting Discussion
This question was not discussed.

Question 3
Does the Agency agree with the sponsor's position that the demonstration unit be treated as promotional material; and therefore, that inclusion of information regarding the demonstration unit in the NDA is not required?

If the Agency does not agree with this position and if inclusion in the NDA is required, does the Agency agree that the proposed data package, as described in Section 10.1.2.6.2 of this briefing document, will be adequate to support distribution of the demonstration unit?

FDA Response
From the CMC perspective, we recommend that you include the information regarding the demonstration/placebo unit in the application as outlined in Table 12. Use separate sections for the drug product and this placebo in the NDA, as in your current IND 110089, to expedite review.

Meeting Discussion
This question was not discussed.

Question 4
Does the Agency agree, pending review and agreement that the results of the PK study provide adequate bridging to the RLDs, that the nonclinical information available in the approved labeling of the RLDs and the publically available information are sufficient to support filing a 505(b)(2) NDA for the proposed indication, and that further nonclinical studies with fluticasone propionate or OPN-375 are not required for NDA filing?

FDA Response
Yes, we agree.

Meeting Discussion
This question was not discussed.

Question 5
Does the Agency agree that it is acceptable to summarize the ISO 10993-1 testing of the drug product packaging components in Section 2.4, Nonclinical Overview (Other Toxicity), and

provide the reports in Section 3.2.P.2.4, Pharmaceutical Development: Container Closure System, with the liquid delivery subassembly component information?

FDA Response
Yes, we agree.

Meeting Discussion
This question was not discussed.

Question 6
Does the Agency agree with this approach and the proposed nonclinical literature cutoff date?

FDA Response
Yes, we agree.

Meeting Discussion
This question was not discussed.

Question 7
Does the Agency agree that the proposed content of the clinical pharmacology package is adequate for filing the 505(b)(2) NDA using Flonase and Flovent HFA NDAs as the RLDs to support NDA filing requirements and labeling for special populations, drug-interactions, pharmacodynamics (HPA axis inhibition studies and QT/QTc assessment)?

FDA Response
Your proposal to reference approved, marketed products Flonase and Flovent HFA for clinical pharmacology related information is reasonable.

Meeting Discussion
This question was not discussed.

Question 8
Does the Agency agree that the clinical studies conducted provide a safety database of adequate size and duration to support approval for the planned NDA indication?

FDA Response
The safety database provided by your completed clinical development program is of adequate size and duration for review of your application. Of note, for the purposes of product labeling, the pivotal efficacy and safety trials for this product are the phase 3 nasal polyposis studies: OPN-FLU-NP-3101 and OPN-FLU-NP-3102. While the data from your open-label safety studies in patients with chronic sinusitis ± nasal polyposis (b) (4) these data should be submitted to the NDA to provide supplemental safety data for your new drug product.

Meeting Discussion
This question was not discussed.

Question 9
Does the Agency agree with the approach for integration and analysis of safety data in the ISS, the subgroup analysis, as well as location in the NDA?

FDA Response
Yes, we agree.

Meeting Discussion
This question was not discussed.

Question 10
Does the Agency agree with this approach for inclusion of the safety data from these clinical studies in module 2, clinical overview and clinical summaries, and the inclusion of only the legacy study reports without data sets in Section 5.3.5.4, Other Study Reports and Related Information, of the NDA?

FDA Response
Yes, we agree.

Meeting Discussion
This question was not discussed.

Question 11
Does the Agency agree that the clinical efficacy database is of an adequate size and duration for review in consideration of approval of the product for the planned NDA indication?

FDA Response
Yes, we agree.

Meeting Discussion
This question was not discussed.

Question 12
Does the Agency agree with OptiNose's approach for the analysis and integration of efficacy data in the ISE, its location in the NDA; and that the requirements for the ISE have been met for NDA filing to support approval for the planned indication?

FDA Response
Yes, we agree.

Meeting Discussion
This question was not discussed.

Question 13
Does the Agency agree that the clinical investigations are adequate to allow for the assessment of the appropriate dose of OPN-375 in the proposed patient population and indication in the review of the NDA?

FDA Response
Yes, we agree.

OptiNose Response
OptiNose would like to seek further guidance to understand whether any additional analyses, beyond what was presented in the briefing package, would be beneficial to facilitate your review of available data or to inform the dosing and administration instructions in the labeling.

Meeting Discussion
OptiNose asked whether FDA has recommendations for additional analyses. FDA requested the Sponsor submit a complete responder analysis for the elimination of polyps.

Question 14
Does the Agency agree that (b) (4)

FDA Response
No, we do not agree. Your pivotal efficacy and safety studies should be complete at the time of filing

OptiNose Response
OptiNose acknowledges the response and will provide a final, completed clinical study report for OPN-FLU-NP-3101 in the application with final data integrated in the ISS as appropriate.

Meeting Discussion
This question was not discussed.

Question 15
Does the Agency agree with the proposed plan of providing individual CRFs and patient narratives in the NDA?

FDA Response
Yes, we agree.

Meeting Discussion
This question was not discussed.

Question 16
Does the Agency agree with the proposed clinical data standardization plan for submission of electronic clinical study data in the NDA?

FDA Response
Yes, we agree. Submit electronic datasets for all clinical studies that will be submitted to the NDA to support efficacy and safety of the study drug.

Meeting Discussion
This question was not discussed.

Question 17
Does the Agency agree with this approach and the clinical literature cutoff date?

FDA Response
Yes, we agree.

Meeting Discussion
This question was not discussed.

Question 18
Does the Agency agree that the indication proposed is supported by the 2 phase 3 pivotal adequate and well-controlled clinical studies?

FDA Response
No, we do not agree. (b) (4)

OptiNose Response
OptiNose would like to request further clarification and discussion of the comments regarding the proposed indication.

Meeting Discussion
OptiNose commented that polyps and nasal congestion were the two endpoints studied in their development program and asked for further clarification of the Agency's advice regarding the indication statement. FDA responded that (b) (4)

Question 19
Does the Agency agree that content and wording for the OPN-375 draft labeling to be submitted in the NDA, modeled after the approved labeling of the RLDs Flonase and Flovent HFA, is appropriate based on the results from Study OPN-FLU- 1102?

FDA Response
Yes, we agree.

Meeting Discussion
This question was not discussed.

Question 20
Does the Agency concur with the presentation of (b) (4)

FDA Response
(b) (4)

OptiNose Response
(b) (4)

Meeting Discussion
(b) (4)

Question 21
Does the Agency agree that both the Flonase NDA and Flovent HFA NDA can be used as RLDs for the OPN-375 505(b)(2) application provided the results of Study OPN-FLU-1102 adequately demonstrate that the systemic exposure from OPN-375 is less than Flovent HFA 440 µg?

FDA Response
Yes, we agree.

Meeting Discussion
This question was not discussed.

Question 22
Does the Agency consider providing financial certification for the 2 phase 3 pivotal efficacy trials adequate?

FDA Response
Yes, we agree.

Meeting Discussion
This question was not discussed.

Question 23
OptiNose plans to include a request for a (b) (4) *pediatric waiver for pediatric assessment in children < 6 years of age given that the disease state is unlikely to exist in children under 6 years of age, and a request for a deferral of the pediatric data in children 6 to 17 years of age in the NDA based on the Written Response Letter and will submit these requests in Section 1.9, Pediatric Administrative Information. Does the Agency agree with this approach?*

FDA Response
See PREA REQUIREMENTS under Section 3 of this document.

Meeting Discussion
This question was not discussed.

Question 24
Does the Agency agree with inclusion of the summative user validation study report as adequate supportive evidence of human factors evaluation for review, and the proposed location of the document in the NDA to support approval?

FDA Response
The location is acceptable; however, whether the inclusion of the study report will be adequate to support approval will be a review issue. Furthermore, you stated that you have completed an iterative series of formative studies. In addition to the summative user validation study protocol, user-related risk analysis and results, submit the results of the formative studies and any changes made to the device based on the outcome of these studies and/or instructions for use in Word format.

OptiNose Response
OptiNose will include in the application the summative user validation study report, the summative user validation study protocol, the uFMEA, as well as a Human Factors Engineering/Usability engineering report including a summary of the results of the formative evaluations and changes made based on the outcome of those formative evaluations. We would like to clarify which documentation the reviewer would like provided in Word format, whether this is the Instructions for Use, or the full requested information.

Meeting Discussion
OptiNose agreed to include all requested documents in the NDA submission. FDA clarified that the Instructions for Use should be provided in Word format.

Question 25
Does the Agency agree with this assessment that the safety profile of OPN-375 does not warrant the submission of a risk management plan in the NDA?

FDA Response
Yes, we agree.

Meeting Discussion
This question was not discussed.

Question 26
OptiNose requests guidance from the Agency as to the steps necessary to (b) (4)

FDA Response
A response from Labeling and Nomenclature Committee is pending. We will provide a response in a separate communication.

OptiNose Response
OptiNose acknowledges that a response from the Labeling and Nomenclature Committee is pending and will be provided in a separate communication. We would like to provide an overview and demonstration (b) (4)

Meeting Discussion
OptiNose demonstrated (b) (4) **FDA added that errors are expected for a new device and new terminology but advised the Sponsor to submit their proposal to the NDA for review.**

POST MEETING NOTE

After internal discussion with the Labeling and Nomenclature Committee and others, and with consideration given to the differences between the use of this drug product and more typical nasal spray drug products, we have concluded that "nasal spray" should be the term used to describe your dosage form, as indicated on the draft Instructions for Use provided at the meeting.

Question 27

Does the Agency agree with this proposal for the location of the basis of submission statement to support a 505(b)(2) NDA, the NDA table of contents, and are there any specific requests regarding the electronic submission to facilitate the NDA review?

FDA Response

We refer you to the eSUB staff for any eCTD questions (eSUB@fda.hhs.gov). We have no additional comments or requests regarding your planned electronic submission.

Meeting Discussion

This question was not discussed.

Additional Comment

1. Your proposed prescribing information (PI) must conform to the content and format requirements of the Pregnancy and Lactation Labeling Rule (PLLR) which implemented June 30, 2015. You must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

    - The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
    - The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
    - Regulations and related guidance documents
    - A sample tool illustrating the format for Highlights and Contents
    - The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances, and
    - FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

OptiNose Response

Draft labeling pursuant to 21 CFR 201.56(a) and (d) and 201.57 will be submitted in the initial application. To meet the requirements of the PLLR, in addition to reliance on currently available information in the RLD labels, OptiNose intends to conduct a literature search with a cut-off date of October 2015 for any additional published data relevant to informing appropriate Risk Summaries for Pregnancy, Lactation, and Females and Males of Reproductive Potential.

Should any additional relevant data be identified that might be included in the PI, it will be summarized in the application.

Although OPN-375 delivers fluticasone propionate to the nasal cavity for topical administration, the PK study OPN-FLU-1102 provides for bridging to Flovent HFA and therefore labeling will be developed following guidance for drugs that can be systemically absorbed.

Meeting Discussion
OptiNose noted that the proposed PI will follow the PLLR format and will include information obtained in the literature search since the RLD is not in PLLR format. FDA advised the Sponsor to include all the available information in the NDA labeling submission. The PI language will be reviewed and discussed with OptiNose during the NDA review.

Additional Discussion
FDA commented that quality of life and patient benefit are important to assess. FDA noted that SNOT-22 and patient global assessment (b) (4) **should be included in the NDA as supportive evidence of efficacy. FDA further advised OptiNose to submit a complete application with table of contents and working links.**

3. ADDITIONAL INFORMATION

PREA REQUIREMENTS
Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product

development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation

conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**

1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)

d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

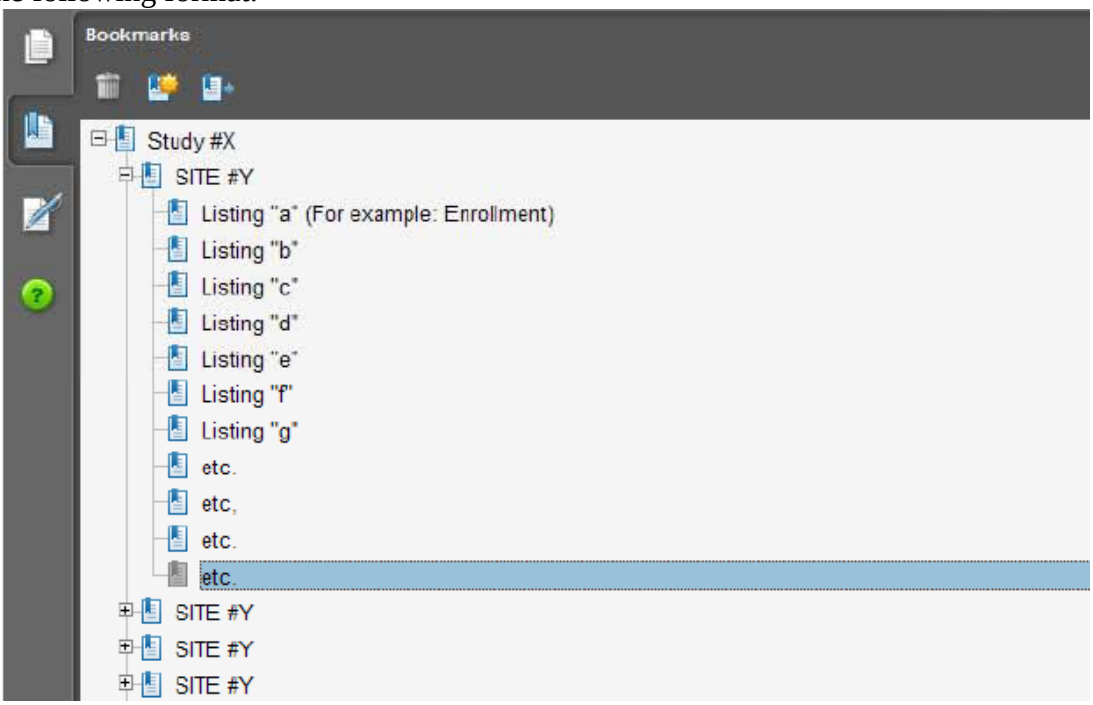
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol

e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

APPEARS THIS WAY ON ORIGINAL

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4. ISSUES REQUIRING FURTHER DISCUSSION
There were no issues requiring further discussion.

5. ACTION ITEMS
There were no action items.

6. ATTACHMENTS AND HANDOUTS
There were no attachments or handouts for the meeting minutes.

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
12/03/2015