

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206099Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 206-099

SUPPL #

HFD # 120

Trade Name [Onzetra Xsail](#)

Generic Name [sumatriptan](#)

Applicant Name [Avanir](#)

Approval Date, If Known [1/27/16](#)

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES

NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

[505\(b\)\(2\) application](#)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES

NO

**1<sup>st</sup> Review Cycle:** [Pharmacodynamic bridging done to Imitrex formulations below. Two efficacy studies were also completed, one of which was included in the approved label. However, these studies were not required and the application could have been approved solely on the basis of BE.](#)

[NDA 20-626 Imitrex nasal spray](#)

[NDA 20-132 Imitrex oral tablets](#)

[NDA 20-080 Imitrex injection](#)

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

d) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA 20-626 Imitrex nasal spray  
NDA 20-132 Imitrex oral tablets  
NDA 20-080 Imitrex injection

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

N/A                      YES                       NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

### PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

Clinical pharmacology studies establishing bioequivalence could have been sufficient to establish efficacy and safety, bridging to the referenced approved NDAs.

Two efficacy studies were done, but not required for this application.

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

YES

NO



(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES

Explain:

NO

Explain:

Investigation #2

YES

Explain:

NO

Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

---

Name of person completing form: Lana Chen

Title: RPM

Date: 2/18/16

Name of Office/Division Director signing form: Eric Bastings, MD

Title: Deputy Director, DNP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/  
-----

LANA Y CHEN  
02/26/2016

ERIC P BASTINGS  
02/26/2016

# ACTION PACKAGE CHECKLIST

(2<sup>nd</sup> cycle AP)

APPLICATION INFORMATION <sup>1</sup>		
NDA # 206-099 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Onzetra Xsail Established/Proper Name: sumatriptan Dosage Form: nasal powder		Applicant: Avanir Agent for Applicant (if applicable): Art Rosenthal
RPM: Lana Chen		Division:
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b></li> </ul> <p><input checked="" type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check: 1/6/16</p> <p><i>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.</i></p>
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>Proposed action AP</li> <li>User Fee Goal Date is <u>2/6/16</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input type="checkbox"/> None    CR 11/26/14
<b>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?</b> Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received  N/A
<b>❖ Application Characteristics<sup>3</sup></b>		N/A

<sup>1</sup> 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.

<sup>2</sup> 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).

<sup>3</sup> 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): 3S  
 (confirm chemical classification at time of approval)

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

**(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

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

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- 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)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	<input type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input type="checkbox"/> Included

<b>Action Letters</b>	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	AP 1/27/16
<b>Labeling</b>	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input type="checkbox"/> Included
❖ Labels <b>(full color</b> carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i>	Acceptable See Tab 3
• Review(s) <i>(indicate date(s))</i>	
Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input type="checkbox"/> None DMEPA: <input checked="" type="checkbox"/> None DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input type="checkbox"/> None SEALD: <input type="checkbox"/> None CSS: <input type="checkbox"/> None Product Quality <input type="checkbox"/> None Other: <input type="checkbox"/> None  See Tab 3
<b>Administrative / Regulatory Documents</b>	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>	Cleared 9/29/14 Cleared 10/13/15 <input type="checkbox"/> Not a (b)(2)
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC 10/22/14 If PeRC review not necessary, explain: _____</li> </ul> </li> </ul>	
<ul style="list-style-type: none"> <li>❖ Breakthrough Therapy Designation</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
<ul style="list-style-type: none"> <li>❖ 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.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include previous action letters, as these are located elsewhere in package</i>)</li> </ul>	See Tab 1
<ul style="list-style-type: none"> <li>❖ 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)</li> </ul>	See Tab 1
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>	See Tab 1
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Advisory Committee Meeting(s)</li> </ul>	<input type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	
<b>Decisional and Summary Memos</b>	
<ul style="list-style-type: none"> <li>❖ Office Director Decisional Memo (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>Division Director Summary Review (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None 1/27/16
<ul style="list-style-type: none"> <li>Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None 1/26/16
<ul style="list-style-type: none"> <li>PMR/PMC Development Templates (<i>indicate total number</i>)</li> </ul>	<input type="checkbox"/> None 1/21/16
<b>Clinical</b>	

❖ Clinical Reviews	See Tab 3
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
• Clinical review(s) <i>(indicate date for each review)</i>	
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Documents and REMS Supporting Document <i>(indicate date(s) of submission(s))</i></li> <li>• REMS Memo(s) and letter(s) <i>(indicate date(s))</i></li> <li>• Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i></li> </ul>	N/A  <input type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) <i>(include copies of OSI letters to investigators)</i>	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
<b>Biostatistics</b> <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
<b>Clinical Pharmacology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input type="checkbox"/> None requested

<b>Nonclinical</b> <input checked="" type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	See Tab 5
• Tertiary review <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections <i>(action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>	<input type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

<b>Day of Approval Activities</b>	
<ul style="list-style-type: none"> <li>❖ For all 505(b)(2) applications:               <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> </li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ For Breakthrough Therapy (BT) Designated drugs:               <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul> </li> </ul>	<input type="checkbox"/> Done N/A ( <i>Send email to CDER OND IO</i> )
<ul style="list-style-type: none"> <li>❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul> </li> </ul>	<input type="checkbox"/> Done N/A
<ul style="list-style-type: none"> <li>❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email</li> </ul>	<input type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter</li> </ul>	<input type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name</li> </ul>	<input type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ Ensure Pediatric Record is accurate</li> </ul>	<input type="checkbox"/> Done
<ul style="list-style-type: none"> <li>❖ Send approval email within one business day to CDER-APPROVALS</li> </ul>	<input type="checkbox"/> Done



NDA 206099

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Avanir Pharmaceuticals, Inc.  
30 Enterprise, Suite 400  
Aliso Viejo, CA 92656

ATTENTION: Arthur Rosenthal  
Executive Director, Regulatory Affairs & Quality

Dear Mr. Rosenthal:

Please refer to your Class 2 resubmission for your New Drug Application (NDA) dated and received May 6, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Sumatriptan Nasal Powder, 11 mg.

We also refer to:

- Your correspondence, dated and received May 26, 2015, requesting review of your proposed proprietary name, Onzetra
- Your amendment, dated and received September 22, 2015, amending the requested proposed proprietary name to, Onzetra Xsail

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

If any of the proposed product characteristics as stated in your September 22, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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 Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application, contact Lana Chen, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1056.

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

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

/s/  
-----

TODD D BRIDGES  
11/04/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 206-099

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

Avanir Pharmaceuticals  
Attention: Arthur Rosenthal  
20 Enterprise, Suite 400  
Aliso Viejo, CA 92656

Dear Mr. Rosenthal:

Please refer to your New Drug Application (NDA) dated and received January 27, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Onzetra Xsail (sumatriptan) nasal powder 11 mg.

On October 21, 2015, we received your October 21, 2015, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is February 6, 2016.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by January 6, 2016.

If you have any questions, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

*{See appended electronic signature page}*

Eric Bastings, M.D.  
Deputy Director  
Division of Neurology Products  
Office of Drug Evaluation I  
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/  
-----

ERIC P BASTINGS  
10/26/2015

**Chen, Lana Y**

---

**From:** Holovac, Mary Ann  
**Sent:** Wednesday, October 14, 2015 3:50 PM  
**To:** Chen, Lana Y  
**Cc:** Locicero, Colleen L; Duvall, Beth A; Sharma, Khushboo; Holovac, Mary Ann  
**Subject:** FW: NDA 206099 Onzetra (Sumatriptan Succinate) nasal powder - cleared for action

Lana,

We discussed this application (again) at Tuesday's 505(b)(2) clearance meeting. This application is cleared for action from a 505(b)(2) perspective.

No changes are needed on the draft assessment. If you are not approving this cycle, please defer archiving in DARRTS until you are headed towards approval (in which case you would need to have the application cleared again). If that's the case, please let us know when the RS arrives so that we can add it anew to our clearance queue.

Please let me know if you have any questions.

Mary Ann

---

**From:** Holovac, Mary Ann  
**Sent:** Monday, September 29, 2014 3:34 PM  
**To:** Kishore, Vandna N  
**Cc:** Locicero, Colleen L; Bertha, Amy; Duvall, Beth A; Holovac, Mary Ann  
**Subject:** NDA 206099 Onzetra (Sumatriptan Succinate) nasal powder - cleared for action

Vandna,

We discussed this application at today's 505(b)(2) clearance meeting. This application is cleared for action from a 505(b)(2) perspective.

No changes are needed on the draft assessment. If you are not approving this cycle, please defer archiving in DARRTS until you are headed towards approval (in which case you would need to have the application cleared again). If that's the case, please let us know when the RS arrives so that we can add it anew to our clearance queue. Great job on the assessment! It is unusual that no changes are needed!

You noted in your 9/22/14 email below that there was a possibility of taking a Tentative Approval (TA) action. Please be advised that a TA action is only possible if the application is ready for approval but for patent or exclusivity issues. As there are no unexpired patent or exclusivities a TA action is not possible

Please let me know if you have any questions.

Mary Ann

---

**From:** Kishore, Vandna N

**DRAFT**

**505(b)(2) ASSESSMENT**

<b>Application Information</b>		
NDA # 206-099	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Onzetra Xsail Established/Proper Name: sumatriptan Dosage Form: nasal powder Strengths: 22mg		
Applicant: Avanir		
Date of Receipt: 5/6/15 (RS)		
PDUFA Goal Date: 2/6/15 (6+3)		Action Goal Date (if different): Targeting Jan 22, 2016 or sooner if possible
RPM: Lana Chen		
Proposed Indication(s): Migraine		

**GENERAL INFORMATION**

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



APPEARS THIS WAY ON  
ORIGINAL

**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 20-080 Imitrex injection	FDA's previous finding of safety and effectiveness (clinical and nonclinical)
NDA 20-132 Imtrex tablets	FDA's previous finding of safety and effectiveness (clinical and nonclinical)
NDA 20-626 Imitrex nasal spray	FDA's previous finding of safety and effectiveness (clinical and nonclinical)

\*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature<sup>1</sup>. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

BA/ PK study—see Clin Pharm Review for details

The bracketing of Onzetra pharmacokinetics between those of Imitrex Nasal Spray and Imitrex Tablet and Injection is adequate to support the systemic safety and efficacy of Onzetra.

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES  NO

*If "NO," proceed to question #5.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO

*If "NO," proceed to question #5.*

*If "YES", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?  
 YES  NO

**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO   
*If "NO," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Imitrex injection	NDA 20-080	Y
Imtrex tablets	NDA 20-132	Y
Imitrex nasal spray	NDA 20-626	Y

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO   
*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*  
*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES  NO   
*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES  NO   
*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES  NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES  NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a change in dosage form to nasal powder.

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

*If "NO" to (a) proceed to question #11.*

*If "YES" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A  YES  NO

*If this application relies only on non product-specific published literature, answer "N/A"  
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

*If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s): N/A

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO

*If "NO", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A  YES  NO

*If this application relies only on non product-specific published literature, answer "N/A"*

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

**PATENT CERTIFICATION/STATEMENTS**

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

No unexpired patents

Listed drug/Patent number(s):

No patents listed  *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): 9119932

Expiry date(s): 23 April 2024

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the

application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):  
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?  
YES  NO

*If "NO", please contact the applicant and request the signed certification.*

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.  
YES  NO

*If "NO", please contact the applicant and request the documentation.*

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

*Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 206099

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Avanir Pharmaceuticals, Inc.  
30 Enterprise, Suite 400  
Aliso Viejo, CA 92656

ATTENTION: Arthur Rosenthal  
Executive Director, Regulatory Affairs & Quality

Dear Mr. Rosenthal:

Please refer to your Class 2 resubmission for your New Drug Application (NDA) dated and received May 6, 2015, submitted under section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act for Sumatriptan Nasal Powder, 11 mg.

We also refer to your correspondence, dated and received May 26, 2015, requesting review of your proposed proprietary name, Onzetra.

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

If any of the proposed product characteristics as stated in your May 26, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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 Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application, contact Lana Chen, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1056.

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

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

/s/  
-----

TODD D BRIDGES  
08/17/2015



NDA 206-099

**ACKNOWLEDGE –  
CLASS 2 RESUBMISSION**

Avanair Pharmaceuticals  
Attention: Arthur Rosenthal  
20 Enterprise, Suite 400  
Aliso Viejo, CA 92656

Dear Mr. Rosenthal:

We acknowledge receipt of your resubmission on May 6, 2015 to your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Onzetra (sumatriptan) nasal powder 22 mg.

We consider this a complete, class 2 response to our November 26, 2014 action letter. Therefore, the user fee goal date is November 6, 2015.

If you have any questions, call me at (301) 796-1056.

Sincerely,

*{See appended electronic signature page}*

Lana Y. Chen, R.Ph.  
Senior Regulatory Project Manager  
Division of Neurology Products  
Office of Drug Evaluation I  
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/  
-----

LANA Y CHEN  
06/02/2015



NDA 206099

**DISCIPLINE REVIEW LETTER**

Avanir Pharmaceuticals  
Attention: Arthur Rosenthal, R.A.C.  
Senior Director, Regulatory Affairs & Quality  
20 Enterprise, Suite 200  
Aliso Viejo, CA 92656

Dear Mr. Rosenthal:

Please refer to your New Drug Application (NDA) dated January 27, 2014, received January 27, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Onzetra (Sumatriptan Nasal Powder), 22mg in the Xsail Breath Powered Delivery Device.

The review of your submission by the Division of Medication Error Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE) is complete, and has identified the following deficiencies:

The human factors validation study was unable to show that the intended population is able to use the product safely and effectively. Only Fourteen (14) users (52%) safely and effectively completed the product use process by simulating delivery of a “full treatment dose.” Two users used more than two nosepieces to simulate administration of a total dose. Seven of the 56 capsules used by 27 participants during testing scenarios remained unpierced. Four users had failures performing the piercing/inhalation tasks in the correct order to achieve effective dosing of Onzetra. Additionally, two users failed to administer medication to the second nostril. We are also concerned with your proposal that patients will be able ascertain whether or not the piercing process was successful through visualization alone as this was not validated in your study. The photos you provided suggest that the difference may not be readily apparent.

Most of the task failures noted in the study would result in patients receiving either an under-dose or not receiving the medication at all resulting in treatment failures. Thus, we recommend you further evaluate the root cause(s) of the failures seen in your validation study. You should implement corrective and preventative measures to address the failures and concern we outlined, optimize the product-user interface, and validate these changes in another human factors study.

We have determined that the identified deficiencies preclude discussion of labeling changes and/or postmarketing requirements/commitments at this time.

We are providing these comments to you before completing our review of your entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Vandna Kishore, Regulatory Project Manager, at (301) 796-4193.

Sincerely,

*{See appended electronic signature page}*

Eric Bastings, MD  
Deputy Director  
Division of Neurology Products  
Office of Drug Evaluation I  
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/  
-----

ERIC P BASTINGS  
10/29/2014

**PeRC PREA Subcommittee Meeting Minutes  
October 22, 2014**

**PeRC Members Attending:**

Wiley Chambers

George Greeley

Rosemary Addy (Did not review NON-RESPONSIVE )

Melissa Tassinari

Robert “Skip” Nelson

Tom Smith

Karen Davis-Bruno (Did not review NON-RESPONSIVE )

Kevin Krudys

Olivia Ziolkowski

Barbara Buch

Julia Pinto (Did not review NON-RESPONSIVE )

Dionna Green

Michelle Roth-Cline

Freda Cooner

Daiva Shetty

Diane Murphy

**PREA**

10:10	NDA	NON-RESPONSIVE		
10:30	NDA	206099	Onzetra Partial Waiver/Deferral/Plan	Acute treatment of migraine with or without aura in adults
10:50	NDA	NON-RESPONSIVE		
11:05	NDA			
	<i>BLA</i>			
	<i>NDA</i>			

NON-RESPONSIVE

**Onzetra Partial Waiver/Deferral/Plan**

- Proposed Indication: Acute treatment of migraine with or without aura in adults
- The Division acknowledged that this application was submitted on 1/27/14 and did not have an Agreed iPSP. Transition within the Division led to a delay in the review of the NDA and failure to review and reach an Agreed iPSP with the sponsor. This application is not in compliance with the requirement under FDASIA to obtain an Agreed iPSP prior to submission of the marketing application.
- This application triggered PREA as a new: active ingredient, dosage form, and route of administration.
- The PDUFA goal date is November 27, 2014 (Thanksgiving, therefore action date will be earlier)
- *PeRC Recommendations:*
  - The PeRC agreed with the waiver in patients ages birth to less than 6 years because studies would be impossible or highly impractical because there are too few patients and to the deferral in patients 6 to 17 years because the product is ready for approval in adults and additional safety and effectiveness data are needed in this pediatric age group.

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

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

/s/  
-----

GEORGE E GREELEY  
11/05/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

---

Food and Drug Administration  
Silver Spring, MD 20993

NDA 206099

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Avanir Pharmaceuticals, Inc.  
20 Enterprise  
Suite 200  
Aliso Viejo, CA 92656

ATTENTION: Arthur Rosenthal, R.A.C.  
Senior Director, Regulatory & Quality

Dear Mr. Rosenthal:

Please refer to your New Drug Application (NDA) dated and received January 27, 2014, submitted under section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act for Sumatriptan Nasal Powder, 22mg.

We also refer to your correspondence, dated and received May 6, 2014, requesting review of your proposed proprietary name, Onzetra.

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

If any of the proposed product characteristics as stated in your May 6, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application, contact Vandna Kishore, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4193.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH  
Deputy Director  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
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/  
-----

TODD D BRIDGES on behalf of KELLIE A TAYLOR  
07/28/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 206099

**PROPRIETARY NAME REQUEST  
UNACCEPTABLE**

Avanir Pharmaceuticals, Inc.  
20 Enterprise, Suite 200  
Aliso Viejo, CA 92656

ATTENTION: Arthur Rosenthal  
Senior Director, Regulatory Affairs & Quality

Dear Mr. Rosenthal:

Please refer to your New Drug Application (NDA) dated and received January 27, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Sumatriptan Nasal Powder, 11 mg.

We also refer to your correspondence, dated and received January 27, 2014, requesting review of your proposed proprietary name, [REDACTED] (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable [REDACTED] (b) (4):



Please note that the Federal Food Drug and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a proposed trade name or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C. 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See 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> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application, contact Vanda Kishore, Regulatory Project Manager in the Office of New Drugs at (301) 796-4193.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH  
Deputy Director  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
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/  
-----

TODD D BRIDGES on behalf of KELLIE A TAYLOR  
03/26/2014



NDA 206099

**FILING COMMUNICATION -  
FILING REVIEW ISSUES IDENTIFIED**

Avanir Pharmaceuticals  
Attention: Arthur Rosenthal, R.A.C.  
Senior Director, Regulatory Affairs & Quality  
20 Enterprise, Suite 200  
Aliso Viejo, CA 92656

Dear Mr. Rosenthal:

Please refer to your New Drug Application (NDA) dated January 27, 2014, received January 27, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for (b)(4) (Sumatriptan Nasal Powder), 22mg in the Xsail Breath Powered Delivery Device.

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 November 26, 2014.

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 October 30, 2014.

During our filing review of your application, we identified the following potential review issues:

Biopharmaceutics:

We do not agree with the use of a 90% confidence intervals approach to establish bioequivalence based on vitro testing. Under the Population BE method, for each comparative in vitro test, FDA recommends the calculation of a 95% upper confidence bound of either the reference-scaled or constant-scaled linearized criterion as a measure of equivalence between the test and reference products. The confidence interval is compared to

an acceptance limit that is based on fixed statistical parameters. The 95% upper confidence bound for linearized criteria  $H\eta$  must be  $\leq 0$  (refer to Draft Guidance on Budesonide Suspension for Inhalation published in Sep 2012 and the June 1999 Draft Guidance and Statistical Information for In Vitro Bioequivalence Data).

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

Biometrics Review Information Request:

1. For Study OPN-SUM-MIG-3301 and OPTUK-MSPP-PRO002, please provide executable SAS programs that create analysis datasets and efficacy analysis results.
2. For Study OPTUK-MSPP-PRO002, ADEF dataset only includes 105 subjects in the Per Protocol (PP) population. Please provide ADEF dataset that includes efficacy information for all randomized subjects (n=117).

Biopharmaceutics Review Information Request:

1. Please submit the complete set of data as SAS transport files for the batches used in the population BE analysis. We refer you to the Budesonide Suspension for Inhalation Guidance for Industry for recommendations in terms of format of the data and what constitutes a complete set of data to run the in vitro BE analysis between the Test and Reference products.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. The **bolded** HL Limitation Statement must include the following verbatim statement: **“These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).”** The name of drug product should appear in UPPER CASE letters.

We request that you resubmit labeling that addresses these issues by April 4, 2014. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

**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), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, 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.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

If you have any questions, call Vandna Kishore, Regulatory Project Manager, at (301) 796-4193.

Sincerely,

*{See appended electronic signature page}*

Eric Bastings, MD  
Deputy Director  
Division of Neurology Products  
Office of Drug Evaluation I  
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/  
-----

ERIC P BASTINGS  
03/21/2014



IND 110,090

**MEETING MINUTES**

OptiNose US Inc  
Attention: Helena Correia  
Regulatory Affairs Consultant  
1010 Stony Hill Road, Suite 375  
Yardley, PA 19067

Dear Ms. Correia:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (sumatriptan nasal).

We also refer to your May 14, 2013 correspondence requesting a pre-NDA meeting to discuss the content and format of a 505(b)(2) application.

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 Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

*{See appended electronic signature page}*

Eric Bastings, MD  
Acting Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** Pre-NDA  
  
**Meeting Date:** July 22, 2013  
**Meeting Location:** FDA White Oak  
  
**Application Number:** 110,090  
**Product Name:** sumatriptan  
**Indication:** Migraine  
**Sponsor/Applicant Name:** OptiNose US

**FDA ATTENDEES (tentative)**

**Division of Neurology Products**

Eric Bastings, MD, Acting Director  
Nicholas Kozauer, MD, Clinical Team Leader  
Nushin Todd, MD, Clinical Reviewer  
Charles Jewell, PhD, Acting Pharmaceutical Assessment Lead  
Jagan Parepally, PhD, Clinical Pharmacology Reviewer  
Sharon Yan, PhD, Statistical Reviewer  
Kun Jin, PhD, Statistical Team Leader  
Lana Chen, RPh, Project Manager  
  
Deepika A. Lakhani, Ph.D., Biopharmaceutics Reviewer, ONDQA  
Vasant Malshet, Ph.D., Biomedical Engineer, ENT Devices Branch, CDRH  
Quynh Nhu Nguyen, Combination Products Human Factors Specialists, CDRH,  
Human Factors Premarket Evaluation Team  
Julie Villanueva Neshiewat, PharmD, Safety Evaluator,  
Division of Medication Error Prevention and Analysis (DMEPA)  
Irene Chan, PharmD, Safety Team Leader, DMEPA  
Ermias Zerlassie, OSE Project Manager (via phone)

**SPONSOR ATTENDEES**

(b) (4)	Regulatory and Quality Consultant	OptiNose
(b) (4)	Clinical and Regulatory Project Manager	(b) (4)
Tony Flint, BSc, Ph.D	Head of Quality Assurance and Regulatory Affairs	OptiNose
Ramy Mahmoud, MD, MPH	Chief Operating Officer	OptiNose

John Messina, Pharm.D	Vice President, Clinical Development	OptiNose
Elliot Offman, B.Pharm, MSc	Clinical Pharmacology Consultant	(b) (4)
Arthur Rosenthal	Sr. Director, Regulatory Affairs and Quality	Avanir
Colin Sheldrake, BEng, DPhil	Head of Device Development	OptiNose
Paul Shin	Senior Director, Clinical Research	Avanir
Joao Siffert, MD	Chief Scientific Officer	Avanir

## DISCUSSION

### **Question 1: 505(b)(2) Reference for Safety Pharmacology and Toxicology Data**

For the proposed (b) (4) SUMATRIPTAN NDA, the Sponsor intends to incorporate by reference via the 505(b)(2) pathway the nonclinical data submitted to NDA 020080 (Imitrex for injection; Glaxo Smithkline), NDA 020132 (Imitrex tablet; GSK) and NDA 020626 (Imitrex nasal spray; GSK) in support of the active drug, sumatriptan succinate. Clinical pharmacokinetic and scintigraphy studies provide evidence that neither systemic drug levels nor levels at the site of administration (the epithelium of the nasal cavity) are higher in extent or duration with (b) (4) SUMATRIPTAN than with the reference products. Further, there are no excipients used in the (b) (4) SUMATRIPTAN drug product formulation and no impurities or degradants produced during manufacturing or that appear on stability that would require safety assessment. Therefore, no additional nonclinical studies were performed or are planned for the drug in support of the NDA.

**Does the Division agree with the proposed 505(b)(2) approach for the nonclinical data for sumatriptan succinate in support of the proposed NDA and that no additional nonclinical studies are required?**

#### **FDA Preliminary Response:**

No additional nonclinical studies will be needed to support an NDA, provided there are no safety concerns (e.g., impurities, leachables/extractables) that would require nonclinical assessment.

#### **Meeting Discussion:**

None.

### **Question 2: 505(b)(2) Reference for Population Exposure to Assess Clinical Safety**

A total of 222 subjects will have received a least a single dose of (b) (4) SUMATRIPTAN in the clinical program conducted in support of the proposed NDA. For the proposed (b) (4) SUMATRIPTAN NDA, the Sponsor intends to incorporate by reference via the 505(b)(2) pathway data in the NDA 020080 (Imitrex for injection; Glaxo Smithkline), NDA 020132 (Imitrex tablet; GSK) for systemic exposure and NDA 020626 (Imitrex nasal spray; GSK) for local exposure. These references are being done in order to fulfil the requirements of the ICH E1A Guideline for Industry “The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Longterm Treatment of Non-Life-Threatening Conditions” for the active drug, sumatriptan succinate. Clinical pharmacokinetic and scintigraphy studies provide evidence that exposure to sumatriptan from administration of (b) (4) SUMATRIPTAN does not exceed that of the reference product systemically or to the site of administration in the nasal cavity. Therefore, the Sponsor believes that requirements for population exposure are met by referencing the cited marketing applications of previous innovator products via the 505(b)(2) pathway.

**Does the Division agree with the proposed 505(b)(2) approach to meet the requirements for the extent of exposure of sumatriptan succinate in support of the proposed NDA?**

**FDA Preliminary Response:**

We agree, on face, with the proposed 505(b)(2) approach in support of the NDA. Adequacy of the population exposure to sumatriptan, however, is a review issue and will be determined during the NDA review process.

**Meeting Discussion:**

None.

**Question 3: Biopharmaceutics and Clinical Pharmacology**

The Sponsor believes that the completed biopharmaceutics and clinical pharmacology package is adequate to support the NDA for use in the proposed patient population.

**Does the Division agree?**

**FDA Preliminary Response:**

On face, the completed Clinical Pharmacology studies appear to be adequate.

On face, the proposed Biopharmaceutics studies seem adequate. As discussed in the minutes of our meeting on April 10, 2013, you must submit the biowaiver request in the NDA, supported by

the data for ED-DCU and EP-PSD using the population bioequivalence (PBE) approach to demonstrate comparable performance. Your suggested flow rate of 30 L/min must be supported by the flow rate characterization study to support the suitability of this nominal flow rate for the PBE approach. The granting of a biowaiver will be a review issue.

#### **ADDITIONAL COMMENT**

There is a large difference between the dose delivered when tested *in vitro* (10 mg) and the dose administered to subjects in the clinical trials (~7.5 mg), based on residual dose in device. We are concerned that the drug delivery may not be consistent between the patients. You should provide evidence to show that the actual drug delivered is consistent among patients.

#### **Meeting Discussion:**

The sponsor provided residual dose data (n=40 capsules) from the devices used in pivotal Phase 3 study showing that the consistency of drug delivery. The Agency agreed that the data characterizes the drug delivery consistency and requested that the sponsor submit such information in the NDA.

#### **Question 4: Clinical Efficacy Program**

The clinical efficacy program conducted with (b) (4) SUMATRIPTAN in support of the proposed NDA is comprised of a single adequate and well-controlled Phase 3 study (OPN-SUM- MIG-3301) and a supportive Phase 2 study (OPTUK-MSPP PRO 002). The Sponsor believes that results from these studies provide sufficient evidence of efficacy in the treatment of patients with acute migraine to justify submission of an NDA for the proposed use.

**Does the Division agree?**

#### **FDA Preliminary Response:**

In form, your clinical studies can potentially provide sufficient evidence of efficacy and therefore support the submission of your planned NDA.

#### **Meeting Discussion:**

The sponsor reported that the completed comparative PK study (Study 1302) has demonstrated the exposure (AUC and C<sub>max</sub>) produced by (b) (4) is equivalent to or higher than the approved product (Imitrex Nasal Spray, 20 mg). Given this information, they asked confirmation from the Agency that the efficacy requirement can be fulfilled by “pain relief” and that a statistically significant separation from placebo on a co-primary measure of associated symptoms is not required.

The Agency stated that their response remains the same as previously discussed with the sponsor: “unless your product is bioequivalent to (or has higher exposure than) another approved dosage form of Imitrex®, we would require statistical significance on migraine associated symptoms as well.”

**Question 5: ISE Analyses**

For the NDA, the Sponsor intends to summarize efficacy results from the single adequate and well-controlled Phase 3 study (OPN-SUM-MIG-3301) and the supporting Phase 2 study (OPTUK-MSPP PRO 002) separately. No integration or pooling of data from these two studies is planned (See Appendix 1 for description of planned study groupings and analysis).

**Does the division agree with the proposed analysis plan for efficacy data?**

**FDA Preliminary Response:**

We agree.

**Meeting Discussion:**

None.

**Question 6: ISS Analyses**

For the NDA, the Sponsor intends to integrate and summarize safety results from the Phase 3 study (OPN-SUM-MIG-3301) and the supporting Phase 2 study (OPTUK-MSPP PRO 002). Safety data from Phase 1/Bioavailability studies (OPTUK-MSPP PRO 001 in migraine patients and OPN-SUM-1302 in healthy subjects) will be summarized separately with no data integration. See Appendix 1 for description of planned study groupings and analysis.

**Does the division agree with the analysis plan for safety data?**

**FDA Preliminary Response:**

We agree.

**Meeting Discussion:**

None.

**Question 7: Usability Validation Testing**

The development of the (b) (4) Breath Powered Powder device has followed the FDA Quality Systems Regulations (21 CFR 820), the recognized consensus standards AAMI / ANSI / IEC 62366:2007 and ANSI/AAMI HE75:2009, and the FDA's current recommendations for medical device design optimization through human factors analysis and testing. The

Sponsor has completed a human factors study designed to obtain anthropometric data on defined naso-facial dimensions and to evaluate models of the investigational devices by assessing ergonomic fit in nose, mouth, and hands as well as device usability. In addition, a study evaluating device usability in conjunction with aspects of the instructions for use (IFU) has been completed.

OptiNose is preparing to complete the final usability validation study to determine whether or not (b) (4) SUMATRIPTAN will be used appropriately by end users. The objective of this study is to demonstrate that the production versions of the instructional inserts and product design can enable first-time (b) (4) Breath Powered Powder Device end-users, who have undergone no formal training, to use the device without the occurrence of preventable use errors or difficulties that could result in harm.

OptiNose has submitted the protocol for this validation study ([CLS-1015-PCL1 Rev A SNDS Validation Protocol- Submission #0020](#)) along with a document summarizing the Human Factors Engineering and Usability Engineering work completed to date to the division on June 10, 2013.

**Dose FDA agree that the approach taken in human factors testing and analyses along with the planned user verification and validation study (protocol provided) is adequate?**

**FDA Preliminary Response:**

We do not agree with your proposed study protocol for the following reasons:

- We do not agree with using empty nosepieces in your study since a sub-task success criterion for dispensing drug is “user blows with sufficient force so that the drug capsule can be heard to rattle.” If the nosepieces in your study are empty (i.e., no capsule), it is unclear how study participants will be able to verify that the medication was successfully dispensed if there is no “rattle” sound with empty nosepieces. Therefore, we recommend using nosepieces that include a placebo drug capsule, capable of producing the same audible feedback expected with the marketed product.
- You state that the study tasks identified are based on a use-related risk analysis. In your Use Failure Modes and Effects Analysis (UFMEA), you identified five essential tasks: referring to instructional materials, preparing medication for delivery, positioning the device for drug delivery, dispensing drug, and product knowledge. You also stated that there were no critical tasks associated with product use. We do not agree with your assessment. We consider underdose, no treatment, and overdose as having a negative clinical impact on the patient. Any tasks that would result in a negative clinical impact on the patient are considered critical tasks. For example, if the task “Fully depress the device button one time only to pierce the drug capsule in the nosepiece and releases” is not done appropriately, it could result in no treatment, and therefore, would have a negative clinical impact on the patient. This task should be classified as a critical task. As another example, this product requires the user to use two nosepieces, one nosepiece

in each nostril, to deliver a complete dose. Therefore, after dispensing the drug into the first nostril, the user is required to discard the first nosepiece, attach the second nosepiece, press a button on the device to pierce the capsule, and then blow with sufficient force into the mouthpiece to deliver the drug via the second nosepiece. Since the potential use error for each of these steps can result in an underdosing error, these steps are considered critical tasks. Reclassify the aforementioned tasks as critical and ensure you adequately capture use error data for these tasks.

- You state that users completing the use process task by self-administering a simulated full unit-dose using the nasal delivery, but are observed to have subtask use errors, will be judged as having completed the product use-process task successfully. We do not agree and would classify these subtask use errors as close call errors that require further evaluation.
- We note your inclusion criteria list candidates who are articulate, thorough, and thoughtful in his/her response. It is unclear if this criterion represents a specific minimum education level. Ensure your usability study includes participants that reflect the range in education and literacy levels expected in the general U.S. population.

In addition, we require clarification regarding the following:

- It is unclear how patients determine when they receive a full dose vs. a partial dose based on the “rattle” sound. Does an initial “rattle” sound indicate a full dose is received, or does the rattle sound need to continue for a minimum amount of time (i.e. rattle for two seconds) to indicate a full dose is received? Please describe how a patient will determine if a partial dose is received vs. a full dose, and test that patients understand this difference in the study. Information about determining if a full dose vs. a partial dose is delivered may be helpful to include in the Instructions for Use (IFU).
- Please describe how a patient will determine if a nosepiece is used vs. new, and test that patients understand this difference in the study. Information about determining if a nosepiece is used or new may be helpful to include in the Instructions for Use (IFU).
- In the samples sent to the Agency, the capsules contained in the nosepiece are clear. Please verify if you intend for the marketed capsules in the nosepieces to be clear and if patients will be able to see if powder in the capsule after using the nosepiece.
- Under Section 11.2 Risk Assessment (page 24 of 27 of the proposed protocol), it states “Based on analysis of available information, anticipated adverse investigational device effects that may occur during this study are listed in section 3.7 of this protocol,” however, section 3.7 is missing in the protocol. Please ensure this information is provided when you submit your results report.

Furthermore, we have the following comments regarding your proposed labels and labeling:

- We note that the cover of the IFU contains abbreviated steps (b) (4). (b) (4). We recommend removing these abbreviated steps so users do not rely

on this information instead of reading the full Instructions for Use, which contains more details for properly administering the medication.

- As currently presented, the IFU refers to (b) (4) which is consistent with the alternate packaging configuration of two nosepieces per pouch. Revise the IFU to refer to the currently proposed packaging configuration (b) (4). We recommend including a list, diagram, or images of all components needed for one dose at the beginning of the IFU.

### **Meeting Discussion:**

The Sponsor clarified the nosepieces used in the validation study will contain an empty capsule (without powder) and will produce the same “rattle” or “vibration” that patients would expect to feel and hear with nosepieces containing the proposed product. The Sponsor clarified the “rattle” or “vibration” indicates the patient is blowing with sufficient force, but this “rattle” or “vibration” does not indicate that a full dose is received.

The Sponsor stated that regardless of a task being classified as critical or essential, all use errors will be investigated for root cause and reported in the study results. The Sponsor also agreed to classify subtask use errors as close call errors, which would be further investigated for a root cause. The Sponsor indicated the inclusion criteria of candidates who are articulate, thorough, and thoughtful in his/her response have been used in prior studies and expects this criterion to result in participants with a range of education levels. The Sponsor stated that although the intended to market capsules are clear, there is no intention for patients to visually inspect the capsules to determine if a full dose is received. The Sponsor also stated there are no indicators for a patient to determine if a partial dose or a full dose is administered. The Sponsor stated that the Instructions for Use (IFU) tell patients (b) (4). The Sponsor stated that since the submission of the meeting package, the device (b) (4). The Sponsor further commented the validation study will evaluate if participants do not use a new nosepiece.

The Agency questioned if patients with dexterity issues can depress the button on the device. The Sponsor responded the force needed to depress the button is slightly less than other marketed products and agreed to inspect the capsules after use to confirm that all patients in the validation study could depress the button and pierce the capsule. The Sponsor will update the reference to the anticipated adverse investigational device effects to the appropriate section of the protocol. The Sponsor understood the Agency’s concern regarding the (b) (4) IFU. The Sponsor proposed moving the (b) (4) IFU from the front page to the last page as a reminder to the patient. The Agency agreed that this seemed reasonable and should be tested in the validation study. The Sponsor agreed to revise the IFU by removing reference to the (b) (4) and agreed to include a list and diagram of all components needed for one dose at the beginning of the IFU.

#### **4.4 Regulatory Questions**

No supporting information is deemed necessary or provided for the following questions.

##### **Question 8: Exemption from 510(k) Premarket Notification Requirements**

(b) (4) SUMATRIPTAN is a combination product comprised of the drug product (encapsulated sumatriptan succinate, packaged in a disposable nosepiece assembly), and the drug delivery device, that will be packaged together in a cardboard carton. Accordingly, the Sponsor proposes to submit a marketing application – an NDA [505 (b)(2)] to the Division of Neurology Drug Products – that will include supporting information for both the drug and device components that comprise the final product.

The Sponsor believes that the (b) (4) Breath Powered™ Sumatriptan Powder Device is a Class I device exempt from premarket notification requirements according to 21 CFR 874.5220 Ear, Nose, and Throat Drug Administration Device.

**Does the Division agree with the approach to the NDA submission and that the device is exempt from 510(k) premarket notification requirements?**

##### **FDA Preliminary Response:**

We agree that (b) (4) Breath Powered™ Sumatriptan power device is Class I device exempt from the pre-market notification requirements according to 21 CFR 874.5220 - Ear, Nose and Throat Drug Administration Device. However, because this is a new application for this device the company provided the following biocompatibility testing data for the patient contacting materials:

- Cytotoxicity
- Sensitization
- Intra-cutaneous irritation.

##### **Meeting Discussion:**

None.

**Question 9: Timing of Submission of Pediatric Investigation Plans**

With respect to obligations under the Pediatric Research Equity Act (PREA), the Sponsor proposes to include a request with justification for waiver or deferral of pediatric investigations in the initial NDA submission and not earlier.

**Does the Division agree to submission of the request for deferral or waiver of pediatric studies in the NDA?**

**FDA Preliminary Response:**

Your proposal appears acceptable and in line with the following Agency guidelines with respect to the submission of Pediatric Study Plans based on the timelines outlined in your submission:

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- If your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- If your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

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. For additional guidance on submission of the PSP, including a PSP Template, please refer to:  
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>  
In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov).

**Meeting Discussion:**

None.

**Question 10: Approach to ISS and 2.7.4 Summary of Clinical Safety**

The Sponsor proposes to integrate the planned ISS analyses into Section 2.7.4 Clinical Summary of Safety and will not provide a separate ISS document. The size of the clinical program suggests that the ISS will be small enough to allow incorporation into Section 2.7.4 and therefore, a separate ISS document is not necessary. Results of the ISS analyses will be provided in Module 5.

**Does the Division agree with the Sponsor's plan to incorporate the results of the ISS analyses in Section 2.7.4 rather than in a separate document?**

**FDA Preliminary Response:**

We agree.

**Meeting Discussion:**

None.

**Question 11: Approach to ISE and 2.7.3**

As described in Question 5, the Sponsor does not intend to integrate efficacy data across studies and, therefore, does not intend to provide a separate ISE document. All efficacy results will be summarized in Section 2.7.3 Clinical Summary of Efficacy, and efficacy data will be provided in Module 5.

**Does the Division agree with the Sponsor's plan to discuss the efficacy analyses in Section 2.7.3 rather than in a separate document?**

**FDA Preliminary Response:**

We agree.

**Meeting Discussion:**

None.

**Question 12: Labeled Dose Strength**

Per the FDA minutes from the Type C CMC meeting in April 2013, OptiNose was asked to label the dose strength of the drug product as (b) (4) Sumatriptan/ Brandname, 11 mg (sumatriptan base). It is to be noted that the previous development data and documentation refers to the dose strength of the product as (b) (4)

(b) (4)  
(b) (4). It should also be noted that a mean of approximately 7.5 mg of the sumatriptan base has been shown to be delivered to the patient in each administration. All future documentation is proposed to be revised to conform with the Agency's preference for 11 mg (sumatriptan base) as the labeled potency statement  
**Does the FDA concur with this approach?**

**FDA Preliminary Response:**

We agree that the labeled potency should be 11 mg in future documentation. In sections where existing documents, e.g., completed study reports, refer to (b) (4) we recommend including a brief statement about the relationship between capsule content (11 mg) and the emitted dose (b) (4) measured in in-vitro studies.

**Meeting Discussion:**

None.

**Question 13: Alternate Packaging Configuration**

At the Type C pre-NDA CMC Meeting held on April 10, 2013, availability of the stability data at the time of the NDA filing was discussed and the following was concluded based on the [FDA Meeting Minutes from April 10, 2013 Meeting](#).

*During the discussion at the meeting the agency reminded Optinose that shelf life of the product is based on primary stability data and any additional clinical batches will be considered as supportive data. The agency was open to accept six months of the stability data at the time of NDA submission with a subsequent submission for the 12 month stability data within five months of NDA submission.*

The Sponsor intends to submit and commercialize the product in the packaging configuration discussed at the meeting, and understands that shelf-life will be determined based on stability data for that configuration.

As part of ongoing product development, the Sponsor intends to explore a (b) (4) configuration with 2 nosepieces per pouch, which may be conducive to improving patient compliance. (b) (4)

design would contain the complete proposed dose of 2 nosepieces (b) (4) and there would be no change to packaging material or operating principles of the packaging operation.

The Sponsor intends to manufacture 3 batches of the 2-nosepiece-per-pouch packaging configuration by the intended commercial process. The pouch size for the 2 nose pieces will be (b) (4)

(b) (4)  
(b) (4). It is anticipated that the stability will be similar.

Investigation of this (b) (4) configuration is being planned to proceed concurrently with the review of the NDA, and to produce data based upon 3 batches for up to 6 months at accelerated and long term conditions before the mid-cycle review, and for up to 12 months at the real time condition sometime after approval.

*Question: The sponsor proposes to include in the NDA a plan (comparability protocol) for*

*evaluating the 2-nosepiece-per-pouch configuration (stability, ship testing, and user validation), accompanied by any necessary modification to labeling to clearly state that 2 nosepieces are in a pouch. This proposed plan* (b) (4)  
(b) (4)  
(b) (4) *and the data will be used to establish an*  
*appropriate shelf life for the 2-nosepiece configuration.* (b) (4)  
(b) (4)  
(b) (4) *Does the Agency concur with this approach and agree to review the*  
*comparability protocol in the NDA?*

### **FDA Preliminary Response:**

You may submit a comparability protocol for assessment of the impact of the manufacturing change (i.e., (b) (4) two nosepieces per pouch) on product quality in the original NDA for review. This may include any supporting data that are available at the time of NDA submission. (b) (4)  
(b) (4)

### **Meeting Discussion:**

None.

### **Question 14: NDA Presentation and Format Topics**

The Sponsor seeks confirmation of agreement on the following NDA content and format topics:

- a) The Sponsor proposes to provide the quality information for the drug substance in Module 3.2.S, for the drug product in Module 3.2.P and for the Breath-Powered™ Device under Module 3 Section 3.2.R. Module 2.3 (Quality Overall Summary) would mirror the organization of Module 3. Study reports specific to the device, such as usability validation testing, will be provided in Module 5 Section 5.3.5.4 “Other Study Reports and Related Information”, as recommended by the eSub group, and Module 3 Section 3.2.R. **Is this approach acceptable to the Division?**
- b) During clinical trials of (b) (4) SUMATRIPTAN, there were no deaths or discontinuations due to an adverse event, and therefore, no CRFs are planned to be submitted in the NDA. **Are there any other categories, beyond deaths or discontinuations due to AEs, for which the Division would like CRFs to be submitted?**
- c) During pivotal clinical trials of (b) (4) SUMATRIPTAN, there were no deaths, discontinuations due to AEs, or SAEs reported, and therefore, no patient

narratives are planned to be provided in the NDA. **Are there any other categories of adverse events for which the Division would like narratives submitted in the NDA?**

- d) The Sponsor intends to submit Case Report Tabulation (CRT) as part of the NDA package. The CRT will include documentation of data (define.xml) and Study Data Tabulation Model (SDTM) for clinical studies OPTUK-MSPP PRO 002, OPN-SUM-MIG-3301, and OPN-SUM-1302. In addition, the Sponsor plans to submit analysis data published in scientific data set format (SDS 1.6 – ADaM IG 1.0) along with source data published in SDS 1.6 (ADaM IG

1.0, SAS .XPT) format for studies OPTUK-MSPP PRO 002, OPN-SUM-MIG-3301, and OPN-SUM-1302. **Does the Division agree?**

- e) In the NDA, the Sponsor intends to submit copies of all references cited in pivotal or supporting CSRs, and important references for earlier studies. Other references will be available upon request during the review. **Does the Division agree with this approach?**

- f) The NDA will be submitted using the International Nonproprietary Name (INN) for the drug substance and the Sponsor's code name for the device ("Breath-Powered<sup>TM</sup> Sumatriptan Powder device") while the drug and device trade names are undergoing review and approval under IND 110090. **Does the Division agree with this approach?**

#### **FDA Preliminary Response:**

- a. This is acceptable from CMC perspective. However, we note that the proposed Table of Contents includes device labeling in Module 3.2.R.4.13-15. The device labeling should be included in Module 1.
- b. Your comments for parts b and c in this question imply that there were SAEs reported in the supportive study. Therefore, we request that you provide CRFs and patient narratives of SAEs for the pivotal and supportive clinical studies.
- c. See response to part b above.
- d. While we agree in form to your proposal, we may have additional specific instructions related to data organization. If so, these will be included in the final pre-NDA meeting minutes.
- e. We agree.
- f. If you plan to submit your NDA application within the next 6 months, we recommend submitting your request for review of your proposed proprietary name(s) to the NDA application. If you do not intend to submit your NDA application within the next 6 months, you can submit your request for review of your proposed proprietary name(s) to the IND application. Please note that if a proposed proprietary name is reviewed and found conditionally acceptable under the IND application, the name will still need to be submitted for review under the NDA. Pending review of trade names and

confirmation of dosage form designation, we recommend that you refer to the drug and devices using the following nomenclature as appropriate.

“Tradename” (sumatriptan nasal powder)

“Device Tradename” delivery device

**Meeting Discussion/Post Meeting Comments:**

a. None

b and c. You clarified that while there have been no SAEs to date, you will provide patient narratives and CRFs of any SAEs reported from the ongoing supportive clinical study. We found this approach acceptable.

d. We agree with your proposal and have no further requests.

e and f. None

**Question 15: Outstanding Commitments**

The Sponsor believes there are no outstanding regulatory commitments pertaining to IND 110090.

**Is the Division aware of any outstanding agreements with the Sponsor pertaining to this IND?**

**FDA Preliminary Response:**

We are not aware of any outstanding agreements pertaining to the IND.

**Meeting Discussion:**

None.

**Question 16: 120 Day Safety Update**

The clinical program in support of the planned NDA is complete and safety data from these studies will be summarized and integrated as appropriate and provided in the initial NDA submission. Additionally, a Phase 3 study (OPN-SUM-MIG-3302) comparing (b)(4) SUMATRIPTAN to oral sumatriptan is ongoing and all then-available blinded safety data from this study will be summarized in the initial NDA submission as a progress report. The Sponsor believes that safety information from this study is not pivotal to an assessment of safety of (b)(4) SUMATRIPTAN in the marketing application, which references safety information for innovator products via the 505(b)(2) pathway. The Sponsor does not intend to incorporate safety results from this study once completed and unblinded into the integrated safety analyses conducted for the NDA. Accordingly, the Sponsor proposes that a full 120 day safety update is not needed and proposes to submit the CSR for Study OPN-SUM-MIG-3302 as the 120-day safety update.

**Does the Division agree to accept the CSR for the ongoing blinded study to meet the requirement for a 120 day safety update?**

**FDA Preliminary Response:**

We agree.

**Meeting Discussion:**

None.

**PREA REQUIREMENTS**

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting held on or after November 6, 2012. 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.

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 Pediatric and Maternal Health Staff at 301-796-2200 or email [pdit@fda.hhs.gov](mailto: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. As you develop your proposed PI, we encourage you to review the following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.

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

/s/  
-----

ERIC P BASTINGS  
08/21/2013