

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206099Orig1s000**

**CHEMISTRY REVIEW(S)**



QUALITY ASSESSMENT



Recommendation: Approve

NDA 206099

Review # 3
January 25, 2016

Table with 2 columns: Drug Name/Dosage Form, Strength, Route of Administration, Rx/OTC Dispensed, Applicant, US agent, if applicable. Values include Onzetra (Sumatriptan Nasal Powder), 11 mg, Intranasal, Rx, Avanir Pharmaceuticals, N/A.

Table with 2 columns: SUBMISSION(S) REVIEWED, DOCUMENT DATE. Lists review history including Resubmission (May 6, 2015), Quality Amendments (Aug 6, 2015, Aug 10, 2015, Sep 9, 2015), and Labeling/Container-Carton (Sep 2, 2015).

Quality Review Team

Table with 3 columns: DISCIPLINE, REVIEWER, BRANCH/DIVISION. Lists team members for various disciplines such as Drug Substance, Drug Product, Process, Microbiology, Facility, Biopharmaceutics, Regulatory Business Process Manager, Application Technical Lead, Laboratory (OTR), CDRH, and Environmental Assessment (EA).

## Table of Contents

<b>Table of Contents .....</b>	<b>2</b>
<b>Executive Summary .....</b>	<b>3</b>
<b>Primary Quality Review.....</b>	<b>5</b>
<b>ASSESSMENT OF THE FACILITIES .....</b>	<b>5</b>
2.3.S DRUG SUBSTANCE .....	5
2.3.P DRUG PRODUCT.....	7

## Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This review is an addendum to the addendum to the Office of Pharmaceutical Quality (OPQ) integrated review for NDA 206099 dated October 10, 2015. At this time, all outstanding facility issues are resolved and APPROVAL of the application is recommended.

The application and facility history are summarized below.

ONZETRA is a drug-device product used for nasal delivery of a powder form of the drug substance, sumatriptan succinate, via a proprietary breath-powered delivery device. The product is intended for the acute treatment of migraine headache with or without aura. The device consists of a flexible mouthpiece and a (b) (4) nosepiece, containing sumatriptan succinate in a hypromellose capsule, connected via a (b) (4) shell. The device is intended to deliver sumatriptan into the nasal cavity using the patient's exhaled breath and the device (b) (4) while the device is being used to deliver drug.

Avanir Pharmaceuticals (Avanir) submitted a 505 (b)(2) NDA for the product on January 27, 2014. In the original NDA, the firm proposed a contract manufacturer, (b) (4). (b) (4). All quality related issues were resolved during the first review cycle and the application was recommended for approval from a CMC perspective. However, due to outstanding human factors concerns regarding usability of the device and the potential for medication, the Agency issued a complete response (CR) letter on November 26, 2014.

When Avanir resubmitted the NDA on May 26, 2015, the applicant withdrew (b) (4) as a manufacturing site and submitted a new contract manufacturer, UPM Pharmaceuticals, Bristol, Tennessee (UPM). Following an August 14, 2015 inspection, the District Office initially classified the UPM facility as potential official action indicated (pOAI) and made a Withhold recommendation. Thus, the OPQ review dated October 10, 2015 recommended that the Agency issue a second CR letter. Other than the UPM facility status, there were no outstanding quality deficiencies.

On October 21, 2015, Avanir amended the NDA to reinstate (b) (4) as a drug product manufacturing site. This was classified as a major amendment, due to the need to reassess the (b) (4) facility status, and the PDUFA goal date was extended from November 6, 2015 to February 6, 2016. In consultation with the CDRH Office of

Compliance, the OPQ/OPF Facility reviewer, Steve Hertz, has confirmed that the status of (b)(4) remains acceptable from both drug and device perspectives.

During the review clock extension triggered by the amendment that reinstated the (b)(4) facility, the CDER Office of Compliance completed their review of the UPM inspection observations, and UPM's responses. Based on that review, the status of UPM was reclassified from pOAI to voluntary action indicated (VAI) and the Withhold recommendation revised to Acceptable. An overall Acceptable facility recommendation was entered on January 26, 2016.

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

None

**II. Summary of Quality Assessments**

**A. Drug Substance Quality Summary**

Refer to the Drug Substance Quality Summary in Review # 2. There have been no changes to supporting information for the drug substance since completion of Review #2.

**B. Drug Product Quality Summary**

Refer to the Drug Product Quality Summary in Review # 2. Other than reinstatement of the (b)(4) manufacturing site, as discussed above, there have been no changes to supporting information for the drug product since completion of Review #2.

**C. Summary of Drug Product Intended Use**

The product, sumatriptan succinate nasal powder, is a drug-device combination product intended for self-administration of sumatriptan succinate using a provided Xsail™ powered delivery device.

**Overall Assessment and Signatures: Executive Summary**

**Application Technical Lead Signature:**

Martha R. Heimann, Ph.D.  
CMC Lead, Neurology  
Office of New Drug Products

Martha R.  
Heimann -S

Digitally signed by Martha R. Heimann  
-S  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=13000915  
27, cn=Martha R. Heimann -S  
Date: 2016.01.25 22:15:52 -05'00'



**QUALITY ASSESSMENT**



**Recommendation: Complete Response**

**NDA 206099  
Review # 2**

<b>Drug Name/Dosage Form</b>	Onzetra (Sumatriptan Nasal Powder)
<b>Strength</b>	22 mg (two nosepieces, each containing 11 mg sumatriptan base)
<b>Route of Administration</b>	Intranasal
<b>Rx/OTC Dispensed</b>	Rx
<b>Applicant</b>	Avanir Pharmaceuticals
<b>US agent, if applicable</b>	N/A

<b>SUBMISSION(S) REVIEWED</b>	<b>DOCUMENT DATE</b>
Resubmission	May 6, 2015
Quality Amendment	Aug 6, 2015
Quality Amendment	Aug 10, 2015
Labeling/Container-Carton	Sep 2, 2015

**Quality Review Team**

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>BRANCH/DIVISION</b>
Drug Substance	N/A	
Drug Product	Tom Wong	
Process	N/A	
Microbiology	N/A	
Facility	Steve Hertz	
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Dahlia A. Woody	
Application Technical Lead		
Laboratory (OTR)	N/A	
CDRH	Jamie Kamon-Branazio	REGO, DMQ, OC, CDRH, OMPT
Environmental Assessment (EA)	N/A	

## Table of Contents

<b>Table of Contents .....</b>	<b>2</b>
<b>Quality Review Data Sheet .....</b>	<b>3</b>
<b>Executive Summary .....</b>	<b>4</b>
<b>Primary Quality Review.....</b>	<b>7</b>
ASSESSMENT OF THE DRUG SUBSTANCE.....	7
ASSESSMENT OF THE DRUG PRODUCT .....	8
2.3.P DRUG PRODUCT.....	8
R.2 Comparability Protocols.....	15
I. Review of Common Technical Document-Quality (CTD-Q) Module 1 .....	16
Labeling & Package Insert.....	16
ASSESSMENT OF THE FACILITIES .....	25
2.3.S DRUG SUBSTANCE .....	25
2.3.P DRUG PRODUCT.....	26

## Quality Review Data Sheet

**1. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

The type II drug substance DMF (b) (4) has been reviewed with adequate status. All other type III DMFs do not need review since sufficient information on the capsule shell and packaging components are provided in the application (see Chemistry Review #1 in DARRTS).

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

**Not Applicable**

**2. CONSULTS:**

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

## Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From a Quality (CMC) perspective, approval of NDA 206099 cannot be recommended at this time. Approval of the application was recommended from a CMC perspective at the end of the first review cycle. However; the Agency issued a complete response (CR) letter on November 26, 2014. In the May 26, 2015 resubmission, the applicant withdrew the original drug product manufacturing site (b) (4) and submitted a new contract manufacturer, UPM Pharmaceuticals, Bristol, TN. The UPM facility is currently under a potential official action indicated (OAI) alert. Thus, a Withhold recommendation for the facility and an overall Withhold recommendation have been entered by the Office of Process and Facilities.

There are no other outstanding CMC deficiencies. Therefore, it is recommended that a CR letter citing the CGMP compliance status of the UPM Pharmaceuticals be issued.

If there is a change to the facility status, or if the applicant amends the application to provide for a CGMP compliant manufacturing site, the overall Quality recommendation will be updated in an addendum to this review.

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

None

### II. Summary of Quality Assessments

#### A. Drug Substance Quality Summary

The drug substance is sumatriptan succinate, USP. The applicant referred to DMF (b) (4) for detailed information on the drug substance. This DMF has been previously reviewed and the last review was performed by Dr. Maria Manzoni on April 22, 2013. All subsequent submissions have been reviewed by Thomas Wong and the submissions are letters of authorization. The current status of this DMF remains adequate.

Sumatriptan is a selective 5-hydroxy-tryptamine receptor subtype 1 (5-HT<sub>1</sub>) agonist. It is a small molecule with molecular formula for the succinate salt as C<sub>14</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>S·C<sub>4</sub>H<sub>6</sub>O<sub>4</sub> and molecular weight 590.7. Sumatriptan succinate is a white to almost white crystalline powder and is freely soluble in water.

(b) (4)

(b) (4). The drug substance has no chiral centers, non-hygroscopic, and is chemically stable when it is stored at (b) (4)

Available 48 months long-term (b) (4) stability data supports the proposed retest period of (b) (4) months for the drug substance (b) (4)

## B. Drug Product Quality Summary

The product, sumatriptan succinate nasal powder, is a drug-device combination product intended for self-administration of sumatriptan succinate. The drug delivery system, Xsail™ powered delivery device, consists of a reusable device body incorporating a flexible mouthpiece device and a single-use, disposable, pre-filled nosepiece containing a filled drug capsule. Each nosepiece contains 11 mg of sumatriptan (as 15.4 mg sumatriptan succinate) and two nosepieces (one used in each nostril) constitute a full 22 mg dose. The trade name for sumatriptan succinate nasal powder is Onzetra™. Each hydroxypropyl methylcellulose contains 11 mg of sumatriptan (as 15.4 mg sumatriptan succinate). The proposed commercial batch size is (b) (4) nosepieces and the manufacturing site of the product has been revised in the resubmission to a contract manufacturing facility, UPM Pharmaceuticals. In the original NDA, the proposed manufacturing site was (b) (4). The capsule containing sumatriptan succinate is housed in a disposable nosepiece. Two nosepieces each containing 11 mg sumatriptan are then placed into (b) (4) foil (b) (4) pouch constituted as one dose. Eight (b) (4) foil pouch containing each foil containing 2 disposable nosepieces with two AVP-825 reusable devices (b) (4) and Instruction for Use and Package Insert are then placed in (b) (4) the (b) (4) for the commercial drug product. The product will be stored at controlled room temperature of 20°C - 25°C with excursions permitted 15°C - 30°C. Although only 12 months long-term stability data is available for the primary registration batches in the resubmission, the additional stability data in the resubmission with 18 months of the supporting stability data for the 2 nosepieces per pouch configuration and 24 months of supporting stability data for the 1 nosepiece per pouch configuration together with 6 months stability for all pouch configurations at 40°C/75 %RH storage conditions justify the proposed expiry dating of 36 months for the product when packaged in the proposed commercial packages and stored in the afore-mentioned storage conditions.

## C. Summary of Drug Product Intended Use

The product, sumatriptan succinate nasal powder, is a drug-device combination product intended for self-administration of sumatriptan succinate using a provided Xsail™ powered delivery device.



**OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE  
SUMMARY**

APPEARS THIS WAY ON ORIGINAL

**Application Technical Lead Signature:**

Martha R.  
Heimann -S

Digitally signed by Martha R. Heimann -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=13C0091527,  
cn=Martha R. Heimann -S  
Date: 2015.10.07 16:35:17 -0400

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**I. Review of Common Technical Document-Quality (CTD-Q) Module 1**

**Labeling & Package Insert**

**1. Package Insert**

**(a) “Highlights” Section (21CFR 201.57(a))**

(Amendment #0027 dated 9/2/2015)

**ONZETRA™ (sumatriptan nasal powder)** (b) (4)  
**Xsail™** (b) (4)

Item	Information Provided in NDA	Reviewer’s Assessment
<b>Product title, Drug name (201.57(a)(2))</b>		
Proprietary name and established name	Proprietary: Onzetra Established Name: Sumatriptan succinate	DEMPA has accepted Onzetra as the proprietary name on 8/13/15 (see review in DARRTS)
Dosage form, route of administration	Dosage: Nasal Powder Route: Intranasal	Acceptable
Controlled drug substance symbol (if applicable)	The product is not a controlled substance.	N/A
<b>Dosage Forms and Strengths (201.57(a)(8))</b>		
A concise summary of dosage forms and strengths	ONZETRA is supplied in a disposable nosepiece containing a capsule with sumatriptan powder and a reusable Xsail Delivery System body. Each capsule contains 11 mg of sumatriptan base (equivalent to 15.4 mg of sumatriptan succinate nasal powder). (b) (4)	Acceptable. The expression of product strength is the active moiety, sumatriptan, with equivalency statement of the salt form

(b) “Full Prescribing Information” Section

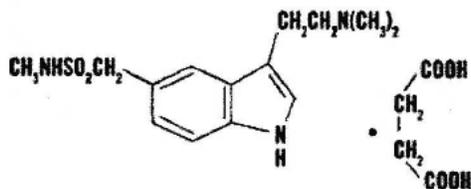
**# 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))**

Item	Information Provided in NDA	Reviewer’s Assessment
Available dosage forms	Injection	Acceptable
Strengths: in metric system	Each capsule contains 11 mg sumatriptan base (equivalent to 15.4 mg of sumatriptan succinate nasal powder)	Acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	The capsule is a clear, (b) (4) capsule with 825 printed on one side	Acceptable. The products is used with Xsail Delivery System only.

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

ONZETRA uses a (b) (4) disposable nosepiece which is attached by the patient to an Xsail Delivery System body which has a mouthpiece and a piercing mechanism. The nosepiece contains a capsule filled with a dry powder form of sumatriptan succinate for nasal administration only with the Xsail Delivery System. Each capsule contains 11 mg sumatriptan base (equivalent to 15.4 mg of sumatriptan succinate nasal powder), and two nosepieces comprise a single dose. ONZETRA is for nasal administration only. Use of the Xsail Delivery System is for ONZETRA only (b) (4).

The active component of ONZETRA is sumatriptan, a selective 5-hydroxy-tryptamine receptor subtype 1 (5-HT<sub>1</sub>) agonist. Sumatriptan delivered as the succinate salt is chemically designated as 3-[2-(dimethylamino)ethyl]-N-methyl-indole-5-methanesulfonamide succinate (1:1), and it has the following structure:



The empirical formula is C<sub>14</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>S • C<sub>4</sub>H<sub>6</sub>O<sub>4</sub>, representing a molecular weight of 413.5. Sumatriptan succinate is a white to off-white powder that is readily soluble in water and in saline. The Xsail Delivery System is used to deliver the dry powder contained in the ONZETRA disposable nosepiece (in a capsule) into the nostril using breath exhaled into the Xsail body (see the Instructions for Use labeling). The Xsail Delivery System has a flexible mouthpiece to adjust to individual anatomic variations. Under standardized *in vitro* testing, the Xsail Delivery System delivers a mean of 10 mg sumatriptan per nosepiece when tested at a flow rate of 30 L/min for 4 seconds (2 L total). The amount of sumatriptan delivered to the nasal cavity will depend on patient factors such as expiratory flow. Delivered dose was measured in patients with migraine headache treated in clinical trials to evaluate the efficacy of the product. In these trials, each nosepiece delivered an average dose of 7.5-8.1 mg, providing a total dose of 15-16.2 mg per treatment episode from two nosepieces.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Proprietary: Onzetra Established Name: Sumatriptan succinate	DEMPA has accepted Onzetra as the proprietary name on 8/13/15 (see review in DARRTS)
Dosage form, route of administration	Dosage: Nasal Powder Route: Intranasal	Acceptable
Active moiety expression of strength with equivalence statement for salt (if applicable)	ONZETRA is supplied in a disposable nosepiece containing a capsule with sumatriptan powder and a reusable Xsail Delivery System body. Each capsule contains 11 mg of sumatriptan base (equivalent to 15.4 mg of sumatriptan succinate nasal powder). Use with the Xsail Delivery System only .	Acceptable. The expression of product strength is the active moiety, sumatriptan, with equivalency statement of the salt form
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	N/A	Acceptable. The product contains only the neat drug substance and does not contain any excipient.
Statement of being sterile (if applicable)	N/A	Acceptable. The product is intended for intranasal use.
Pharmacological/ therapeutic class	Sumatriptan is a selective 5-hydroxy-tryptamine receptor subtype 1 (5-HT <sub>1</sub> ) agonist and is indicated for the acute treatment of migraine attacks, with or without aura in adults.	Acceptable
Chemical name, structural formula, molecular weight	See the above photocopy of the package insert, Section # 11	Information is accurate
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa, solubility, or pH)	Sumatriptan succinate is a white to off-white powder that is readily soluble in water and in saline.	Acceptable

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

ONZETRA is available in (b) (4) disposable nosepieces containing 11 mg sumatriptan base (equivalent to 15.4 mg of sumatriptan succinate). (b) (4)

The following table provides a description of the packaging configurations:

Description	Contents	NDC Code
8 Dose Kit	8 pouches containing 2 nosepieces per pouch, 22 mg sumatriptan nasal powder, (each nosepiece contains 11 mg sumatriptan) 2 Xsail Delivery System bodies	64597-311-08

**Storage Recommendations**

Store at room temperature between 20° C to 25° C (68° F to 77° F), with excursions permitted between 15° C to 30° C (59° F to 86° F). Do not store in the refrigerator or freezer. Use nosepiece immediately after removing from foil pouch.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	See above photo copy of package insert, Section #16	Acceptable
Available units (e.g., bottles of 100 tablets)	8 Dose kit - 8 pouches containing 2 nosepieces per pouch, 22 mg sumatriptan nasal powder, (each nosepiece contains 11 mg sumatriptan) 2 Xsail Delivery System bodies	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC numbers are provided	Acceptable
Special handling (e.g., protect from light, do not freeze)	Do not store in the refrigerator or freezer. Use nosepiece immediately after removing from foil pouch	Acceptable
Storage conditions	Store at room temperature between 20 °C to 25 °C (68 °F to 77 °F), with excursions permitted between 15 °C to 30 °C (59 °F to 86 °F)	Acceptable

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

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured by UPM Pharmaceuticals Bristol, TN 37620 for Avanir Pharmaceuticals, Inc. Aliso Viejo, CA 92656	Acceptable. Obtained from Patient Information.

**Conclusion: Acceptable. Final container label will be finalized with other review disciplines during labeling meetings.**

**2. Labels**

**1) Immediate Container Label (Amendment #0027 dated 9/2/2015)**

POUCH FRONT

POUCH BACK



Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The font size and prominence of both proprietary and establish name is adequate.	Final decisions will be made jointly with DMEPA
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Expression of product strength is in free form.	Acceptable
Net contents (21 CFR 201.51(a))	2 nosepieces	Acceptable
Lot number per 21 CFR 201.18	No space is provided for entry.	Need to confirm with the applicant that the lot number will be printed on the pouch
Expiration date per 21 CFR 201.17	No space is provided for entry.	Need to confirm with the applicant that the expiration date will be printed on the pouch
"Rx only" statement per 21 CFR 201.100(b)(1)	"Rx only" statement is present	Acceptable
Storage (not required)	Not required. Stated in cartoon container	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC number is printed on the label	Acceptable
Bar Code per 21 CFR 201.25(c)(2)**	Printed on the label	Acceptable
Name of manufacturer/distributor	Printed on the label	Acceptable
Others	For use with Xsail™ intranasal device only	Acceptable

\*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

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

**Conclusion: Acceptable. Final container label will be finalized with other review disciplines during labeling meetings.**

**2) Cartons (Amendment #0027 dated 9/2/2015)**

(b) (4)



# QUALITY ASSESSMENT



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	The font size and prominence of both proprietary and establish name is adequate.	Final decisions will be made jointly with DMEPA
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Expression of product strength is in free form.	Acceptable
Net contents (21 CFR 201.51(a))	(b) (4)	Acceptable
Lot number per 21 CFR 201.18	Space is provided for entry.	Acceptable
Expiration date per 21 CFR 201.17	Space is provided for entry.	Acceptable
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables[ 201.10(a), 21CFR201.100(b)(5)(iii)]	N/A	Acceptable. The product contains only the neat drug substance and does not contain any excipient.
Sterility Information (if applicable)	N/A	
"Rx only" statement per 21 CFR 201.100(b)(1)	Statement is in label	Acceptable
Storage Conditions		
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC number is printed on the container label.	Acceptable
Bar Code per 21 CFR 201.25(c)(2)**	Printed on carton label	Acceptable
Name of manufacturer/distributor	Printed on the label	Acceptable
"See package insert for dosage information" (21 CFR 201.55)	"Before use, please read Instruction for Use" is printed on the carton label.	Acceptable
"Keep out of reach of children" (optional for Rx, required for OTC)	The statement is printed on the carton label.	Acceptable
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	For intranasal use only	Acceptable
Other	Do not refrigerate. (b) (4). Dispose of nosepieces after use (b) (4)	Acceptable



## QUALITY ASSESSMENT



**Conclusion: Acceptable. Final container label will be finalized with other review disciplines during labeling meetings.**

**Conclusion: Acceptable**

### OVERALL ASSESSMENT AND SIGNATURES: LABELING

**Reviewer's Assessment and Signature: Acceptable**

**Thomas Wong, Ph.D., ONDP/Division of New Drug Products I/Branch I**

**Secondary Review Comments and Concurrence: I concur.**

**Wendy I. Wilson-Lee, Ph.D., Branch Chief (Acting), ONDP/DNDP1/Branch 1**

**ASSESSMENT OF THE FACILITIES**

**2.3.S DRUG SUBSTANCE**

**2.3.S.2 Manufacture**

**S.2.1 Manufacturer(s)**

4. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment name	FEI Number	Responsibilities and profile codes	Initial Risks	Current status	Final Recommendation
(b) (4)			Medium (VAI classification history)	Acceptable	Acceptable
UPM PHARMACEUTICALS INC.	1000208638	CSS, CTL	Medium (DS and DP manufacturing)	pOAI (QA functions)	Withhold
(b) (4)			Medium (VAI classification history)	Acceptable	Acceptable

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
(b) (4)			See below	7	6	5	18	File review
UPM PHARMACEUTICALS INC.	1000208638	CSS	See below	8	10	5	23	File review
(b) (4)			See below	8	5	5	18	File review

**Applicant's Response:**

**Reviewer's Assessment:** The (b) (4)  
(b) (4) facility was inspected on (b) (4) and was classified VAI.

(b) (4)

The district office made an acceptable recommendation based on file review. The UPM PHARMACEUTICALS INC facility was inspected on 8/14/15 for profiles CSS and CTL and was classified OAI (final classification pending) for inadequate quality assurance at the facility. The firm is responsible for release of the API, storage, (b) (4) testing and release, release of nosepiece components, (b) (4) (b) (4) nosepiece assembly, (b) (4) testing, release and stability testing, primary and secondary packaging, labeling, finished product and retain samples storage. The district office made a withhold recommendation based on the recent inspection classification. The (b) (4) (b) (4) facility was inspected on (b) (4) for profile CTL and was classified VAI. The firm performs analytical testing and release of the drug substance and drug product release and stability testing. The district office made an acceptable recommendation based on file review.

### 2.3.P DRUG PRODUCT

#### 2.3.P.3 Manufacture

##### *P.3.1 Manufacturer(s)*

5. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment name	FEI Number	Responsibilities and profile codes	Initial Risks	Current status	Final Recommendation
UPM PHARMACEUTICALS INC.	1000208638	DKA, CTL	High (DS and DP [i.e. DKA] manufacturing)	pOAI (QA functions)	Withhold
		(b) (4) CTL	Medium (VAI inspection history)	Acceptable	Acceptable
		(b) (4)	High (prior compliance status with CDRH)	Acceptable	Acceptable
		(b) (4)	High (prior inspection history)	No Further Evaluation	No Further Evaluation

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
UPM PHARMACEUTICALS INC.	1000208638	DKA	See below	8	45	5	61	PAI
	(b) (4)	CTL	See below	8	5	5	18	File review
	(b) (4)		See below	27	8	5	80	CDRH consult
	(b) (4)		See below	33	8	5	43	CDRH consult

**Applicant's Response:**

**Reviewer's Assessment:** The UPM PHARMACEUTICALS INC facility was inspected on 8/14/15 for profiles DKA and CTL and was classified OAI (final classification pending) for inadequate quality assurance at the facility. The firm is responsible for release of the API, storage, (b) (4) testing and release, release of nosepiece components, (b) (4), nosepiece assembly, (b) (4) testing, release and stability testing, primary and secondary

packaging, labeling, finished product and retain samples storage. The district office made a withhold recommendation based on the recent inspection classification. The (b)(4) facility was inspected on (b)(4) for profile CTL and was classified VAI. The firm performs analytical testing and release of the drug substance and drug product release and stability testing. The district office made an acceptable recommendation based on file review. A consult was sent to CDRH to evaluate the (b)(4) facility. Per CDRH, “An inspection at (b)(4) was conducted on (b)(4). The inspection was classified VAI, and the district recommended to withhold the NDA application. The firm was cited for the following observations: 1) (b)(4) results cannot be fully verified by subsequent inspection and test has not been validated according to established procedures; and 2) Procedures (b)(4) have not been adequately established. However, the firm provided sufficient information (b)(4) (b)(4) in their response (b)(4). Therefore, a pre-approval inspection is not needed for this firm at this time.” (b)(4) (b)(4) The district office (CDRH) made an acceptable recommendation based on file review. A consult was sent to CDRH to evaluate the (b)(4) facility. Per CDRH, “No inspectional history was found in FACTS or Turbo EIR for (b)(4). The firm is responsible for manufacturing (b)(4). Since the firm is a (b)(4) supplier controlled by the applicant, an inspection is not required. However, the applicant must show how supplier controls are established and maintained, including receiving and acceptance activities for the device constituent.” The district office (CDRH) recommendation was for no further evaluation of the facility.

**OVERALL ASSESSMENT AND SIGNATURES: FACILITIES**



## QUALITY ASSESSMENT



**Reviewer's Assessment and Signature:** The overall manufacturing inspection recommendation for this application is to withhold, due to the current facility compliance classification of UPM PHARMACEUTICALS, INC. | FEI: 1000208638 | DUNS: 032125469.

Steven Hertz  
10/5/15

**Secondary Review Comments and Concurrence:**

I concur with the facility reviewer's recommendation to withhold this application.

Zhihao Peter Qiu, Ph.D.  
OPQ/OPF/DIA  
10/5/2015