

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206940Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

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

Date: May 26, 2015

From: Yichun Sun, Ph.D.

Review Chemist

Division of New Drug Products II

Office of New Drug Products

Yichun
Sun -S

Digitally signed by Yichun Sun -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Yichun Sun -S,
0.9.2342.19200300.100.1.1=1300
393310
Date: 2015.05.26 12:05:23 -04'00'

Through: Moo-Jhong Rhee, Ph.D.

Chief, Branch V

Division of New Drug Products II

Office of New Drug Products

Moojhong
Rhee -S

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DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Moojhong
Rhee -S,
0.9.2342.19200300.100.1.1=1300041261
Date: 2015.05.26 13:57:00 -04'00'

To: CMC Review #1 of NDA 206940

Subject: Final Approval Recommendation for NDA 206940

At the time when the CMC review #1 was written, resolution of issues on **Labels and Labeling** was pending.

Label/Labeling

On May 22, 2015, the NDA applicant submitted an amendment providing the finalized mock up carton and blister labels. Additionally, the applicant also agreed to all the CMC changes made to the package insert. All the labels/labeling issues are now **satisfactorily resolved**. The CMC sections of the final package insert, and mock up container and carton labels are attached (**Attachment - 1**).

Recommendation:

All pending issues on Label/Labeling are now satisfactorily resolved for the NDA. Therefore, from the ONDP's perspective, this NDA is recommended for **APPROVAL**. An expiration dating period of **24 months** is granted for the drug product of NDA 206940.

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

A. Labeling & Package Insert

1. Package Insert

(a) “Highlights” Section

VIBERZI (eluxadoline) tablets, for oral use, C-X
Initial U.S. Approval: YYYY

DOSAGE FORMS AND STRENGTHS

75 mg and 100 mg tablets

Evaluation:

Item	Comments on the Information Provided in NDA
Drug name (201.57(a)(2))	
Proprietary name and established name	The proprietary name, VIBERZI, is acceptable. The established name is correctly described as eluxadoline. Satisfactory
Dosage form, route of administration	The dosage form is tablets and route of administration is oral. Satisfactory
Controlled drug substance symbol (if applicable)	C-X
Dosage Forms and Strengths (201.57(a)(8))	75 mg and 100 mg tablets Satisfactory
Whether the drug product is scored	N/A

This section is Satisfactory.

(b) “Full Prescribing Information” Section

#3. Dosage Form and Strength

- 75 mg tablets: capsule-shaped tablets are coated in pale-yellow to light tan color debossed with “FX75” on one side. Each tablet contains 75 mg eluxadoline.
- 100 mg tablets: capsule-shaped tablets are coated in pink-orange to peach color debossed with “FX100” on one side. Each tablet contains 100 mg eluxadoline.

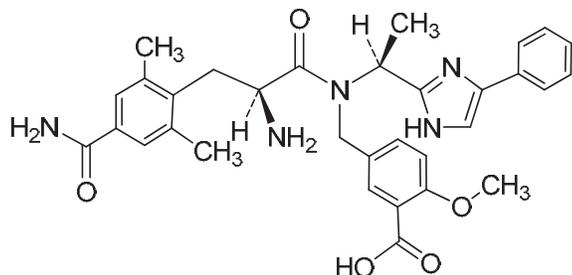
Evaluation:

Item	Comments on the Information Provided in NDA
Available dosage forms and strengths: in metric system	The dosage form is tablets. The strengths are 75 mg per tablet and 100 mg per tablet. Satisfactory
Active moiety expression of strength with equivalence statement (if applicable)	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	<ul style="list-style-type: none">• 75 mg tablets: capsule-shaped tablets are coated in pale-yellow to light tan color debossed with “FX75” on one side. Each tablet contains 75 mg eluxadoline.• 100 mg tablets: capsule-shaped tablets are coated in pink-orange to peach color debossed with “FX100” on one side. Each tablet contains 100 mg eluxadoline. Satisfactory
Other	N/A

This section is satisfactory.

#11. Description

The active ingredient in VIBERZI is eluxadoline, a mu-opioid receptor agonist. The full chemical name is 5-[[[(2S)-2-amino-3-[4-(aminocarbonyl)-2,6-dimethylphenyl]-1-oxopropyl][(1S)-1-(4-phenyl-1H-imidazol-2-yl)ethyl]amino]methyl]-2-methoxybenzoic acid. Eluxadoline has a molecular weight of 569.65 and a molecular formula of C₃₂H₃₅N₅O₅. The chemical structure of eluxadoline is:



VIBERZI is available as 75 mg and 100 mg tablets for oral administration. In addition to the active ingredient, eluxadoline, each tablet contains the following inactive ingredients: silicified microcrystalline cellulose, colloidal silica,

crospovidone, mannitol, magnesium stearate, and Opadry II (partially hydrolyzed polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, and iron oxide red).

Evaluation:

Item	Comments on the Information Provided in NDA
Proprietary name and established name	The proprietary name (VIBERZI) is acceptable. The established name is eluxadoline. Satisfactory
Dosage form and route of administration	Tablets for oral use. Satisfactory
Active moiety expression of strength with equivalence statement (if applicable)	N/A
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)).	Each tablet contains the following inactive ingredients: silicified microcrystalline cellulose, silicon dioxide, crospovidone, mannitol, magnesium stearate, partially hydrolyzed polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, and iron oxide red. Satisfactory
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	A mu-opioid receptor agonist. Satisfactory
Chemical name, structural formula, molecular weight	Chemical name and structural formula are correctly described in this section. The molecular weight is correctly listed. Satisfactory
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	None

This section is satisfactory.

#16. How Supplied/Storage and Handling

VIBERZI is available as:

- 75 mg tablets: capsule-shaped tablets, coated in pale-yellow to light tan color, debossed with “FX75” on one side.

Bottle of 60: NDC 0456-5375-60

- 100 mg tablets: capsule-shaped tablets, coated in pink-orange to peach color, debossed with “FX100” on one side.

Bottle of 60: NDC 0456-5310-60

Store VIBERZI tablets at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

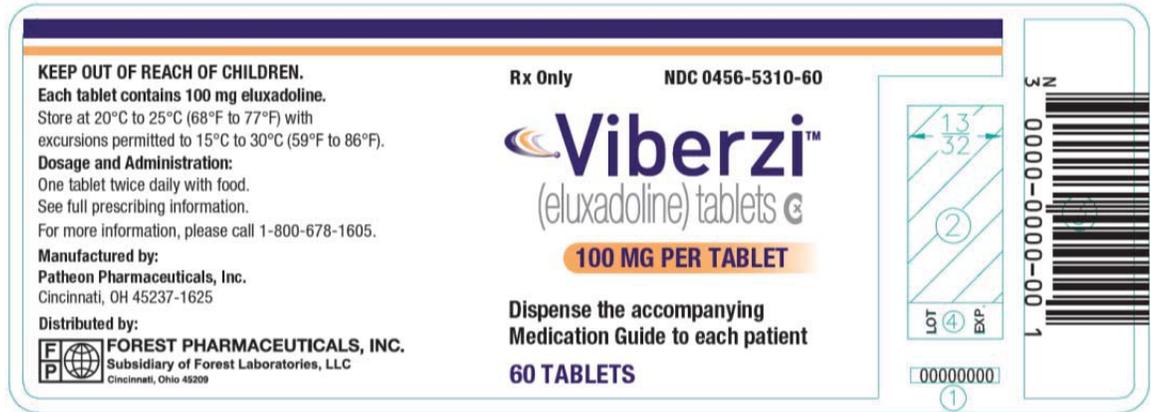
Evaluation:

Item	Comments on the Information Provided in NDA
Strength of dosage form	Strengths are correctly described as 75 mg and 100 mg tablets, respectively. Satisfactory
Available units (e.g., bottles of 100 tablets)	Available units are correctly described as bottles of 60 tablets for each strength of the tablets. Satisfactory
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC Number is stated: 0456-5375-60 for the 75 mg tablets. NDC Number is stated: 0456-5310-60 for the 100 mg tablets. Satisfactory
Special handling (e.g., protect from light)	N/A
Storage conditions	Storage condition is described as: Store VIBERZI tablets at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Satisfactory
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Stated at the end of the labeling as: Manufactured by: Patheon Pharmaceuticals, Inc. Distributed by: Forest Pharmaceuticals, Inc. Satisfactory
Other	N/A

This section is satisfactory.

2. Immediate container label

Bottle Label (60 ct 100 mg Tablets)

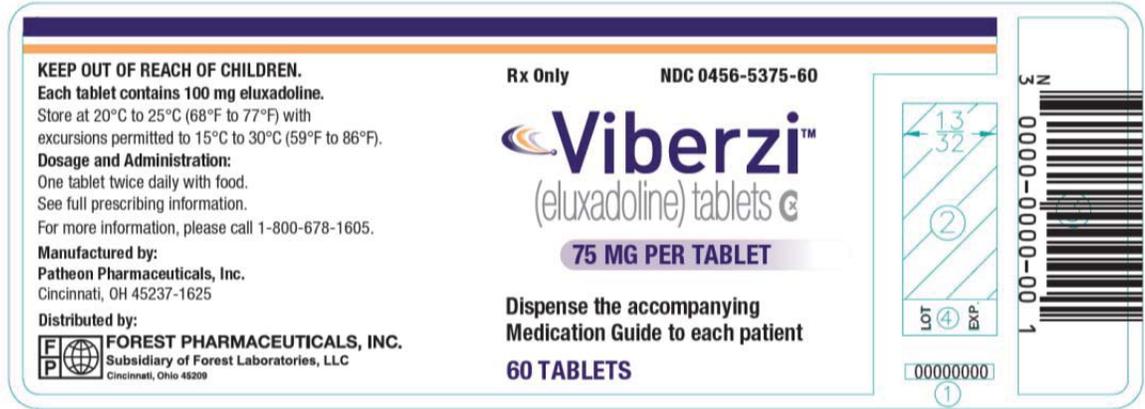


Evaluation:

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The proprietary name (Viberzi) is acceptable. The established name, eluxadoline, is presented correctly. Satisfactory
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength (100 mg) is correctly expressed. Satisfactory
Net contents (21 CFR 201.51(a))	A net content of 60 tablets is correctly expressed. Satisfactory
“Rx only” displayed prominently on the main panel	The statement is prominently displayed. Satisfactory
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	NDC number (0456-5310-60) is indicated. Satisfactory
Lot number and expiration date (21 CFR 201.17)	There is space allocated for this information. Satisfactory
Storage conditions	Storage condition is correctly described. Satisfactory
Bar code (21CFR 201.25)	Barcode is indicated. Satisfactory
Name of manufacturer/distributor	The name of manufacturer is correctly described per 21CFR 201.1. Satisfactory
And others, if space is available	N/A

The bottle label is satisfactory.

Bottle Label (60 ct 75 mg Tablets)



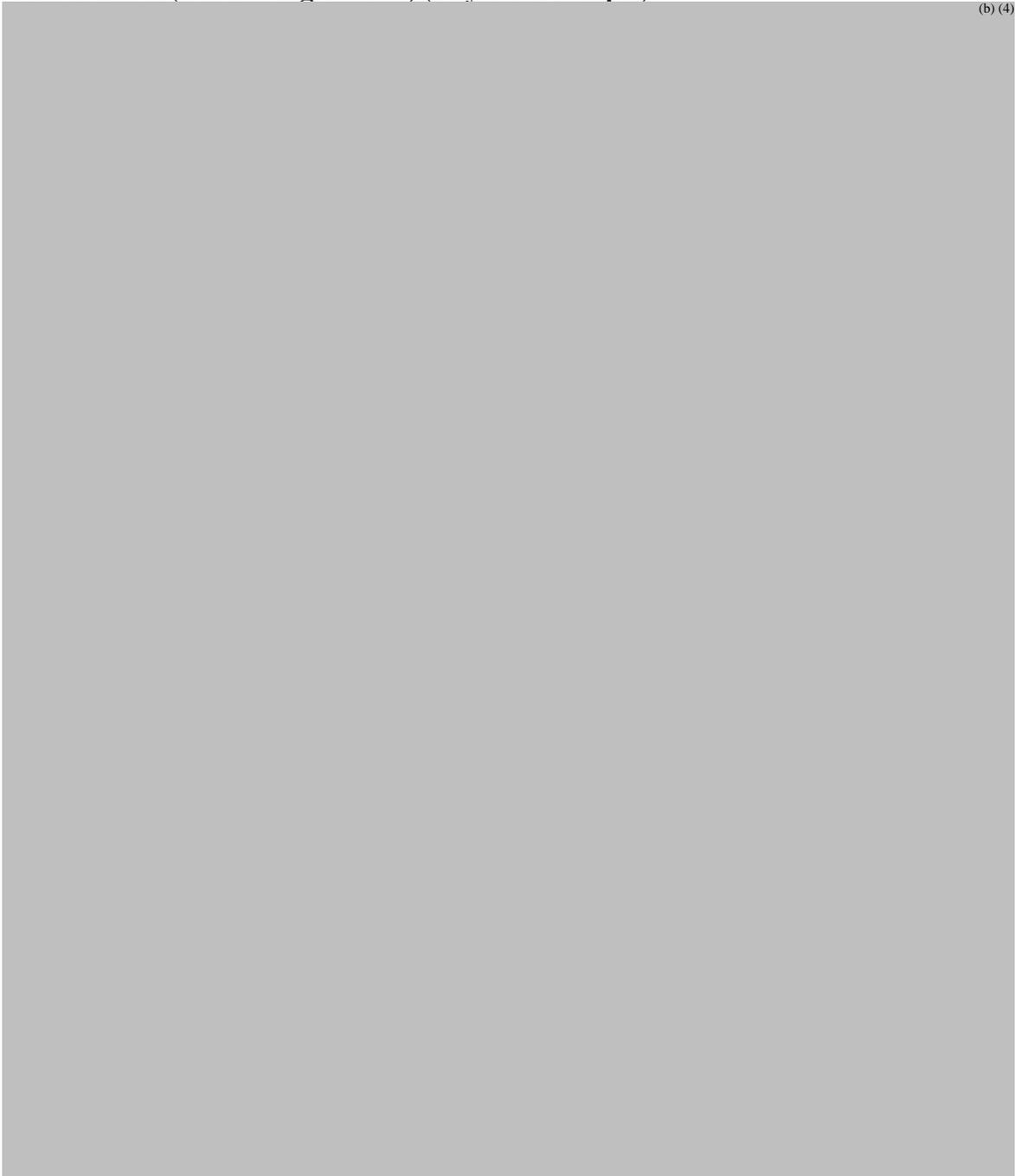
Evaluation:

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The proprietary name (Viberzi) is acceptable. The established name, eluxadoline, is presented correctly. Satisfactory
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength (75 mg) is correctly expressed. Satisfactory
Net contents (21 CFR 201.51(a))	A net content of 60 tablets is correctly expressed. Satisfactory
“Rx only” displayed prominently on the main panel	The statement is prominently displayed. Satisfactory
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	NDC number (0456-5375-60) is indicated. Satisfactory
Lot number and expiration date (21 CFR 201.17)	There is space allocated for this information. Satisfactory
Storage conditions	Storage condition is correctly described. Satisfactory
Bar code (21CFR 201.25)	Barcode is indicated. Satisfactory
Name of manufacturer/distributor	The name of manufacturer is correctly described per 21CFR 201.1. Satisfactory
And others, if space is available	N/A

The bottle label is satisfactory.

Blister Label (8 ct 100 mg Tablets) (Physician Sample)

(b) (4)



Evaluation:

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The proprietary name (Viberzi) is acceptable. The established name, eluxadoline, is presented correctly. Satisfactory
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength (100 mg) is correctly expressed. Satisfactory
“Rx only” displayed prominently on the main panel	The statement is prominently displayed. Satisfactory
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	NDC number is not indicated. However, it is not required. Satisfactory
Lot number and expiration date (21 CFR 201.17)	There is space allocated for this information. Satisfactory
Bar code (21CFR 201.25)	Not required for physician samples. Satisfactory
Name of manufacturer/distributor	The name of distributor is correctly described per 21CFR 201.1. Satisfactory

The blister label for 8 ct 100 mg Tablets (physician sample) is satisfactory.

Blister Label (8 ct 75 mg Tablets) (Physician Sample)

(b) (4)



Evaluation:

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The proprietary name (Viberzi) is acceptable. The established name, eluxadoline, is presented correctly. Satisfactory
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength (75 mg) is correctly expressed. Satisfactory
“Rx only” displayed prominently on the main panel	The statement is prominently displayed. Satisfactory
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	NDC number is not indicated. However, it is not required. Satisfactory
Lot number and expiration date (21 CFR 201.17)	There is space allocated for this information. Satisfactory
Bar code (21CFR 201.25)	Not required for physician samples. Satisfactory
Name of manufacturer/distributor	The name of distributor is correctly described per 21CFR 201.1. Satisfactory

The blister label for 8 ct 75 mg Tablets (physician sample) is satisfactory.

Carton Label for Blister Card of 8 ct 100 mg Tablets (Physician Sample)



Evaluation:

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The proprietary name (Viberzi) is acceptable. The established name, eluxadoline, is presented correctly. Satisfactory
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength (100 mg) is correctly expressed. Satisfactory
Net contents (21 CFR 201.51(a))	Net content of 8 tablets is correctly expressed. Satisfactory
“Rx only” displayed prominently on the main panel	The statement is prominently displayed. Satisfactory
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	NDC number (NDC 0456-5310-08) is indicated. Satisfactory
Lot number and expiration date (21 CFR 201.17)	There is space allocated for this information. Satisfactory
Storage conditions	Storage condition is correctly described. Satisfactory
Bar code (21CFR 201.25)	Barcode is indicated. Satisfactory
Name of manufacturer/distributor	The name of distributor is correctly described per 21CFR 201.1. Satisfactory
And others, if space is available	N/A

The carton label for the 8 ct of 100 mg tablets is satisfactory.

Carton Label for Blister Card of 8 ct 75 mg Tablets (Physician Sample)

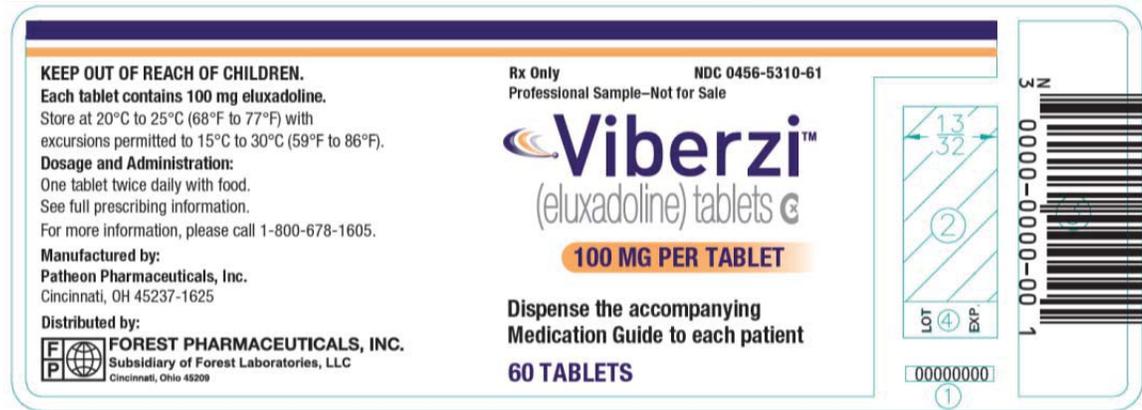


Evaluation:

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The proprietary name (Viberzi) is acceptable. The established name, eluxadoline, is presented correctly. Satisfactory
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength (75 mg) is correctly expressed. Satisfactory
Net contents (21 CFR 201.51(a))	A net content of 8 tablets is correctly expressed. Satisfactory
“Rx only” displayed prominently on the main panel	The statement is prominently displayed. Satisfactory
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	NDC number (NDC 0456-5375-08) is indicated. Satisfactory
Lot number and expiration date (21 CFR 201.17)	There is space allocated for this information. Satisfactory
Storage conditions	Storage condition is correctly described. Satisfactory
Bar code (21CFR 201.25)	Barcode is indicated. Satisfactory
Name of manufacturer/distributor	The name of distributor is correctly described per 21CFR 201.1. Satisfactory
And others, if space is available	N/A

The carton label for the 8 ct of 75 mg tablets is satisfactory.

Bottle Label (60 ct 100 mg Tablets) (Physician Sample)

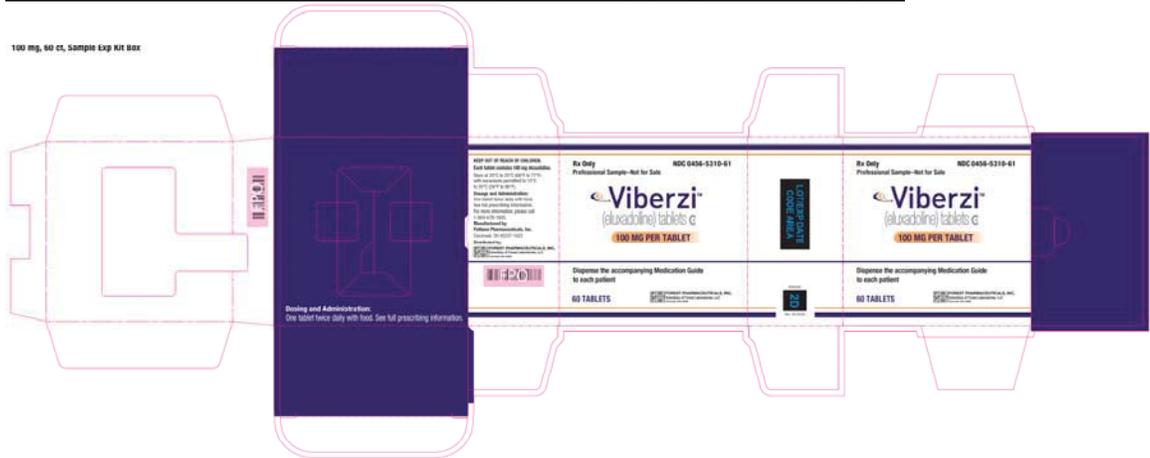


Evaluation:

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The proprietary name (Viberzi) is acceptable. The established name, eluxadoline, is presented correctly. Satisfactory
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength (100 mg) is correctly expressed. Satisfactory
Net contents (21 CFR 201.51(a))	Net content of 60 tablets is correctly expressed. Satisfactory
“Rx only” displayed prominently on the main panel	The statement is prominently displayed. Satisfactory
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	NDC number (0456-5310-61) is indicated. Satisfactory
Lot number and expiration date (21 CFR 201.17)	There is space allocated for this information. Satisfactory
Storage conditions	Storage condition is correctly described. Satisfactory
Bar code (21CFR 201.25)	Barcode is indicated. Satisfactory
Name of manufacturer/distributor	The name of manufacturer is correctly described per 21CFR 201.1. Satisfactory
And others, if space is available	N/A

The bottle label of the physician sample is satisfactory.

Carton Label for Bottle (60 ct 100 mg Tablets) (Physician Sample)



Evaluation:

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The proprietary name (Viberzi) is acceptable. The established name, eluxadoline, is presented correctly. Satisfactory
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength (100 mg) is correctly expressed. Satisfactory
Net contents (21 CFR 201.51(a))	Net content of 60 tablets is correctly expressed. Satisfactory
“Rx only” displayed prominently on the main panel	The statement is prominently displayed. Satisfactory
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	NDC number (0456-5310-61) is indicated. Satisfactory
Lot number and expiration date (21 CFR 201.17)	There is space allocated for this information. Satisfactory
Storage conditions	Storage condition is correctly described. Satisfactory
Bar code (21CFR 201.25)	Barcode is indicated. Satisfactory
Name of manufacturer/distributor	The name of manufacturer is correctly described per 21CFR 201.1. Satisfactory
And others, if space is available	N/A

The carton label for the physician sample bottle of 60 ct of 100 mg tablets is satisfactory.

Kit Tray Label for 5 Bottles (60 ct 100 mg Tablets per Bottle) (Physician Sample)

(b) (4)



Kit Sleeve Label for 5 Bottles (60 ct 100 mg Tablets per Bottle) (Physician Sample)

(b) (4)



Evaluation:

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The proprietary name (Viberzi) is acceptable. The established name, eluxadoline, is presented correctly. Satisfactory
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength (100 mg) is correctly expressed. Satisfactory
Net contents (21 CFR 201.51(a))	5 Kits, each patient kit contains 60 tablets. Satisfactory
“Rx only” displayed prominently on the main panel	The statement is prominently displayed. Satisfactory
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	NDC number is indicated on the tray. Satisfactory
Lot number and expiration date (21 CFR 201.17)	There is space allocated for this information. Satisfactory
Storage conditions	Storage condition is correctly described. Satisfactory
Bar code (21CFR 201.25)	Barcode is indicated. Satisfactory
Name of manufacturer/distributor	The name of manufacturer is correctly described per 21CFR 201.1. Satisfactory
And others, if space is available	N/A

The kit label for the physician sample of bottle of 60 ct of 100 mg tablets is satisfactory.

NDA 206940

 ^{(b) (4)}™ (Eluxadoline) Tablets

Furiex Pharmaceuticals

Yichun Sun, Ph.D.

**Branch V
Division of New Drug Products II
Office of New Drug Products**

**CMC REVIEW OF NDA 206940
For the Division of Gastroenterology and Inborn Errors Products
(HFD-180)**

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Chemistry Review Data Sheet

1. NDA: 206940
2. REVIEW #: 1
3. REVIEW DATE: 4-March-2015
4. REVIEWER: Yichun Sun, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 79214	21-December-2007
EOP 2 meeting minutes (IND 79214)	24-January-2014
Pre-NDA CMC meeting minutes	14-February-2014

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	26-June-2014
Amendment	09-January-2015
Amendment	20-February-2015

7. NAME & ADDRESS OF APPLICANT:

Name: Furiex Pharmaceuticals
Address: 3900 Paramount Parkway, Suite 150
Morrisville, NC 27560
Representative: Paul S. Covington, MD
Telephone: 910-558-6834

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: (b) (4) (pending)
- b) Non-Proprietary Name (USAN): Eluxadoline
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDP only):

- Chem. Type: 1
- Submission Priority: Priority Review

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Mixed mu opioid receptor (μ OR) agonist/delta opioid receptor (δ OR) antagonist

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 75 mg and 100 mg tablets

13. ROUTE OF ADMINISTRATION: Oral

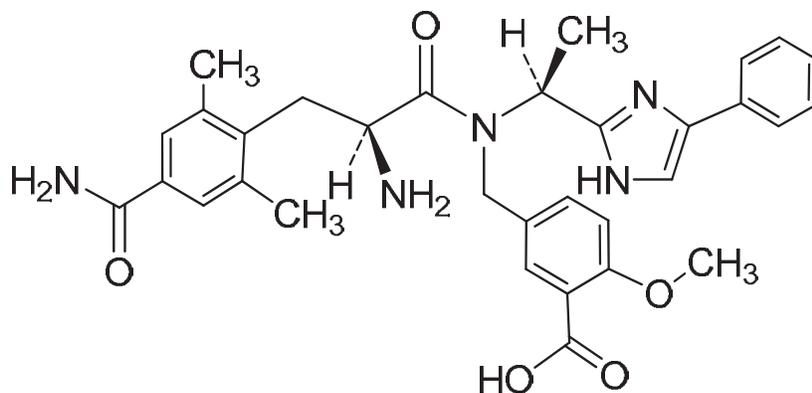
14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical Structure of Eluxadoline

Empirical formula: $C_{32}H_{35}N_5O_5$

Molecular weight: 569.65

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	4	Adequate	NA	NA
	III		4	Adequate	NA	NA	
	III		4	Adequate	NA	NA	
	III		4	Adequate	NA	NA	
	III		4	Adequate	NA	NA	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: NA

18. STATUS:

ONDP:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	----	----
EES	Acceptable	January 15, 2015	C. Capacci-Daniel
Pharm/Tox	N/A	----	----
Biopharm	Acceptable	February 10, 2015	A. Noory
LNC	N/A	----	----
Methods Validation*	Acceptable	January 22, 2015	M. L. Trehy
DMEPA	N/A	----	----
EA	Claim for Categorical Exclusion is granted.	December 5, 2014	R. A. Bloom
Quality Microbiology	Approval	August 1, 2014	B. S. Riley

Note: The request of methods validation consult was sent to the Division of Pharmaceutical Analysis (DPA), Office of Testing and Research on August 15, 2014. The results of method validation from DPA were received on January 22, 2015. The methods are acceptable for quality control and regulatory purposes with modification according to the methods validation report summary provided by DPA. The recommended changes in the summary report were sent to the applicant on February 11, 2015 in the T-con agenda, which was held on February 12, 2015. The applicant accepted all the recommended changes on February 12, 2015 and amended the pertinent sections of the NDA on February 20, 2015.

The Chemistry Review for NDA 206940

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product.

The Office of Compliance has made an overall 'acceptable' recommendation for the facilities involved in this application.

However, the label/labeling issues have *not* been resolved yet.

Therefore, from the ONDP perspective, this NDA is not ready for approval in its present form per 21 CFR 314.125 (b)(6) until all those remaining issues are satisfactorily resolved.

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

The applicant commits to re-evaluate the dissolution acceptance criterion after dissolution data from at least 30 lots of commercial drug products are available, or a maximum period of 1 year post-launch. Additionally, a 15 minute time-point will be added to the dissolution test at time of product release and in the stability protocol where profiles will be followed at 10, 15, 20 and 30 minutes. The final evaluation will include an assessment of whether the dissolution criterion of $Q = \text{■}^{(b)(4)}\%$ can be applied at 10-minutes or 15-minutes, instead of the 20-minute interval.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

The active ingredient used in $\text{■}^{(b)(4)}$ tablets, which is indicated for the treatment of diarrhea and abdominal pain in men and women with diarrhea predominant irritable bowel syndrome (IBS-d), is Eluxadoline. Eluxadoline is known chemically as 5-[[[(2S)-2-amino-3-[4-(aminocarbonyl)-2,6 dimethylphenyl]-1-oxopropyl][(1S)-1-(4-phenyl-1H-imidazol-2-yl)ethyl]amino]methyl]-2-methoxybenzoic acid. Eluxadoline is a $\text{■}^{(b)(4)}$ which is a locally active, mixed mu opioid receptor (μOR) agonist/delta opioid receptor (δOR) antagonist. Eluxadoline drug substance is a white crystalline powder. It has a melting point of 189.4°C. Its solubility is pH dependent. It is soluble in 0.1 N HCl. It is slightly soluble in pH 4 citrate buffer. It is slightly soluble in water. It is sparingly soluble in pH 10 borate buffer. It is freely soluble in 0.1N NaOH. It has dissociation coefficients of $\text{pKa}1 = 7.11$; $\text{pKa}2 = 4.70$; $\text{pKa}3 = 3.77$. It has partition coefficients of $\text{cLog P (Zwitterionic)} = 0.90$; $\text{cLog P (Unit Negative Charge)} = 0.64$.

(b) (4)

The identity, purity, assay and quality of the drug substance are adequately controlled by the in-process controls and the drug substance specification. The packaging materials used in the container closure system of the drug substance are deemed safe for packaging the drug substance. The drug substance is stable for at least (b) (4) months at room temperature and stable for (b) (4) months at accelerated test conditions. The proposed retest period of (b) (4) months is deemed acceptable.

Drug Product

The drug product, (b) (4) (Eluxadoline) tablets, is proposed to be used for the treatment of irritable bowel syndrome with diarrhea (IBS-D). (b) (4) is available as 75 mg and 100 mg tablets for oral administration. (b) (4) 75 mg tablets are capsule-shaped, coated in pale-yellow to light tan color and debossed with "FX75" on one side. (b) (4) 100 mg tablets are capsule-shaped, coated, pink-orange to peach color, and debossed with "FX100" on one side. In addition to the active ingredient, Eluxadoline, each tablet contains the following inactive ingredients: silicified microcrystalline cellulose, silicon dioxide, crospovidone, mannitol, magnesium stearate and Opadry II. The core tablets are prepared by (b) (4)

The identity, purity, assay and quality of the drug product are adequately controlled by the drug product specification. The tablets (60 counts) are packaged in white (b) (4) opaque high density polyethylene (HDPE) bottles with (b) (4) screw caps (b) (4). The proposed expiration dating period of 24 months is supported by the primary and supportive stability data. The drug product would qualify for categorical exclusion from the preparation of an environmental assessment according to 21 CFR 25.31(b).

B. Description of How the Drug Product is Intended to be Used

(b) (4) is a locally active, mixed mu opioid receptor (μ OR) agonist and delta opioid receptor (δ OR) antagonist with very low oral bioavailability, indicated in adults for the treatment of irritable bowel syndrome with diarrhea (IBS-D).

The recommended dose of (b) (4) is one 75 mg tablet or 100 mg tablet, taken orally twice daily with food.

C. Basis for Not-Approval Recommendation

21CFR 314.125(b)(6)

- Label and labeling issues are not resolved. (see the **List of Deficiencies**, p. 215)

III. Life Cycle Knowledge Management

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Risk Ranking *	Risk Mitigation approach in control strategy	Risk Evaluation	Lifecycle Considerations/ Comments**
Assay/Impurities	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • scale/equipment • Site 	L	The excipients are selected based on the results of compatibility study. The drug product is manufactured by (b) (4). The drug product is packaged in white high density polyethylene bottles closed with (b) (4) screw-caps. Assay and impurities are monitored at release and during stability study.	Acceptable	N/A
Physical stability (solid state)	The API is a white crystalline powder.	L	(b) (4)	Acceptable	N/A
Content Uniformity	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • scale/equipment 	L	Content uniformity of the drug product is ensured by the (b) (4).	Acceptable	N/A

	<ul style="list-style-type: none"> • Site 		(b) (4)		
Microbial Limits	<ul style="list-style-type: none"> • Raw materials • Manufacturing process 	L	<p>API meets the microbial specifications. All of the excipients used in the tablet formulation are tested to meet the Compendial specifications. The drug product is manufactured according to Good Manufacturing Practices (GMPs) and (b) (4) is part of the manufacturing operation. Microbial Limits Tests are included in the drug product specification.</p>	Acceptable	N/A
Dissolution	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • scale/equipment • Site 	L	<p>The drug product is formulated to (b) (4)</p> <p style="background-color: #cccccc;">(b) (4)</p> <p>Additionally, the applicant commits to evaluate the dissolution performance of more batches of the drug product to potentially tighten the dissolution acceptance criterion.</p>	Acceptable	<p>The applicant commits to re-evaluate the dissolution acceptance criterion after dissolution data from at least 30 lots of commercial drug products are available, or a maximum period of 1 year post-launch. The final evaluation will include an assessment of whether the dissolution criterion of $Q = (b) (4)\%$ can be applied at 10-minutes or 15-minutes, instead of the 20-minute interval.</p>

III. Administrative

A. Reviewer's Signature

/s/ Y. Sun, Ph.D.

B. Endorsement Block

Yichun Sun, Ph.D.
Reviewer

Yichun
Sun -S

Digitally signed by Yichun Sun -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Yichun Sun -S,
0.9.2342.19200300.100.1.1=130039
3310
Date: 2015.03.04 15:08:04 -05'00'

_____ Date

Moo-Jhong Rhee, Ph.D.
Branch Chief

Moojhong
Rhee -S

Digitally signed by Moojhong Rhee -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Moojhong Rhee -S,
0.9.2342.19200300.100.1.1=130004126
1
Date: 2015.03.04 15:17:38 -05'00'

_____ Date

204 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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NDA 206940-Orig1-New/NDA(1) » Profile Evaluation for PATHEON PHARMACEUTICALS INC - TCM TABLETS, ...

Office of Process and Facilities Recommendation TCM TABLETS, PROMPT RELEASE

Edit Task | Task Actions

Task Summary Task Details Issues Updates **Inspection Management Form**

Inspection Management Form As of 1:30 PM

Inspection Management Form

NDA 206940-Orig1-New/NDA(1)

PATHEON PHARMACEUTICALS INC, TCM TABLETS, PROMPT RELEASE

NOTICE - This application contains a New Molecular Entity.

Facility Name:	DUNS:	FEI:	Address:	Business Operation:	Product Stage Code:	Product Process Code:
PATHEON PHARMACEUTICALS INC	005286822	1510437	2110 E GALBRAITH RD CINCINNATI, OH USA 45237 1625	FDF MANUFACTURER OTHER TESTER PACK STABILITY TESTER	FINISHED DOSAGE FINISHED DOSAGE FINISHED DOSAGE FINISHED DOSAGE	LABELER MANUFACTURER OTHER TESTER PACKAGER STABILITY TESTER

Last Inspection Date: 10/30/2014
Last Inspection Results: Voluntary Action Indicated (VAI)
Action Indicated Status: None
 Facility Summary Report
 FACTS Firm Profile Data
 EER Report
 Previous Inspections Findings

Office of Process and Facilities Recommendation	District Office Recommendation	FACTS Results	Application and Facility Criteria
<input checked="" type="radio"/> Approve Facility <input type="radio"/> Withhold Approval	Inspection Type: Recommendation Recommendation: Approve Facility Recommendation Reasons: Based on File Review Decision Factors: Comments: GMP EI ending 10/20/14 will be classified VAI and all profiles updated to acceptable. process validation can be reviewed in next routine EI at CSO's discretion.	483 Issued: GMP Classification: Sample ID and Type:	Application-Specific Criteria New Molecular Entity Facility-Specific Criteria

Recommendation Reasons
 Based on Profile
 CDER Policy Change
 Deficiency Not Supported by CDER
 District Recommendation

Inspection Re-evaluation Date
 10/20/16

Comments
 10/20/2014 +2yrs
 for TCM

Cancel

Assigned To

Christina Capacci Daniel

Edit Assignment

This was done on
Jan 15, 2015
 (124 days ago)

Status
Complete

This task is waiting on
 District Office Recommendation...

Last Update: Jan 15, 2015
 Submitted On: Oct 28, 2014

Reference Number
 2827510

URL
<https://panoram...endationServlet>

APPEARS THIS WAY ON ORIGINAL

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Prompt

Facility Alerts

This report displays the Alerts associated with facilities for the selected application

No active OAI / POAI Alerts are present against the facilities on selected Projects

Refresh

Facility Summary Report

Present the Office of Process and Facilities (OPF) Review, District Office for Approval Management (DAFAM) and the Region Office detailed information about the facility being inspected for the selected application (b) (4)

- Application Type: --Select Value--
- Application Number: 206940
- Submission Type: --Select Value--
- Submission Number: 1
- Facility Name: --Select Value--
- FEI: 1510437
- Profile: --Select Value--

Office of Process and Facilities Decision/Request TCM TABLETS, PROMPT RELEASE Assigned To: CHRISTINA CAPACCI-DANIEL Phone: Email: CHRISTINA.CAPACCI-DANIEL@FDA.HHS.GOV
 District Office Decision/Request TCM TABLETS, PROMPT RELEASE Assigned To: KATHLEEN CULVER Phone: Email: KATHLEEN.CULVER@FDA.HHS.GOV
 District Office Recommendation TCM TABLETS, PROMPT RELEASE Assigned To: KATHLEEN CULVER Phone: Email: KATHLEEN.CULVER@FDA.HHS.GOV
 Office of Process and Facilities Recommendation TCM TABLETS, PROMPT RELEASE Assigned To: CHRISTINA CAPACCI-DANIEL Phone: Email: CHRISTINA.CAPACCI-DANIEL@FDA.HHS.GOV

District Office Details
This report displays details of District Office decisions/recommendations.

DO Name:
 Facility Inspection District
 Goal Date:
 DO - Facility Inspection Type:
 DO - Facility Recommendation: Acceptable
 DO - Facility Recommender: (b) (4)
 DO - Facility Recommendation Decision Factors:

DO - Facility Recommendation Comments: The Pre-Approval/GMP Inspection for FACTS Assignment (b) (4) (b) (4) The inspection focused on two applications (206940 & (b) (4) which were the subjects of product specific (206940) and GMP (b) (4) Inspection Requests. Systems covered during the inspection include Quality and Laboratory Control Systems. No deficiencies were cited during the inspection and no FDA-483 was issued. The inspection was classified NAI and profile class CSN was covered and found acceptable. Based upon inspection, the District recommends approval of the firm for its listed responsibilities in the application.

District Office Recommendation CSN NON-STERILE API BY CHEMICAL SYNTHESIS Date: 12/30/2014

District Office Recommendation CTL CONTROL TESTING LABORATORY Date: 12/1/2014



APPEARS THIS WAY ON ORIGINAL

ONDQA Initial Quality Assessment (IQA) and Filing Review

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: **206940**

2. DATES AND GOALS:

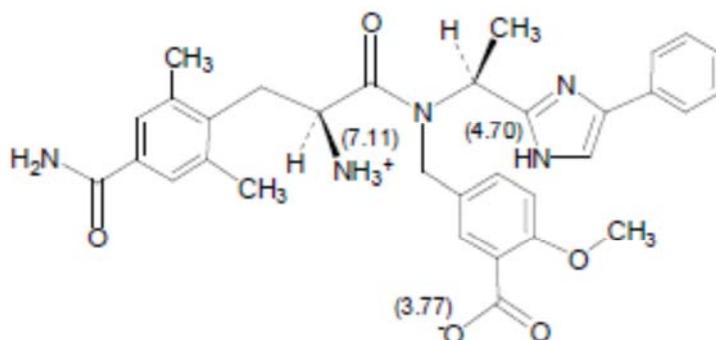
Letter Date: 6/26/2014	Submission Received Date : 7/10/2014
PDUFA Goal Date: 9/26/2014	IQA date 8/19/2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	(b) (4)
Established or Non-Proprietary Name (USAN):	Eluxadoline (USAN)
Dosage Form:	Immediate release tablets
Route of Administration	oral
Strength/Potency	75 mg and 100 mg
Rx/OTC Dispensed:	Rx

INDICATION: treatment of pain and diarrhea associated with diarrhea-predominant Irritable Bowel Syndrome (IBS-d)

4. DRUG SUBSTANCE STRUCTURAL FORMULA:



Molecular weight : 569.65

dissociation constants: pKa1 = 7.11; pKa2 = 4.70; pKa3 = 3.77

only slightly soluble between pH 3.9 and 6.8

Melting point: 189.4 C

5. NAME OF APPLICANT (as indicated on Form 356h):

Furiex Pharmaceuticals

ONDQA Initial Quality Assessment (IQA) and Filing Review

6. SUBMISSION PROPERTIES:

Review Priority:	Priority
Submission Classification (Chemical Classification Code):	Type 1 (NME)
Application Type:	505(b)(1)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	Division of Gastrointestinal and Inborn Error Products (HFD-180)

7. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		x	
Clinical Pharmacology			(included in review team)
Establishment Evaluation Request (EER)	x		Already requested
Pharmacology/Toxicology			(included in review team)
Methods Validation	x		
Environmental Assessment	x		Categorical exclusion
CDRH		x	
Other		x	

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective?

Yes No

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter?

Yes No

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?

Yes No

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter?

Yes No

Biopharmaceutics Comments for 74-Day Letter:

1. Please provide all the dissolution data used to set proposed dissolution specification in an electronic format (e.g., excel).
2. Please provide comparative dissolution data on 12 units of the debossed to-be-marketed product and phase 3 non-debossed for both 75 mg and 100 mg tablets.

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?

Yes No

Microbiology Filing Issues:

This submission is acceptable from a product quality microbiology standpoint and will be recommended for approval.

ONDQA Initial Quality Assessment (IQA) and Filing Review

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
no	no	no	no

Is a team review recommended?		Yes
Reviewers already assigned:	CMC: Yichun Sun, PhD Microbiology: NAI Biopharmaceutics: Assad Noory PhD	

--

ONDQA Initial Quality Assessment (IQA) and Filing Review

Product Summary

(b) (4) (eluxadoline) tablets is indicated for the treatment of pain and diarrhea associated with diarrhea-predominant Irritable Bowel Syndrome (IBS-d). This immediate release product has been developed under IND 79,214 and is intended for twice daily administration. The tablets contain 100 or 75 mg of eluxadoline, which is a new molecular entity. In addition to eluxadoline, each (b) (4) mg tablet contains the following excipients: microcrystalline cellulose, silicon dioxide, crospovidone, mannitol, and magnesium stearate, all of which conform to NF/USP requirements, and Opadry II tablet coating.

The product received fast-track designation in January of 2011.

The only difference between the commercial tablets and those used in pivotal clinical trials is that the commercial tablet will be debossed with an identifier and will be of different color. Also, while the phase 3 product was produced at Patheon (b) (4) the commercial product will be manufactured at Patheon Cincinnati.

For commercial distribution, the product will be packaged in 60-count HDPE bottles, with 12 months of long term stability data submitted in support of expiration dating. Physician samples will be blister-packaged; nine months of stability data are provided to support this packaging configuration.

The submission contains contradictory information regarding the strength of the product that will be commercialized, for example

“Please note that although we are seeking approval for the 100 mg strength only, we are supplying bottle/blister carton labeling for both the 75 mg and 100 mg strengths”

In other locations in the submission, including Form-356h, the applicant indicates that this application is for the 75mg and 100 mg strength. Since clinical data was provided for both strengths, a decision was made at the filing meeting that both strengths should be reviewed in this application review.

ONDQA Initial Quality Assessment (IQA) and Filing Review

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	√		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	√		
3.	Are all the pages in the CMC section legible?	√		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	√		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			NA, (b)(4) drug substance

ONDQA Initial Quality Assessment (IQA) and Filing Review

	Parameter	Yes	No	Comment
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		

ONDQA Initial Quality Assessment (IQA) and Filing Review

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	√		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	√		Claim of categorical exclusion Asked Cathy for consult

ONDQA Initial Quality Assessment (IQA) and Filing Review

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	√		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	√		
14.	Does the section contain information regarding the characterization of the DS?	√		
15.	Does the section contain controls for the DS?	√		
16.	Has stability data and analysis been provided for the drug substance?	√		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		√	Not required
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		√	Not required

ONDQA Initial Quality Assessment (IQA) and Filing Review

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	√		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	√		
21.	Is there a batch production record and a proposed master batch record?	√		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	√		
23.	Have any biowaivers been requested?		√	
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	√		
25.	Does the section contain controls of the final drug product?	√		
26.	Has stability data and analysis been provided to support the requested expiration date?	√		Commercial product is bottles of 60 tablets – 12 months of stability data have been provided. Nine months of stability data have been submitted for blister-packaged physician samples
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		√	Not required
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		√	Not required

ONDQA Initial Quality Assessment (IQA) and Filing Review

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	√		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product		√	Not required

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	√		(b) (4) DMF (b) (4) Packaging (b) (4) DMF DMF DMF DMF

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	√		
33.	Have the immediate container and carton labels been provided?	√		

ONDQA Initial Quality Assessment (IQA) and Filing Review

Biopharmaceutics Filing Review Checklist

The following parameters are usually necessary to initiate a full Biopharmaceutics review (i.e., the NDA is complete enough to review but may have deficiencies). On **initial** overview of the NDA application for filing:

J. BIOPHARMACEUTICS				
	Parameter	Yes	No	Comment
34.	Does the application contain dissolution data?	X		
35.	Is the dissolution test part of the DP specifications?	X		“Q = ^(b) ₍₄₎ % of label claim at 20 minutes”
36.	Does the application contain the dissolution method development report including data supporting the discriminating ability?	X		
37.	Is there a validation package for the analytical method and dissolution methodology?	X		
38.	Does the application include a biowaiver request?		X	Both strengths were used in the bio studies.
39.	Is there information/data supporting the biowaiver request?			N/A
40.	Is there enough information to assess the extended release designation claim?			N/A
41.	Does the application include an IVIVC model?		X	
42.	Does the application include information/data on in vitro alcohol dose-dumping potential?			N/A
43.	Is there any in vivo BA or BE information in the submission?	X		BA and Food effect: EDI-1002, CPS-1009. OCP will review that.
44.	Is there any design space proposed using in vitro release as a response variable?		X	
45.	Is the control strategy related to in vitro drug release?			N/A
K.				
	Parameter			Comment
46.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			NDA is fileable

ONDQA Initial Quality Assessment (IQA) and Filing Review

47.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			NDA is fileable
48.	Are there any potential review issues identified?		X	
49.	Are there any comments to be sent to the Applicant as part of the 74-Day letter?	X		<ol style="list-style-type: none"> 1. Please provide all the dissolution data used to set proposed dissolution specification in an electronic format (e.g., excel). 2. To provide comparative dissolution profile of debossed versus non-debossed tablets using both 75 mg and 100 mg tablets.
50.	Are there any internal comments to other disciplines:		X	

See appended electronic signature page

Marie Kowblansky, PhD

CMC-Lead

Division II

Office of New Drug Quality Assessment

{See appended electronic signature page}

Assad Noory, PhD

Biopharmaceutics Reviewer

Office of New Drug Quality Assessment

{See appended electronic signature page}

Tapash Ghosh, PhD

Biopharmaceutics Team Leader

Office of New Drug Quality Assessment

{See appended electronic signature page}

Moo-Jhong Rhee, PhD

Branch Chief

Division II

Office of New Drug Quality Assessment

ONDQA Initial Quality Assessment (IQA) and Filing Review

NDA RISK ASSESSMENT TABLE

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations/ Comments
Assay, stability	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site 	L			
Physical stability (solid state)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	L			
Content Uniformity	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site 	M			
Dissolution	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site 	L			
Impurities/related substances/residual solvents	<ul style="list-style-type: none"> • Formulation • Excipient change • Process parameters • Scale/equipment • Site 	L			
Microbial limits	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site 	L			
Leakage	<ul style="list-style-type: none"> • Formulation • Excipient change • Process parameters • Scale/equipment • Site 	L			
Antioxidant & Preservative	<ul style="list-style-type: none"> • Formulation • Excipient change • Process parameters • Scale/equipment • Site 	L			

ONDQA Initial Quality Assessment (IQA) and Filing Review

IQA RISK ASSESSMENT

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment	Risk
Assay, stability	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site 	1	2	Release (1) Stability (3)	Release (2) stability (6)		L
Physical stability (solid state)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	3	2	4	24		L
Content Uniformity	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site 	3	3	4	36		M
Dissolution	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site 	2	3	3	18	Dissolution test should be performed before batch release.	L
Impurities/related substances/residual solvents	<ul style="list-style-type: none"> • Formulation • Excipient change • Process parameters • Scale/equipment • Site 	4	2	3	24	Single impurity above ICH identification limit (qualified at 0.1%)	L
Microbial limits	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site 	1	2	3	6		L

The evaluation from the IQA table was transferred to the following NDA table that can be used by the primary reviewer as a part of the NDA review.

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

/s/

MARIE KOWBLANSKY
08/19/2014

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Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre- Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

I. Review Cover Sheet

- 1. OMPQ Reviewer: Christina Capacci-Daniel

- 2. NDA/BLA Number: NDA 206940
 Submission Date: 27 June 2014
 21st C. Review Goal Date: 28 Nov. 2014
 PDUFA Goal Date: 27 Feb. 2015

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	(b) (4)
Established or Non-Proprietary Name (USAN) and strength:	Eluxadoline
Dosage Form:	Immediate release tablet

4. SUBMISSION PROPERTIES:

Review Priority :	PRIORITY
Applicant Name:	Furiex Pharmaceuticals Inc.
Responsible Organization (OND Division):	DGIEP

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II. Application Detail

1. INDICATION: Treatment of diarrhea and abdominal pain symptoms in men and women with diarrhea predominant irritable bowel syndrome (IBS-d).
2. ROUTE OF ADMINISTRATION: Oral
3. STRENGTH/POTENCY: 75mg and 100mg
4. Rx/OTC DISPENSED: Rx OTC
5. ELECTRONIC SUBMISSION (yes/no)? YES
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V	<input checked="" type="checkbox"/>			Fast Track Designation granted
2.	Breakthrough Therapy Designation		<input checked="" type="checkbox"/>		
3.	Orphan Drug Designation		<input checked="" type="checkbox"/>		
4.	Unapproved New Drug		<input checked="" type="checkbox"/>		
5.	Medically Necessary Determination		<input checked="" type="checkbox"/>		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		<input checked="" type="checkbox"/>		
7.	Rolling Submission		<input checked="" type="checkbox"/>		
8.	Drug/device combination product with consult		<input checked="" type="checkbox"/>		
9.	Complex manufacturing		<input checked="" type="checkbox"/>		
10.	Other (e.g., expedited for an unlisted reason)		<input checked="" type="checkbox"/>		

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III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	Yes	No	Comment
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	<input checked="" type="checkbox"/>		
12.	Do all sites indicate they are ready to be inspected (on 356h)?	<input checked="" type="checkbox"/>		
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	<input checked="" type="checkbox"/>		Single list of API and DP manufacturers included in the "Cover Letters" section of the NDA submission
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	<input checked="" type="checkbox"/>		Microbial testing; XRPD & NMR testing; (b) (4)
15.	Additional notes (non-filing issue)	<input checked="" type="checkbox"/>		
	1. Are all sites registered or have FEI #?			
	2. Do comments in EES indicate a request to participate on inspection(s)?	<input checked="" type="checkbox"/>		
	3. Is this first application by the applicant?		<input checked="" type="checkbox"/>	However, Furiex had only one previous NDA ((b) (4)) in 2005 that received a "Not Approvable" letter based on safety and efficacy concerns.

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

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B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
16.	Have any Comparability Protocols been requested?		<input checked="" type="checkbox"/>	

IMA CONCLUSION				
	Parameter	Yes	No	Comment
17.	Does this application fit one of the EES Product Specific Categories?	<input checked="" type="checkbox"/>		NME
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	<input checked="" type="checkbox"/>		EES corresponds to information on the 356h. EERs have been initially processed.
19.	From a CGMP/facilities perspective, is the application fileable? If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	<input checked="" type="checkbox"/>		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology <input type="checkbox"/>	RTRT Proposal <input type="checkbox"/>	PAT <input type="checkbox"/>	Drug/Device Combo <input type="checkbox"/>
PET <input type="checkbox"/>	Design Space <input type="checkbox"/>	Continuous Mfg <input type="checkbox"/>	Naturally derived API <input type="checkbox"/>
Other (explain):		<input checked="" type="checkbox"/> None Applicable	

Manufacturing Highlights				
1. Drug Substance				
	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		<input checked="" type="checkbox"/>	(b) (4)
(b) (4)				

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2. Drug Product

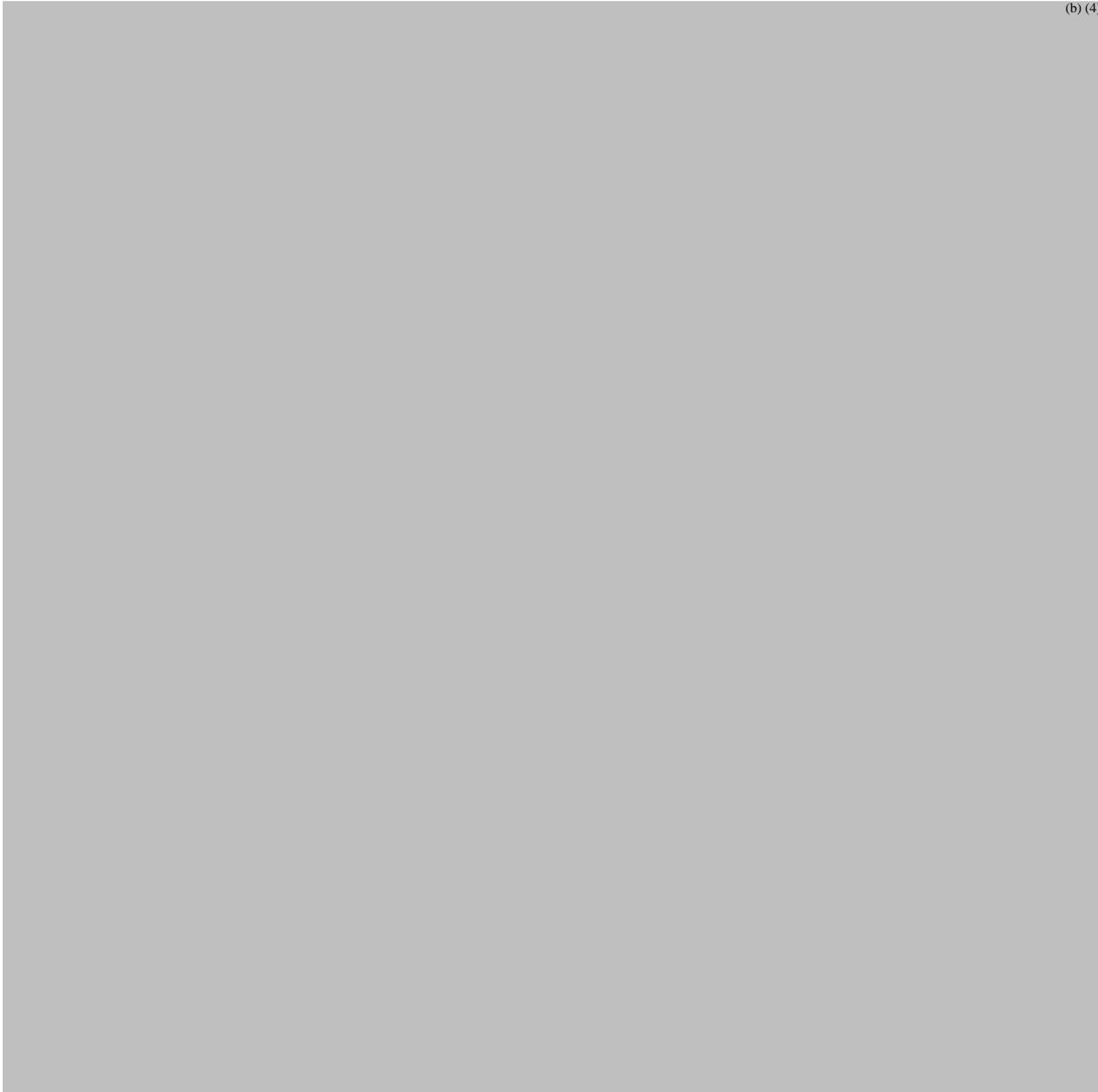
	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		<input checked="" type="checkbox"/>	<ul style="list-style-type: none"> • (b) (4) coated tablet • (b) (4) • (b) (4) % (w/w) API in tablet • (b) (4) • “FX100” debossing proposed for commercial product, not performed for registration batches; (b) (4)/visual inspection difference should be assessed

Process Step

Component

In-process Control

(b) (4)



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3. Facility-Related Risks (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc.). Describe any potential 21CFR 211 compliance issues.

- [REDACTED] ^{(b) (4)} has minimal FDA manufacturing history and has mainly been an intermediate and starting material supplier. The Production System was last covered in the [REDACTED] ^{(b) (4)} inspection.

4. Drug Product Facility Inspectional History that could impact the manufacturing of this product

- There are no outstanding compliance issues.

Additional information not covered above

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Manufacturing Facilities Chart (generated 6 Aug 2014):

Establishment Name	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Inspection History, Dates, Classifications	Most Recent Milestone	Compliance Status	Comment
(b) (4)			USA	API manufacture, testing, packaging, stability	CSN	CSN NAI (b) (4)	ASSIGNED INSPECTION TO IB (PS&GMP)	PN	PAI requested for NME & >3years since last inspection KTM/PIB will be issued
			USA	API Microbial Testing	CTL	CTL NAI (b) (4)	OC REC	AC	OC Rec based on file review
			USA	AP (b) (4) testing	CTL	CTL NAI (b) (4)	ASSIGNED INSPECTION TO IB (PS&GMP)	PN	At PDUFA will be >3years since last inspection DO escalated to PS&GMP
			USA	Photostability storage	CTL	CTL NAI (b) (4)	OC REC	AC	OC Rec based on file review
			USA	API XRPD and NMR testing	CTL	CTL NAI (b) (4)	OC REC	AC	OC Rec based on file review
PATHEON PHARMACEUTICALS INC	1510437	CIN	USA	DP manufacture, testing, packaging, labelling and stability	TCM	TCM VAI 5/13/2013	SUBMITTED TO DO (PS&GMP)	PN	PAI requested for (b) (4) KTM/PIB will be issued

V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no, Yes to questions 11-12) YES
Based on Section IV, is a KTM warranted for any PAI? (yes/no). If yes, please identify the sites in the above chart.
<ul style="list-style-type: none">• A KTM or Pre-Inspection Briefing will be issued for the API manufacturer (b) (4) to cover in-process testing of (b) (4).• A KTM or Pre-Inspection Briefing will be issued for the DP manufacturer (Patheon Pharmaceuticals Inc.) to cover (b) (4).
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no) NO
Comments for 74 Day Letter
1.
2.
3.

REVIEW AND APPROVAL (DARRTS)

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

/s/

CHRISTINA A CAPACCI-DANIEL
08/15/2014

MAHESH R RAMANADHAM
08/15/2014