

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207233Orig1s000**

**CHEMISTRY REVIEW(S)**



**NDA 207233**  
**Review # 1**  
**Review Date 09/18/2015**

<b>Drug Name/Dosage Form</b>	Vivlodex Capsules
<b>Strength</b>	5 mg and 10 mg
<b>Route of Administration</b>	Oral
<b>Rx/OTC Dispensed</b>	Rx
<b>Applicant</b>	Iroko Properties, Inc.
<b>US agent, if applicable</b>	None

<b>SUBMISSION(S) REVIEWED</b>	<b>DOCUMENT DATE</b>
Original submission - 0000	12/23/2014
Amendment - 006	5/4/2015
Amendment - 009	7/21/2015
Amendment - 0012	7/30/2015

**Quality Review Team**

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>SECONDARY</b>	<b>BRANCH/DIVISION</b>
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Project/Business Process Manager	Steven Kinsley, Ph.D.	N/A	OPRO
Application Technical Lead	Ciby Abraham, Ph.D.	N/A	Branch II/ONDP

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## Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

2. RELATED/SUPPORTING DOCUMENTS:

A. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND 114045	

3. CONSULTS:

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

## Executive Summary

### The Executive Summary

#### I. Recommendations

##### A. Recommendation and Conclusion on Approvability

Based on the recommendation from the following disciplines, drug substance, process, microbiology, biopharmaceutics, facilities, and drug product, CMC recommends the approval of Vivlodex 5 mg and 10 mg capsules.

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

N/A

#### II. Summary of Chemistry Assessments

##### A. Description of the Product

###### *Drug Substance*

The drug substance, Meloxicam is manufactured by (b) (4) and is referenced in DMF# (b) (4) (adequate, last reviewed 6/2/2015). Meloxicam is a pale yellow (b) (4) with no chiral centers. The drug substance has a (b) (4) month retest period.

###### *Drug Product*

The drug product Vivlodex is manufactured by (b) (4). Vivlodex immediate release 5 mg and 10 mg capsules are manufactured from a (b) (4). Vivlodex capsules are stored in 100 cc round HDPE bottles with a 38 mm (b) (4) in 90-count bottles and 30-count bottles. Physician samples of Vivlodex capsules 5 mg and 10 mg will be provided in (b) (4) count blister (b) (4) in clear (b) (4) film with push through foil. Based on the stability data provided, an expiry of 24-months will be granted for the 5 mg and 10

mg capsules when stored in the 90-count and 30-count 100 cc HDPE bottles with the storage statement “Store at 25°C (77°F); excursions permitted between 15° and 30°C (59° and 86°F).” For the <sup>(b)</sup><sub>(4)</sub> count blister <sup>(b)</sup><sub>(4)</sub> 24-month expiry will be granted for the 5 mg and 10 mg capsules the storage statement “Store at 25°C (77°F); excursions permitted between 15° and 30°C (59° and 86°F) protected from moisture.”

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

Vivlodex 5 mg and 10 mg capsules are for the indication of management of osteoarthritis pain.

#### **C. Basis for Approvability or Not-Approval Recommendation**

The sponsor has provided adequate information to support the manufacturing and control of the drug substance, process, microbiology, biopharmaceutics, facilities, and drug product. The application is therefore recommended for approval.

**Executive Risk Assessment Summary**

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"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	L	-	N/A	-
Physical stability (API)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	L	-	N/A	-
Content uniformity	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	M	Appropriate in process controls are in place	Acceptable	-
Microbial Limits	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	L	-	-	-
Dissolution	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> <li>• Exclude major reformulations                             <ul style="list-style-type: none"> <li>• Alcohol dose dumping</li> </ul> </li> </ul>	L	-	-	-

\*Risk ranking applies to product attribute/CQA

\*\*For example, post marketing commitment, knowledge management post approval, etc.

### III. Administrative

#### A. Reviewer's Signature

Ciby J. Abraham  
-A

Digitally signed by Ciby J. Abraham -A  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,  
ou=People,  
0.9.2342.19200300.100.1.1=2000827346, cn=Ciby  
J. Abraham -A  
Date: 2015.09.18 19:32:15 -04'00'

Ciby J. Abraham, Ph.D.  
Quality Assessment Lead (Acting)  
Application Technical Lead  
ONDP/DIVII/Branch IV

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Note: additional reviewers can be added, as appropriate

## ASSESSMENT OF THE BIOPHARMACEUTICS

33. Are the in-vitro dissolution test and acceptance criteria adequate for assuring consistent bioavailability of the drug product?

The drug substance Meloxicam (BCS class II drug) has an increasing solubility from pH 5.0 to pH 6.8. The solubility at pH 6.1 is 0.0427 mg/mL, which is approximately four times of the dose strength. The Vivlodex Capsules are provided in 2 strengths, 5 mg and 10 mg. Both strengths are manufactured from a (b) (4) encapsulated in hard gelatin capsule shells. The two strengths are achieved by different fill weights in Size 1 and Size 2 capsules. The two dosage strength tablets are compositionally proportional and the formulation is a conventional immediate release formulation. The approval of the lower strength (5 mg) is based on the results of a dose-proportionally study (MEL1-12-04) reviewed by OCP. The to-be-marketed formulation is the same product used in the pivotal clinical studies. A manufacturing site change is being proposed from (b) (4)

### DISSOLUTION METHOD

The dissolution method and acceptance criterion are summarized in Table 1. The acceptance criterion was agreed upon with the Applicant on Aug 17, 2015 in their response to IR comments.

Table 1. Recommended Dissolution Method and Acceptance Criterion

<b>Apparatus</b>	USP Type I, basket
<b>Cannula</b>	Metal
<b>Stirring Speed</b>	100 rpm
<b>Medium</b>	pH 6.1 Phosphate buffer with 0.1% SLS
<b>Medium Volume</b>	500 mL for 5 mg capsules 1000 mL for 10 mg capsules
<b>Sampling Times</b>	5, 10, 20, 30 and 45 minutes
<b>Acceptance Criterion</b>	$Q \geq (b) (4) \%$ at 10 minutes
<b>Detection</b>	HPLC/UV, $\lambda=364$ nm

### Dissolution Method Development

The dissolution method was evaluated to determine the effect that varying dissolution parameters would have on the *in vitro* drug release (for more detail refer to Drug Product at [\cdsesub1\evsprod\NDA207233\0000\m3\32-body-data\32p-drug-prod\active\32p2-pharm-dev](#)). The following method parameters were evaluated.

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**Reviewer's Assessment:**

The Applicant conducted studies to determine the solubility of the drug substance, pH of the dissolution medium, basket rotation speed, SLS concentration in the dissolution medium, etc. Together with the originally proposed dissolution testing acceptance criterion (Q= <sup>(b)</sup><sub>(4)</sub>% at <sup>(b)</sup><sub>(4)</sub> mins), there are risks associated with the proposed method <sup>(b)</sup><sub>(4)</sub>. The potential risks can be mitigated with the tighter dissolution acceptance criterion (Q= <sup>(b)</sup><sub>(4)</sub>% at 10 mins), which was agreed upon with the Applicant on Aug 17, 2015 in their response to IR comments.

**DISSOLUTION METHOD DISCRIMINATING ABILITY**

(b) (4)

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**Reviewer's Assessment:**

The study results showed that the proposed dissolution method (b) (4)

(b) (4)

(b) (4). To increase the discriminating ability, the review team recommended a tighter dissolution acceptance criterion (e.g. NLT (b) (4)% (Q) of the labeled amount of drug is dissolved in 10 min) which was agreed upon with the Applicant (see section below). The proposed dissolution method is acceptable.

**DISSOLUTION METHOD ACCEPTANCE CRITERIA**

The originally proposed dissolution acceptance criterion was  $Q \geq \frac{(b)}{(4)}\%$  at (b) (4) minutes. However, based on the provided dissolution data, this proposed dissolution acceptance criteria (b) (4) as shown in Figure 7. The Applicant was requested during the review cycle to tighten the dissolution acceptance criterion to  $Q \geq \frac{(b)}{(4)}\%$  at 10 minutes. The Applicant agreed to change the specification for the dissolution method acceptance criterion (Response to IR comments dated 08/17/2015).

Figure 7. Dissolution profiles of primary stability, registration stability and clinical batches manufactured at different sites



**Reviewer's Assessment: DISSOLUTION METHOD ACCEPTANCE CRITERIA**

Based on the rapid dissolution nature of the drug substance (e.g. BCS class II) and dissolution data from primary stability, registration stability and clinical batches, the current dissolution acceptance criteria of  $Q \geq$  <sup>(b) (4)</sup> % at 10 minutes has been agreed upon with the Applicant (refer to submission dated 08/17/2015).

**IMPACT OF CROSSLINKING OF THE CAPSULE ON DISSOLUTION**

Meloxicam Capsules 5 mg in blister <sup>(b) (4)</sup> (Lot L0402782) failed dissolution acceptance criterion under accelerated stability conditions. During the review cycle, the Applicant was asked to provide data to demonstrate that the dissolution failure was not due to the change of drug substance solid state. In response to IR comments dated 07/21/2015, the Applicant conducted experiments and provided data demonstrating that the reduced dissolution rate was due to cross-linking of the hard gelatin capsule shells as shown in Table 8. The stressed capsule contents had normal dissolution profile. The 5 mg Stressed Vivlodex Capsules dissolved normally with the presence of Pancreatin in dissolution media.

**Table 8.** Stressed Vivlodex Capsules Cross-linking Results (Batch L0402782, Stored 6M at 40°C/75%RH)

Time (minutes)	Stressed Vivlodex Capsules 5 mg (as per method)	Stressed Vivlodex Capsules 5 mg 10 minute presoak with Pancreatin in Media	Stressed Capsule Contents
	Mean %Dissolved (n=6)	Mean %Dissolved (n=6)	Mean %Dissolved (n=6)
5	1.9	2.1	92.1
10	4.3	3.0	93.6
20	27.4	90.6	94.5
30	48.9	92.0	95.6
45	65.9	92.5	95.7
60	67.4	92.7	95.9

34. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

**Bridging Across Phases of Drug Product Development**

(b) (4)





**Reviewer's Assessment:**

Since there is no formulation change from clinical to commercial manufacturing, there is no need to bridge the clinical and the to-be-market formulations. The Applicant provided justification for not conducting evaluation of the two drug product manufacturing sites in lower and higher pH dissolution media. In this case, f2 similarity comparison is not applicable because of the rapid dissolution nature of the drug product. Dissolution profiles of the drug products manufactured at different sites are similar as shown in Figure 7.

**OVERALL ASSESSMENT AND SIGNATURES:  
BIOPHARMACEUTICS**

PRODUCT PROPERTY/ IMPACT OF CHANGE/ CQAS	Initial Risk Assessment	Comments	Updated Risk Ranking after Review Cycle	Comments on mitigation strategy
Dissolution	Medium	Medium risk. Risk Assessment based on the data/document submitted by the Applicant and reviewer's previous experience, it appears that the formulation of the drug product and its manufacturing process (b) (4) with respect to dissolution CQA. The possibility that there will be large batch to batch variability in dissolution that can potentially impact safety and efficacy is very low and will be a review issue. Initial risk assessment underestimated the risk in terms of dissolution	Low	At the pH of the dissolution medium, the drug substance has high solubility. The dissolution of the drug product is very rapid due to small particle size of drug substance. A tight dissolution specification of (C <sub>t</sub> ) <sub>(b) (4)</sub> % at 10mins) in place increases the discriminating ability of the dissolution method. Overall dissolution risk is low.

		<p>testing. Following a more thorough review of the data the initial risk assessment was increased to medium risk due to inability of the method to discriminate (b) (4) (b) (4)</p>		
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**Reviewer's Assessment and Signature:**

The Applicant conducted studies to determine the solubility of the drug substance, pH of the dissolution medium, basket rotation speed, SLS concentration in the dissolution medium, and impact of capsule on dissolution. The presence (b) (4) surfactant along with the originally proposed (b) (4) dissolution acceptance criterion (Q= (b) (4) % at (b) (4) minutes), rendered the method (b) (4). This (b) (4) dissolution acceptance criterion (Q= (b) (4) % at 10 minutes) agreed upon with the Applicant on 08/21/2015. The dissolution specifications (b) (4)

Specifically, the dissolution specifications will reject batches with particle size outside the desired particle size range ( (b) (4) is NMT (b) (4) and (b) (4) is NMT (b) (4) )

The Applicant provided dissolution data demonstrating the failure in dissolution for one of the stability batch (Lot L0402782) under accelerated conditions was due to the crosslinking of the capsule shell.

Since there is no formulation change from clinical to commercial manufacturing, there is no need to bridge the clinical and the to-be-market formulations. The Applicant provided data demonstrating the dissolution profiles from the two drug product manufacturing sites are similar.

NDA 207233 (Vivlodex™ Capsules) is **RECOMMENDED FOR APPROVAL** from a Biopharmaceutics perspective. The following dissolution specifications have been agreed upon with the Applicant:

<b>Apparatus</b>	USP Type I, basket
<b>Cannula</b>	Metal
<b>Stirring Speed</b>	100 rpm
<b>Medium</b>	pH 6.1 Phosphate buffer with 0.1% SLS

<b>Medium Volume</b>	500 mL for 5 mg capsules 1000 mL for 10 mg capsules
<b>Sampling Times</b>	5, 10, 20, 30 and 45 minutes
<b>Acceptance Criteria</b>	$Q \geq \frac{(b)}{(4)}\%$ at 10 minutes
<b>Detection</b>	HPLC/UV, $\lambda=364$ nm

**Ge Bai, Ph.D.**  
Biopharmaceutics Reviewer  
Office of New Drug Product  
Division of Biopharmaceutics

**Supervisor Comments and Concurrence:**

**Sandra Suarez**  
Biopharmaceutics Lead (acting)  
Office of New Drug Product  
Division of Biopharmaceutics

Note: additional reviewers can be added, as appropriate

## ASSESSMENT OF MICROBIOLOGY

35. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

**Reviewer's Assessment: Adequate**

Vivlodex (Meloxicam) Capsules, 5 mg and 10 mg are non-sterile. The finished drug product will meet microbial limits set by USP <1111>, USP <61>, and USP<62> at drug product release and for accelerated and long-term stability.

All stability data (accelerated and long-term stability) for 36 exhibit batches [3 batches per drug product strength (5 mg & 10 mg Meloxicam), for 3 container closure system configurations (30 count- bottle, 90 count-bottle, (b)(4) count-blister pack), for both accelerated and long-term stability] conformed to USP <1111>, USP <61>, and USP <62>, with (b)(4) cfu/g for both TYMC and TAMC and *E. coli* absent in (b)(4)g of drug product (for microbial studies on (b)(4) manufactured drug product see *Section 3.2.P.8.3, second file, pg 6-82*).

All stability data (accelerated and long-term stability) for the registration/exhibit batches conformed to USP <1111>, USP<61>, and USP<62>, with (b)(4) cfu/g for both TYMC and TAMC, and *E. coli* absent in (b)(4)g of drug product (for microbial studies on (b)(4) manufactured drug product, see *Section 3.2.P.8.3, fifth file, pg 5-82*).

Information provided is **adequate**.

**Information Request Responses:**

1. Although you have stated that you will conduct Microbiological Examination tests (USP <61> and <62>) as a part of your stability specifications, please confirm whether you will test all batches for microbial limits at release.

**First Cycle Firm's Response [05/04/2015 Amendment]: ... Iroko (b)(4) (b)(4) for microbial limits at release and proposes (b)(4) (b)(4) for microbial testing... All annual stability batches will include Microbiological Examination testing at release and during stability. ... (b)(4) is proposed because the (b)(4) (b)(4) inhibits microbial growth, the primary stability batches show no microbial growth on release and after 12 months of long term storage. Further information can be found in **Section 3.2.P.5.6.1.13 Microbiological Examination of Non-sterile Products (Annual Shelf-Life Testing)** ... Empty capsule shells and excipients are release tested for microbial growth prior to use in manufacturing. .. During validation of the USP microbiological examination methods ... it was found that the (b)(4) inhibited growth of bacteria, yeast and molds used in these tests (see **3.2.P.5.3 Validation of Analytical Procedures- Microbiological Examination**).**

Information provided is **adequate**.

**2.3.P.6 Reference Standards or Materials**

36. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

**Reviewer's Assessment: Adequate**

Microbial ingress for the container closure system is not applicable because this is a solid oral dosage form, having little possibility of microbial growth in the drug product. Information provided is adequate. For more information review the container closure section of this review.

**A APPENDICES****A.2 Adventitious Agents Safety Evaluation**

37. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

**Reviewer's Assessment: Adequate**

(b) (4)

38. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

**Reviewer's Assessment: Adequate**

See comment #37 above.

**OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY**

**Reviewer's Assessment and Signature:** The information provided is adequate.



**QUALITY ASSESSMENT**  
**A/NDA # XXXXXX**



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**Supervisor Comments and Concurrence:**

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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))**  
(Attach proposed text)

Item	Information Provided in NDA	Reviewer’s Assessment
<b>Product title, Drug name (201.57(a)(2))</b>		
Proprietary name and established name	Proprietary: Established Name:	
Dosage form, route of administration	Dosage: Route:	
Controlled drug substance symbol (if applicable)		
<b>Dosage Forms and Strengths (201.57(a)(8))</b>		
A concise summary of dosage forms and strengths		

**Conclusion:**

- (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		
Strengths: in metric system		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.		

**Conclusion:**

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

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name		
Dosage form and route of administration		
Active moiety expression of strength with equivalence statement for salt (if applicable)		
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.		
Statement of being sterile (if applicable)		
Pharmacological/ therapeutic class		
Chemical name, structural formula, molecular weight		
If radioactive, statement of important nuclear characteristics.		
Other important chemical or physical properties (such as pKa, solubility, or pH)		

**Conclusion:**

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

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form		
Available units (e.g., bottles of 100 tablets)		
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		
Special handling (e.g., protect from light, do not freeze)		
Storage conditions		

**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)		

**Conclusion:**

## 2. Labels

### 1) Immediate Container Label

(Attach the proposed container label here)

*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))		
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		
Net contents (21 CFR 201.51(a))		
Lot number per 21 CFR 201.18		
Expiration date per 21 CFR 201.17		
"Rx only" statement per 21 CFR 201.100(b)(1)		
Storage (not required)		
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		
Bar Code per 21 CFR 201.25(c)(2)**		
Name of manufacturer/distributor		
Others		

\*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:**

**2) Cartons**

**(Attach the proposed carton label here)**

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))		
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		
Net contents (21 CFR 201.51(a))		
Lot number per 21 CFR 201.18		
Expiration date per 21 CFR 201.17		
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables][ 201.10(a), 21CFR201.100(b)(5)(iii)]		
Sterility Information (if applicable)		
"Rx only" statement per 21 CFR 201.100(b)(1)		
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)		
Bar Code per 21 CFR 201.25(c)(2)**		
Name of manufacturer/distributor		
"See package insert for dosage information" (21 CFR 201.55)		
"Keep out of reach of children" (optional for Rx, required for OTC)		
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))		

**Conclusion:**

## II. List of Deficiencies To Be Communicated

- A. Drug Substance
- B. Drug Product
- C. **Process**/Facility

1. In DMF 28483 and your application you demonstrate that the process

(b) (4)

(b) (4)



- D. Biopharmaceutics
- E. Microbiology
- F. Label/Labeling

### III. Attachments

#### A. Facility

OVERALL RECOMMENDATION:				
DRUG SUBSTANCE				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
DRUG PRODUCT				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION

#### B. Lifecycle Knowledge Management

##### a) Drug Substance

From Initial Risk Identification			Review Assessment		
Attribute/CQA	Initial Risk Ranking*	Justification	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments**
	H, M, or L			Acceptable or Not Acceptable	

##### b) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments**
		H, M, or L		Acceptable or Not Acceptable	

\*Risk ranking applies to product attribute/CQA

\*\*For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

#### **IV. Administrative**

##### **A. Reviewer's Signature**

##### **B. Endorsement Block**

Reviewer Name/Date: [*Same date as draft review*]

Secondary Reviewer Name/Date:

Project Manager Name/Date:



## QUALITY REVIEW



### Signature

On behalf of the following disciplines, drug substance, process, microbiology, biopharmaceutics, facilities, and drug product, CMC recommends approval.

**Ciby J.  
Abraham -A**

Digitally signed by Ciby J. Abraham -A  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=20008273  
46, cn=Ciby J. Abraham -A  
Date: 2015.10.22 15:20:00 -04'00'

---

Ciby J. Abraham, Ph.D.  
Quality Assessment Lead (Acting)  
Application Technical Lead  
ONDP/DIVII/Branch IV



**NDA 207233**

**Vivlodex™ ( Meloxicam) Capsules**

**Iroko Properties Inc.**

**Venkateswara R. Pavuluri, Ph.D., R. Ph.,  
Office of New Drug Products, Division II**

**Division of Anesthesia, Analgesia and Addiction  
Products**



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## Chemistry Review Data Sheet

**Chemistry Review Sheet**1. NDA #: **207233**

2. REVIEW #: 2

3. REVIEW DATE: October 2, 2015

4. REVIEWER: Venkateswara R. Pavuluri, Ph.D., R. Ph.

5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date**Primary Quality Review** (Assessment of Drug product) **09-18-2015**

6. SUBMISSIONS BEING REVIEWED:

Submission(s) ReviewedDocument Date

Response to Request for Information

09-24-2015

7. NAME AND ADDRESS OF APPLICANT:

Name: Iroko Properties Inc.

Address: Waterfront Drive, PO Box 3469,  
Road Town, Tortola States British Virgin Islands, VG1110

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Vivlodex™ (Meloxicam) Capsules

b) Non-Proprietary Name: Meloxicam capsules.

9. LEGAL BASIS FOR SUBMISSION: FD&amp;C ACT 505(b)(2)

10. PHARMACOLOGICAL CATEGORY:

Management of osteoarthritis pain

11. DOSAGE FORM: Oral Capsules

12. STRENGTH/POTENCY: Two Strengths; 5 mg and 10 mg

13. ROUTE OF ADMINISTRATION: Orally

14. Rx/OTC DISPENSED:  Rx  OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

## Chemistry Review Data Sheet

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

A. Meloxicam

**Chemical name:**

4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide

17. RELATED/SUPPORTED DOCUMENTS:

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Quality information Amendment 0019	207233	1.14.1.1 Draft Carton and Container Labels

18. Status

**ONDP: N/A**

## Review of Labeling Changes

**CHEMISTRY ASSESSMENT (Review of the IR Responses Dt. Sept 24, 2015)****Review Of Common Technical Document-Quality (eCTD-Q) Module 1.14.1: Draft labeling**

**Note:** Information request sent on September 23, 2015 where the following labeling changes for Physician samples was suggested to the sponsor.

**Agency Request**

*Provide revised labeling text for the Physician sample packaging components (Blister and Carton) to contain the following text: "Store at 25°C (77°F); excursions permitted to 15°C - 30°C (59°F-86°F). Protect from moisture."*

**Iroko's Response**

Iroko has revised the proposed Physician sample packaging components (Blister and Carton) to contain labeling text in accordance with your request:

"Store at 25°C (77°F); excursions permitted to 15°C -30°C (59°F-86°F). Protect from moisture."

In addition, Iroko has also revised the Physician Sample Box Holder Cartons to contain the requested labeling text.

*Start of Sponsor Material*

Revised Text for 5 mg Box Holder Physician Sample

(b) (4)

## Review of Labeling Changes

5 mg Carton Physician Sample

(b) (4)



5 mg 1 cc Blister Physician Sample

(b) (4)

*End of Sponsor Material*

**Reviewer Evaluation:** Adequate, revised labeling text for storage conditions of Physician samples (Blister, Carton and Box holder) is in line with the proposed labeling text for commercial packaging of the drug product. The product is approvable from Drug product CMC perspective.

## Review of Labeling Changes

Venkateswara R. Pavuluri -A  
(Affiliate)

Digitally signed by Venkateswara R. Pavuluri -A (Affiliate)  
DN: c=US, o=U.S. Government, ou=HHS, ou=NIH, ou=People,  
0.9.2342.19200300.100.1.1=0011799946, cn=Venkateswara R. Pavuluri -A (Affiliate)  
Date: 2015.10.15 15:05:43 -04'00'

Ciby J.  
Abraham -A

Digitally signed by Ciby J. Abraham -A  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=20008273  
46, cn=Ciby J. Abraham -A  
Date: 2015.10.16 14:34:27 -04'00'

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

**Application #:** 207233      **Submission Type:** NDA 505b(2)      **Established/Proper Name:**  
 Vivlodex™ Capsules

**Applicant:** Iroko

Proprties Inc.

**Letter Date:** 12/23/2014

**Dosage Form:** Capsules

**Chemical Type:** Non-NME

**Stamp Date:** 12/23/2014

**Strength:** 10 (b)(4)

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	<b>DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?</b>	x		CMC: Yes Biopharmaceutics: Yes
2.	If the application is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			
3.	Are there any <b>potential review</b> issues to be forwarded to the Applicant, not including any filing comments stated above?	x		Refer to page 19 for comments to be conveyed to the applicant as part of the 74-day letter.

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

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
17.	Biosimilar product <sup>1</sup>	<input type="checkbox"/>	x	
18.	Combination Product _____	<input type="checkbox"/>	x	
19.	Other _____	<input type="checkbox"/>	x	

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

Regulatory Considerations				
20.	USAN Name Assigned	x	<input type="checkbox"/>	
21.	End of Phase II/Pre-NDA Agreements	x	<input type="checkbox"/>	Agreements met
22.	SPOTS (Special Products On-line Tracking System)	<input type="checkbox"/>	x	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application	<input type="checkbox"/>	x	
24.	Comparability Protocol(s) <sup>2</sup>	<input type="checkbox"/>	x	Not given
25.	Other _____	<input type="checkbox"/>	<input type="checkbox"/>	
Quality Considerations				
26.	Drug Substance Overage	<input type="checkbox"/>	x	
27.	Design Space	Formulation	<input type="checkbox"/>	x
28.		Process	<input type="checkbox"/>	x
29.		Analytical Methods	<input type="checkbox"/>	x
30.		Other	<input type="checkbox"/>	x
31.	Real Time Release Testing (RTRT)	<input type="checkbox"/>	x	
32.	Parametric Release in lieu of Sterility Testing	<input type="checkbox"/>	x	
33.	Alternative Microbiological Test Methods	<input type="checkbox"/>	x	
34.	Process Analytical Technology <sup>1</sup>	<input type="checkbox"/>	x	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	<input type="checkbox"/>	x
36.		Excipients	<input type="checkbox"/>	x
37.		Microbial	<input type="checkbox"/>	x
38.	Unique analytical methodology <sup>1</sup>	<input type="checkbox"/>	x	
39.	Excipients of Human or Animal Origin	x		Lactose monohydrate NF and hard gelatin capsules shells are excipients (b) (4) - (b) (4)
40.	Novel Excipients	<input type="checkbox"/>	x	
41.	Nanomaterials <sup>1</sup>	<input type="checkbox"/>	x	
42.	Hold Times Exceeding 30 Days	<input type="checkbox"/>	x	
43.	Genotoxic Impurities or Structural Alerts	x		Structural alert (b) (4)
44.	Continuous Manufacturing	<input type="checkbox"/>	x	
45.	Other unique manufacturing process <sup>1</sup>	<input type="checkbox"/>	x	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).	<input type="checkbox"/>	x	
47.	New delivery system or dosage form <sup>1</sup>	<input type="checkbox"/>	x	
48.	Novel BE study designs	<input type="checkbox"/>	x	
49.	New product design <sup>1</sup>	<input type="checkbox"/>	x	
50.	Other _____ SoluMatrix Fine Particle Technology _____	x	<input type="checkbox"/>	The SoluMatrix Fine Particle Technology produces a smaller submicron diameter of meloxicam particles compared to the (b) (4) drug substance found in commercial products. The sponsor will use 33% less of the drug substance in their product compared to commercial products.

<sup>1</sup>Contact Office of Testing and Research for review team considerations

<sup>2</sup>Contact Post Marketing Assessment staff for review team considerations

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
<b>GENERAL/ADMINISTRATIVE</b>					
1.	Has an environmental assessment report or categorical exclusion been provided?	x	<input type="checkbox"/>	<input type="checkbox"/>	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? <input type="checkbox"/> Drug Substance <input type="checkbox"/> Drug Product <input type="checkbox"/> Appendices <ul style="list-style-type: none"> <li><input type="checkbox"/> Facilities and Equipment</li> <li><input type="checkbox"/> Adventitious Agents Safety Evaluation</li> <li><input type="checkbox"/> Novel Excipients</li> </ul> <input type="checkbox"/> Regional Information <ul style="list-style-type: none"> <li><input type="checkbox"/> Executed Batch Records</li> <li><input type="checkbox"/> Method Validation Package</li> <li><input type="checkbox"/> Comparability Protocols</li> </ul>	x	<input type="checkbox"/>	<input type="checkbox"/>	
<b>FACILITY INFORMATION</b>					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: <input type="checkbox"/> Name of facility, <input type="checkbox"/> Full address of facility including street, city, state, country <input type="checkbox"/> FEI number for facility (if previously registered with FDA) <input type="checkbox"/> Full name and title, telephone, fax number and email for on-site contact person. <input type="checkbox"/> Is the manufacturing responsibility and function identified for each facility, and <input type="checkbox"/> DMF number (if applicable)	x	<input type="checkbox"/>	<input type="checkbox"/>	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: <input type="checkbox"/> Is a manufacturing schedule provided? <input type="checkbox"/> Is the schedule feasible to conduct an inspection within the review cycle?	x	<input type="checkbox"/>	<input type="checkbox"/>	
<b>DRUG SUBSTANCE INFORMATION</b>					

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

C. FILING CONSIDERATIONS					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	x	<input type="checkbox"/>	<input type="checkbox"/>	
6.	<p>Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> general information</li> <li><input type="checkbox"/> manufacture                             <ul style="list-style-type: none"> <li>○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)</li> <li>○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only</li> <li>○ Includes complete description of product lots and their uses during development – BLA only</li> </ul> </li> <li><input type="checkbox"/> characterization of drug substance</li> <li><input type="checkbox"/> control of drug substance                             <ul style="list-style-type: none"> <li>○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred)</li> <li>○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only</li> </ul> </li> <li><input type="checkbox"/> reference standards or materials</li> <li><input type="checkbox"/> container closure system</li> <li><input type="checkbox"/> stability                             <ul style="list-style-type: none"> <li>○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment</li> </ul> </li> </ul>	x	<input type="checkbox"/>	<input type="checkbox"/>	
DRUG PRODUCT INFORMATION					
7.	<p>Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> Description and Composition of the Drug Product</li> <li><input type="checkbox"/> Pharmaceutical Development                             <ul style="list-style-type: none"> <li>○ Includes descriptions of changes in the manufacturing process from material used</li> </ul> </li> </ul>	x	<input type="checkbox"/>	<input type="checkbox"/>	Pharmaceutical Development – DMF 028483

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

### C. FILING CONSIDERATIONS

	<p>in clinical to commercial production lots</p> <ul style="list-style-type: none"> <li>○ Includes complete description of product lots and their uses during development</li> </ul> <p><input type="checkbox"/> Manufacture</p> <ul style="list-style-type: none"> <li>○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter?</li> </ul> <p><input type="checkbox"/> Control of Excipients</p> <p><input type="checkbox"/> Control of Drug Product</p> <ul style="list-style-type: none"> <li>○ Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)</li> <li>○ Includes data to demonstrate process consistency (i.e. data on process validation lots)</li> <li>○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred)</li> <li>○ Analytical validation package for release test procedures, including dissolution</li> </ul> <p><input type="checkbox"/> Reference Standards or Materials</p> <p><input type="checkbox"/> Container Closure System</p> <ul style="list-style-type: none"> <li>○ Include data outlined in container closure guidance document</li> </ul> <p><input type="checkbox"/> Stability</p> <ul style="list-style-type: none"> <li>○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment</li> </ul> <p><input type="checkbox"/> APPENDICES</p> <p><input type="checkbox"/> REGIONAL INFORMATION</p>				
--	--	--	--	--	--

### BIOPHARMACEUTICS

8.	<p>Does the application contain dissolution data?</p> <ul style="list-style-type: none"> <li>• Is the dissolution test part of the DP specifications?</li> <li>• Does the application contain the dissolution method development report including data supporting the discriminating ability?</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<p>Yes. Dissolution test is part of the DP specification. The proposed dissolution method is as follows:</p> <table border="1" style="width: 100%; border-collapse: collapse; font-size: small;"> <thead> <tr> <th style="text-align: left;">Dissolution apparatus</th> <th style="text-align: left;">USP Type I baskets</th> </tr> </thead> <tbody> <tr> <td>Canula</td> <td>Metal</td> </tr> <tr> <td>Dissolution medium</td> <td>pH 6.1 Phosphate buffer with 0.1% SLS</td> </tr> <tr> <td>Medium temperature</td> <td>37±0.5°C</td> </tr> <tr> <td>Volume</td> <td>500 mL for 5 mg capsules 1000 mL for 10 mg capsules</td> </tr> <tr> <td>Stirring speed</td> <td>100 RPM</td> </tr> <tr> <td>Sampling time</td> <td>5, 10, 20, 30 and 45 minutes</td> </tr> <tr> <td>Timer</td> <td>Calibrated timer</td> </tr> </tbody> </table> <p><a href="#">\\CDSESUB1\evsprod\NDA207233\0000\m3\32-body-data\32p-drug-prod\active\32p5-contr-drug-prod\32p52-analyt-proc</a> Page 2 in the file "32p52-</p>	Dissolution apparatus	USP Type I baskets	Canula	Metal	Dissolution medium	pH 6.1 Phosphate buffer with 0.1% SLS	Medium temperature	37±0.5°C	Volume	500 mL for 5 mg capsules 1000 mL for 10 mg capsules	Stirring speed	100 RPM	Sampling time	5, 10, 20, 30 and 45 minutes	Timer	Calibrated timer
Dissolution apparatus	USP Type I baskets																				
Canula	Metal																				
Dissolution medium	pH 6.1 Phosphate buffer with 0.1% SLS																				
Medium temperature	37±0.5°C																				
Volume	500 mL for 5 mg capsules 1000 mL for 10 mg capsules																				
Stirring speed	100 RPM																				
Sampling time	5, 10, 20, 30 and 45 minutes																				
Timer	Calibrated timer																				

Best Available Copy

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

C. FILING CONSIDERATIONS					
					dissolution- (b) (4).  The submitted Dissolution Method Characterization Report contains data supporting the discriminating ability for (b) (4) and change in critical process parameters. <a href="#">\\CDSESUB1\evsprod\NDA207233\0000\m3\32-body-data\32p-drug-prod\active\32p2-pharm-dev</a> Page 32 in the file "pharmaceutical-development".
9.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Yes. The application contains the complete BE data. (5.3.1.2)  Yes. The PK files are in the correct format. (5.3.1.2)  The BA/BE data will be reviewed by OCP.
10.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	The to-be-marketed product is the same product used in the pivotal clinical studies. There is a manufacturing site change. Dissolution data are being requested to support this change.
11.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	A dose-proportionally study was conducted in support of the lower strength.
12.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	<input type="checkbox"/>	x	<input type="checkbox"/>	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	x	<input type="checkbox"/>	<input type="checkbox"/>	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> <li><input type="checkbox"/> manufacturing flow; adjacent areas</li> <li><input type="checkbox"/> other products in facility</li> <li><input type="checkbox"/> equipment dedication, preparation, sterilization and storage</li> </ul>	<input type="checkbox"/>	<input type="checkbox"/>	x	



# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

	<ul style="list-style-type: none"> <li>parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>					
Microbial Limits	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	1	2	3	(low)	(b) (4)
Dissolution	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> <li>• Exclude major reformulations</li> <li>• Alcohol dose dumping</li> </ul>	2	2	4	16 (low)	<p>Low risk. Risk Assessment based on the data/document submitted by the Applicant and reviewer's previous experience, it appears that the formulation of the drug product and its manufacturing process (b) (4) with respect to dissolution CQA. Current score of 4 for detectability is based on that fact that the sponsor did not provide data showing the current dissolution method has a good discriminating ability on the variation of the properties of</p>

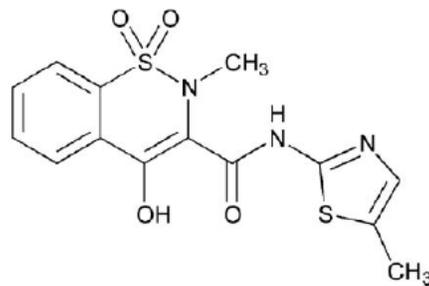
**OFFICE OF PHARMACEUTICAL QUALITY  
FILING REVIEW**

						The possibility that there will be large batch to batch variability in dissolution that can potentially impact safety and efficacy is very low and will be a review issue.
--	--	--	--	--	--	--

**CMC:**

**Drug Substance**

**Structure**



**Molecular Formula:** C<sub>14</sub>H<sub>13</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub>

**Molecular Weight:** 351.4 g/mole

**Genotoxic Impurity**



The drug substance Meloxicam is manufactured and supplied by (b) (4). The full details of the synthesis and manufacturing process can be found in DMF (b) (4) which was last reviewed on April 2012 and was found adequate. The specifications for release is in accordance to the USP monograph. The batch analysis of five lots are shown below and all test results are within specification. The shelf life and retest period for the meloxicam is (b) (4)

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

(b) (4) (b) (4) is a genotoxic impurity and will be addressed by the Pharmacology/toxicology group.

**Table 2.3.S.4-3 Batch Analysis Results for Meloxicam Lots Used to Manufacture Clinical Supply, Primary Stability Batches and Registration Batches**

Cadila Lot Number		MEA1ALR48A	MEA1AMR10A	MEA1AMR11A	MEA9ANR05A	MEA9ANR06A
Test	Acceptance Criteria	Results				
Description	A pale yellow (b) (4)	A pale yellow (b) (4)	A pale yellow (b) (4)	A pale yellow (b) (4)	A pale yellow (b) (4)	A pale yellow (b) (4)
Identification by FT-IR	The infrared absorption spectrum of the test substance is concordant with the working standard spectrum of meloxicam	Complies	Complies	Complies	Complies	Complies
Identification by UV	The UV absorption spectrum of a 0.001% w/v solution of test sample in methanol should exhibit maxima at the same wavelength and the same intensity as the meloxicam standard (b) (4)	Complies	Complies	Complies	Complies	Complies
(b) (4)	(b) (4)	Complies	Complies	Complies	Complies	Complies
Solubility	Soluble in dimethylformamide; slightly soluble in acetone; very slightly soluble in methanol and in alcohol; practically insoluble in water (b) (4)	Complies	Complies	Complies	Complies	Complies
Clarity of solution	(b) (4)	(b) (4)				
Assay by HPLC (%w/w) (b) (4)	NLT (b) (4)% and NMT (b) (4)%	(b) (4)				
Related Compounds by HPLC:	--	--	--	--	--	--
Meloxicam related (b) (4)	NMT (b) (4)%	<LOQ	ND	ND	ND	ND

# OFFICE OF PHARMACEUTICAL QUALITY

## FILING REVIEW

**Table 2.3.S.4-3 Batch Analysis Results for Meloxicam Lots Used to Manufacture Clinical Supply, Primary Stability Batches and Registration Batches**

	(b) (4) Lot Number	MEA1ALR48A	MEA1AMR10A	MEA1AMR11A	MEA9ANR05A	MEA9ANR06A
(b) (4)	NMT (b) (4) %	(b) (4)				
Individual unknown impurities	NMT (b) (4) %	<LOQ	ND	ND	ND	ND
Total impurities	NMT (b) (4) %	(b) (4)			BQL	ND
Residual solvents by HS-GC	(b) (4) NMT (b) (4) ppm	(b) (4)			ND	ND
	(b) (4) NMT (b) (4) ppm	(b) (4)			(b) (4)	
	(b) (4) NMT (b) (4) ppm	ND	ND	ND	(b) (4)	
Residual solvents by GC	(b) (4) NMT (b) (4) ppm	ND	ND	ND	ND	ND
	DMF: NMT (b) (4) ppm	ND	ND	ND	(b) (4)	
Assay by (b) (4)	NLT (b) (4) % and NMT (b) (4) % w/w	(b) (4)				
Loss on drying at (b) (4)	NMT (b) (4) %	(b) (4)				
Residue on ignition (%w/w)	NMT (b) (4) %	(b) (4)				
Heavy metals	NMT (b) (4) ppm	(b) (4)				

Abbreviations: FT-IR = Fourier Transform Infrared; UV = Ultraviolet; NLT = Not Less Than; NMT = Not More Than; %w/w = % weight/weight; Meloxicam related (b) (4) HS-GC = Head Space Gas Chromatography; GC = Gas Chromatography; ND = Not Detected; ppm = parts per million; LOQ = limit of quantitation; BQL = Below Quantitation Limit  
 \*Acceptance criteria available at the time of release testing.

### Facilities

### Drug Substance

**Table 2.3.S.2-1 List of Meloxicam Manufacturer and Testing Sites**

Manufacturer and Testing Sites	Responsibilities
(b) (4)	<ul style="list-style-type: none"> <li>Drug substance manufacturing</li> <li>Drug substance packaging</li> <li>Drug substance release to Iroko</li> <li>Drug substance stability testing</li> </ul>
(b) (4)	<ul style="list-style-type: none"> <li>Drug substance release<sup>a</sup> for manufacturing</li> </ul>
(b) (4)	<ul style="list-style-type: none"> <li>Drug substance release<sup>a</sup> for manufacturing</li> </ul>

<sup>a</sup> Minimum release testing: ID testing and vendor certificate of analysis

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*Drug Product*

**Table 2.3.P.3-1 Vivlodex Capsules List of Manufacturers**

Manufacturers	Responsibilities
(b) (4)	<ul style="list-style-type: none"><li>• Release of excipients and drug substance</li><li>• Manufacture drug product</li><li>• Drug Product in-process testing and controls</li><li>• Release testing of drug product</li><li>• Store and perform stability testing</li></ul> <hr/> <ul style="list-style-type: none"><li>• Release of excipients and drug substance</li><li>• Manufacture drug product</li><li>• Drug Product in-process testing and controls</li><li>• Release testing of drug product</li><li>• Store and perform stability testing</li><li>• Packaging and labeling of drug product</li><li>• Control of packaging container closure components</li></ul>

*Process*

The commercial manufacturing process for Vivlodex™ Capsules consists of (b) (4) identified in 3.2.P.3.3 Description of Manufacturing Process and Process Controls: (b) (4)

(b) (4)

(b) (4)

(b) (4)

The sponsor will use SoluMatrix Fine Particle Technology (b) (4)

(b) (4)

(b) (4)

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excipients (b) (4) Stability: 24 month proposed expiration 25°C (77°F) with excursions permitted to 15°C -30°C (59°F-86°F).

**Table 2.3.P.1-1 Composition of Vivlodex Capsules 5 mg**

Component	Amount per capsule (mg/capsule weight)	Function	Quality Standard
Meloxicam	5.00	Active pharmaceutical ingredient	USP
Lactose monohydrate	(b) (4)	(b) (4)	NF
Sodium lauryl sulfate	(b) (4)	(b) (4)	NF
Microcrystalline cellulose	(b) (4)	(b) (4)	NF
Croscarmellose sodium	(b) (4)	(b) (4)	NF
Sodium stearyl fumarate	(b) (4)	(b) (4)	NF
Total capsule fill weight	125.0	--	--
Size 2 capsule with light pink body with "IP-205" imprinted in white ink and a dark blue cap with "5 mg" imprinted in white ink containing a yellow to pale yellow (b) (4)	1 capsule	Capsule shell	(b) (4)

**Table 2.3.P.1-2 Composition of Vivlodex Capsules 10 mg**

Component	Amount per capsule (mg/capsule weight)	Function	Quality Standard
Meloxicam	10.00	Active pharmaceutical ingredient	USP
Lactose monohydrate	(b) (4)	(b) (4)	NF
Sodium lauryl sulfate	(b) (4)	(b) (4)	NF
Microcrystalline cellulose	(b) (4)	(b) (4)	NF
Croscarmellose sodium	(b) (4)	(b) (4)	NF
Sodium stearyl fumarate	(b) (4)	(b) (4)	NF
Total capsule fill weight	250.0	--	--
Size 1 capsule with pink body with "IP-206" imprinted in white ink and a dark blue cap with "10 mg" imprinted in white ink containing a yellow to pale yellow (b) (4)	1 capsule	Capsule shell	(b) (4)

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**Table 2.3.P.5-9 Batch Analysis Results for the Primary Stability Batches**

Batch Number		L0402782	L0402783	L0402784	L0402785	L0402786	L0402787
Strength		5 mg	5 mg	5 mg	10 mg	10 mg	10 mg
Manufacturing Site		(b) (4)					
Manufacturing Date							
Theoretical Batch Size (capsules)							
Test	Acceptance Criteria <sup>a</sup>	Results					
Appearance	5 mg capsule: Size 2 opaque capsule with dark blue body and one white bar and a light pink cap with one white bar containing a yellow to pale yellow (b) (4)	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
	10 mg capsule: Size 1 opaque capsule with dark blue body and one white bar and a pink cap with one white bar containing a yellow to pale yellow (b) (4)	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Identification by HPLC (retention time)	The HPLC retention time of the main peak in the sample chromatogram is within 0.5 minutes of the retention time of the main peak in the reference standard chromatogram	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Identification by HPLC (UV spectrum)	The sample spectrum must be visually consistent in all essential detail to the standard spectrum	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Assay by HPLC (% label claim)	(b) (4) %	(b) (4)					
Individual known impurity (b) (4)	Report results	ND	ND	ND	ND	ND	ND
Individual unknown impurities	Report results	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
Total impurities	NMT (b) (4) %	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ

**Table 2.3.P.5-9 Batch Analysis Results for the Primary Stability Batches**

(b) (4)

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**Table 2.3.P.5-9 Batch Analysis Results for the Primary Stability Batches**

(b) (4)

***Review Issues Identified:***

- *None.*

**BIOPHARMACEUTICS ASSESSMENT**

**SUMMARY OF BIOPHARMACEUTICS FINDINGS**

***Submission:***

Vivlodex™ (meloxicam) Capsules 5 mg and 10 mg were developed by Iroko Properties Inc. to be bioequivalent to Mabie® Tablets 7.5 mg and 15 mg (NDA020938), manufactured by Boehringer Ingelheim. Mobic® (meloxicam) was developed for the management of osteoarthritis (OA) pain. Vivlodex™ was developed based on the proprietary SoluMatrix Fine Particle Technology™ that significantly reduces drug particle size, promoting enhanced dissolution and absorption of meloxicam to provide efficacious treatment at lower doses than the current for Mobic® (meloxicam) along with potential improved safety profile.

Iroko Properties Inc, conducted several clinical studies and provided study reports with data in this submission. Among these clinical studies, the most relevant two studies are likely to be MEL1-12-04 (Phase I PK pivotal study) and MEL3-12-02 (Phase III efficacy and safety pivotal study). According to the Applicant, results from study MEL1-12-04 show that Vivlodex™ (meloxicam) Capsules 10 mg have similar bioavailability compared to the reference drug product, Mabie® Tablet, 15 mg with 50% shorter  $t_{max}$ . Also, Vivlodex™ (meloxicam) Capsules 5 mg and 10 mg appeared to be dose proportional. According to the Applicant, results from study MEL3-12-02 show Vivlodex™ (meloxicam) Capsules 5 mg and 10 mg have similar efficacy and potentially better safety compared to the reference drug product.

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**Product's Description:** The product, Vivlodex™ (meloxicam) Capsules 5 mg and 10 mg were developed as an immediate release dosage form (b)(4) encapsulation process. The particle size of drug substance is well controlled to be the sub-micron. This enhances the solubility and adsorption of the drug substance. Data from ongoing long term stability study shows that drug product is (b)(4). Statistical model predicts longer than 24 months shelf life. There are two drug product manufacturing sites and both of them conduct dissolution testing. Data will be requested to support the bridging between these two sites.

### **Review Issues Identified:**

- None.

### **Biopharmaceutics Comments for 74-Day Letter:**

1. We acknowledge the data submitted demonstrating that the current dissolution method has the discriminating ability to identify for changes in drug substance particle size. We also acknowledge that the current dissolution method (b)(4)  
(b)(4)
2. Provide individual and mean dissolution values in tabular and graphical form from all pivotal clinical batches used in setting the dissolution acceptance criterion.
3. Provide dissolution profile comparisons with  $f_2$  testing in three different media between the following two drug product manufacturing sites: (b)(4)  
(b)(4)

### **CMC Comments for 74-Day Letter:**

4. Clarify if the acceptance criteria for Meloxicam related (b)(4) is NMT (b)(4)% for the shelf-life specification for Vivlodex capsules 5 mg or (b)(4)% as indicated in the release specification for Vivlodex capsules 5 mg.
5. Add microbial testing to your release specifications for the Vivlodex 5 mg and 10 mg capsules.

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**Ge Bai -S**

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