

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207233Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 207233

HFD # 170

Trade Name: Vivlodex Capsules

Generic Name: meloxicam

Applicant Name: Iroko Pharmaceuticals LLC

Approval Date, If Known: October 22, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(2)

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

YES NO

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

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

It is not a supplement, it is an original NDA

d) Did the applicant request exclusivity?

YES NO

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

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3 years

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

YES

NO

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

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

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

YES

NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES

NO

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

NDA# 021530 Mobic (meloxicam) Oral Suspension

NDA# 020938 Mobic (meloxicam) Tablets

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

Study MEL3-12-02

Study MEL3-12-03

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a

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similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study MEL3-12-02

Study MEL3-12-03

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 114045
YES ! NO
! Explain:

Investigation #2
IND # 114045
YES ! NO
! Explain:

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

Investigation #1
YES ! NO
Explain: ! Explain:

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Investigation #2

YES
Explain:

!
!
! NO
! Explain:

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

YES NO

If yes, explain:

=====

Name of person completing form: Allison Meyer
Title: Regulatory Health Project Manager
Date: October 22, 2015

Name of Office/Division Director signing form: Ellen Fields, MD, Deputy Director
Title: Deputy Director, HFD-170

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

ALLISON MEYER
10/22/2015

ELLEN W FIELDS
10/22/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 207233 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Vivlodex Established/Proper Name: meloxicam Dosage Form: Capsules		Applicant: Iroko Pharmaceuticals LLC Agent for Applicant (if applicable):
RPM: Allison Meyer		Division: DAAAP
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: _____</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>October 23, 2015</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only): 3
 (*confirm chemical classification at time of approval*)

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

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

- | | |
|---|--|
| NDAs: Subpart H | BLAs: Subpart E |
| <input type="checkbox"/> Accelerated approval (21 CFR 314.510) | <input type="checkbox"/> Accelerated approval (21 CFR 601.41) |
| <input type="checkbox"/> Restricted distribution (21 CFR 314.520) | <input type="checkbox"/> Restricted distribution (21 CFR 601.42) |
| Subpart I | Subpart H |
| <input type="checkbox"/> Approval based on animal studies | <input type="checkbox"/> Approval based on animal studies |

- | | |
|---|---|
| <input type="checkbox"/> Submitted in response to a PMR | REMS: <input type="checkbox"/> MedGuide |
| <input type="checkbox"/> Submitted in response to a PMC | <input type="checkbox"/> Communication Plan |
| <input type="checkbox"/> Submitted in response to a Pediatric Written Request | <input type="checkbox"/> ETASU |
| | <input checked="" type="checkbox"/> MedGuide w/o REMS |
| | <input type="checkbox"/> REMS not required |

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP 10/22/15
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 	1/30/15 1/30/15
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: <input type="checkbox"/> None 5/13/15 DMEPA: <input type="checkbox"/> None 8/19/15, 5/28/15 DMPP/PLT (DRISK): <input type="checkbox"/> None 10/13/15 OPDP: <input type="checkbox"/> None 10/8/15 SEALD: <input type="checkbox"/> None CSS: <input type="checkbox"/> None Product Quality <input type="checkbox"/> None Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	2/25/15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) 10/22/15
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>7/8/15</u> If PeRC review not necessary, explain: _____ 	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	10/21/15, 8/26/15, 8/14/15, 8/11/15, 8/4/15, 7/20/15, 7/14/15, 6/5/15, 6/3/15, 5/29/15, 4/23/15, 4/11/15 3/11/15, 3/3/15, 1/20/15, 1/9/15
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 7/22/14
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 11/13/12
<ul style="list-style-type: none"> Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/22/15
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical	
❖ Clinical Reviews	

<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	9/17/15, 2/4/15
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>) 	9/17/15
<ul style="list-style-type: none"> ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> ❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>) 	<input type="checkbox"/> None requested 8/21/15
Clinical Microbiology <input checked="" type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> No separate review
<ul style="list-style-type: none"> Clinical Microbiology Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Statistical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Statistical Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 10/21/15, 1/21/15
Clinical Pharmacology <input type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> Clinical Pharmacology review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 8/31/15, 1/26/15
<ul style="list-style-type: none"> ❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>) 	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Pharmacology/Toxicology Discipline Reviews 	
<ul style="list-style-type: none"> <ul style="list-style-type: none"> ADP/T Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Supervisory Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <ul style="list-style-type: none"> Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 8/31/15, 2/9/15
<ul style="list-style-type: none"> ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No carc
<ul style="list-style-type: none"> ❖ ECAC/CAC report/memo of meeting 	<input checked="" type="checkbox"/> None Included in P/T review, page
<ul style="list-style-type: none"> ❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>) 	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/16/15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	10/16/15
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

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

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/s/

ALLISON MEYER
10/26/2015

Meyer, Allison

From: Paul Kirsch <pkirsch@iroko.com>
Sent: Wednesday, October 21, 2015 6:56 PM
To: Meyer, Allison
Subject: RE: vivlodex package insert
Attachments: VIVLODEX Labeling Response to DAAAP 21 Oct 2015_tracked changes.doc; VIVLODEX Labeling Response to DAAAP 21 Oct 2015_FINAL.doc

Importance: High

We agree with all of the changes made by the Division.
In the final review of the document, we identified some typographical and grammatical errors.
For transparency, I have included a revised version with all changes identified (tracked changes).
I have included a clean version with all of these errors accepted (FINAL), and we consider that version our final label.
Please contact me with any questions or concerns.

Kind regards,

Paul

Paul M. Kirsch
Vice President, Regulatory Affairs
Iroko Pharmaceuticals, LLC
One Kew Place
150 Rouse Boulevard
Philadelphia, PA 19112
(O) +1-267-546-1428
(F) +1-267-546-3004



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From: Meyer, Allison [<mailto:Allison.Meyer@fda.hhs.gov>]
Sent: Wednesday, October 21, 2015 3:03 PM
To: Paul Kirsch
Subject: vivlodex package insert

Please see changes, if you are ok with these, please submit a final label.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

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/s/

ALLISON MEYER
10/22/2015

Meyer, Allison

From: Meyer, Allison
Sent: Wednesday, August 26, 2015 8:07 AM
To: Paul Kirsch (pkirsch@iroko.com)
Subject: clinical IR for Vivlodex

Response to the following is needed by Monday 8/31/15:

1. Despite the lower AUC of Vivlodex 10 mg compared to Mobic 15 mg when taken under fasted conditions, there appears to be a higher incidence of hypertension with Vivlodex 10 mg in clinical trials. In MEL3-12-03, 4.2% of subjects had the treatment-emergent adverse event of hypertension. In the shift table that you sent on June 5, 2015, 13.5% of subjects in MEL3-12-03 had a shift in systolic blood pressure from normal to high from Baseline to Week 52. Yet, in clinical trials described in the Mobic Package Insert, hypertension occurred in less than 2% of patients receiving Mobic at any dose. Do you have additional thoughts on why this may be?
2. In MEL3-12-02, Vivlodex 5 mg appears to have performed similarly to Vivlodex 10 mg for the primary endpoint. Why do you think Vivlodex 10 mg did not display increased efficacy over Vivlodex 5 mg for the primary endpoint?

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
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/s/

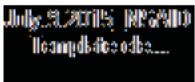
ALLISON MEYER
09/01/2015

Meyer, Allison

From: Meyer, Allison
Sent: Friday, August 14, 2015 10:50 AM
To: Paul Kirsch (pkirsch@iroko.com)
Subject: Vivlodex label

Paul,

Please revise the Vivlodex label to fit into the new NSAID template. This should be similar to the letters you have received for other already approved NSAIDs maintained by your firm. This needs to be done as soon as possible, preferably by August 21, 2015. Let me know if you have any questions.



Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

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/s/

ALLISON MEYER
08/14/2015



NDA 207233

INFORMATION REQUEST

Iroko Properties Inc.
Attention: Paul M. Kirsch, Vice President, Regulatory Affairs
One Kew Place
150 Rouse Blvd
Philadelphia, PA 19112

Dear Mr Kirsch,

Please refer to your original New Drug Application received Tuesday, December 23, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vivlodex (meloxicam) Meloxicam capsules 5 mg and 10 mg strengths.

We are reviewing your submission and have the following comments. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB August 18, 2015.

1. Among the several material attributes and process parameters evaluated, the proposed dissolution specifications ^{(b) (4)}
^{(b) (4)} Furthermore, the current proposed dissolution method and acceptance criterion ^{(b) (4)}

^{(b) (4)} Therefore, we have the following recommendation:

- a) Revise the current dissolution acceptance criterion for both release and stability testing to NLT ^{(b) (4)}% (Q) of labeled amount of meloxicam is dissolved in 10 minutes and submit an updated specification table reflecting this change. This approach will increase the discriminating ability of your proposed dissolution specifications.
- b) Alternatively, agree to set the current method and acceptance criterion as interim with ^{(b) (4)}

2. We acknowledge your response concerning the stability failure of Meloxicam Capsules (Lot 0402782). You have demonstrated, with data, that the lot failure was due to gelatin capsule shell cross-linking and not due to any changes (b) (4). However, the origin of gelatin capsule cross-linking for this particular lot is not clear; is it due to the particular lot of the empty gelatin capsule shells, or packaging, or storage conditions, etc. There appears to be a risk that this drug product may not consistently perform the way it is intended. In this regard discuss a suitable control strategy to address the formation of cross-linking in the gelatin capsule shell, and how you might mitigate cross-linking to ensure consistent quality of the capsule shell in your proposed drug product.
3. We understand that your (b) (4). However, because of unforeseen manufacturing circumstances and variable inputs (e.g. intended or unintended process variations over time, variations in raw materials, etc.), along with the inherent risk to drug product quality associated (b) (4) (b) (4) of your proposed drug product (b) (4) during commercial production. Please establish (b) (4).
4. Method validation Reports: Two sets of method validation reports, one each for the two manufacturing and testing locations, were submitted. However there is no mention of any method transfer or cross verification of the methods between the two sites. Provide information on how the batch analytical data from the two manufacturing locations will be collated and analyzed when commercial lots manufactured.

Sincerely,

Steven
Kinsley -S

Steven Kinsley, Ph.D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Digitally signed by Steven Kinsley -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Steven Kinsley -
S,
0.9.2342.19200300.100.1.1=2001720189
Date: 2015.08.11 17:04:14 -04'00'

Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, August 04, 2015 3:50 PM
To: Paul Kirsch (pkirsch@iroko.com)
Subject: clinical IR

1. In trial MEL3-12-03, 4.2% of subjects had the treatment-emergent adverse event of hypertension, but in the clinical information amendment dated June 5, 2015, Table 2.2 Summary of Shifts in Blood Pressure Values from Normal Values to Low or High Values (Safety Population – MEL3-12-03), 13.5% of subjects appear to have had a shift in systolic blood pressure from normal to high from Baseline to Week 52. Explain why these changes in systolic BP were not reported as adverse events.
2. Are there any other shifts in vital signs or labs that were not reflected in the adverse event reporting?

Response to the following is needed by 8/7/15.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

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/s/

ALLISON MEYER
08/06/2015

**PeRC Meeting Minutes
July 8, 2015**

PeRC Members Attending:

Lynne Yao

Wiley Chambers

George Greeley

Freeda Crooner

Tom Smith

Daiva Shetty

Peter Starke Non Responsive

Lily Mulugeta

Robert "Skip" Nelson

Kevin Krudys

Belinda Hayes

Ruthanna Davi Non Responsive

Shrikant Pagay

Rosemary Addy

Greg Reaman

Linda Lewis Non Responsive

Maura O'Leary Non Responsive

Adrienne Hornatko-Munoz

Barbara Buch

Olivia Ziolkowski

Agenda

Non Responsive

NDA

207233

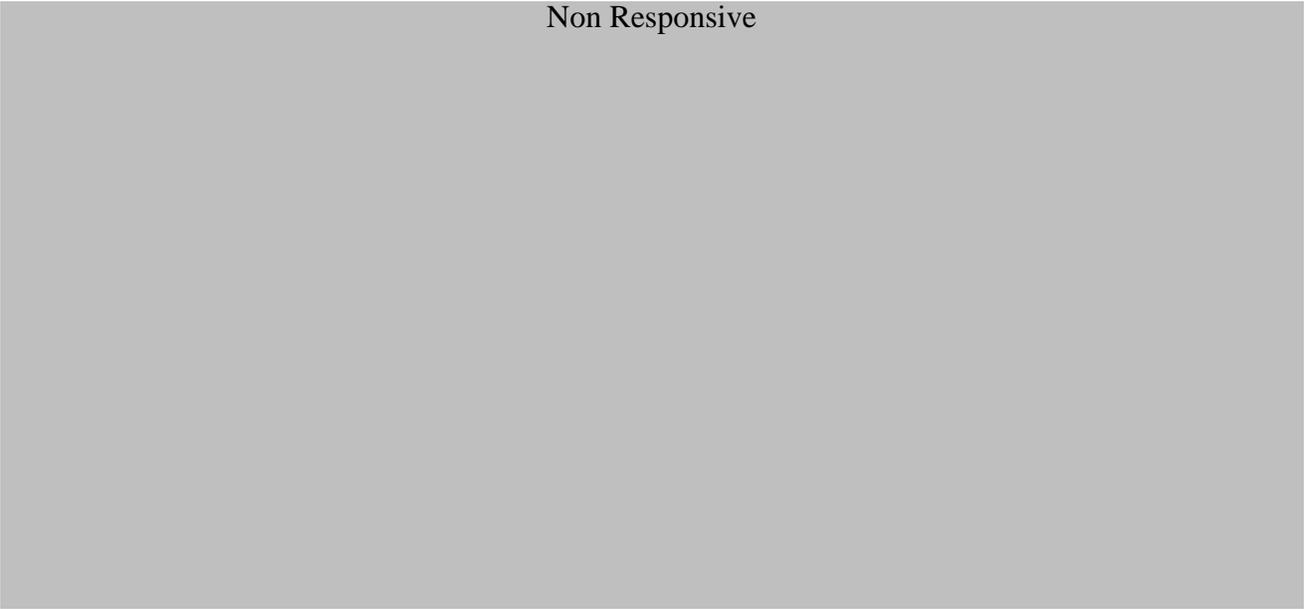
*Vivlodex (meloxicam) Full Waiver
w/Agreed iPSP*

(b) (4) of Osteoarthritis

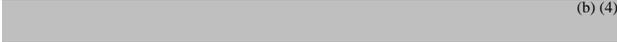
Non Responsive

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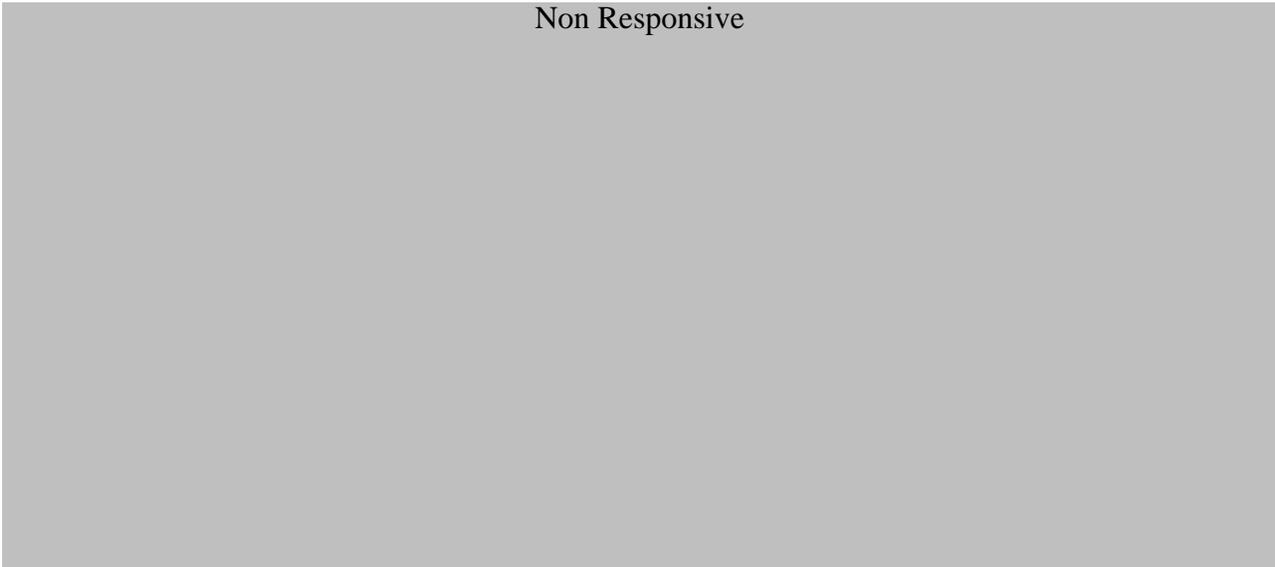
Non Responsive



Vivlodex (meloxicam) Full Waiver

- Proposed Indication:  (b) (4)
- ***PeRC Recommendations:***
 - The PeRC agreed with the Division to grant a full waiver because studies would be impossible or highly impractical because the disease/condition does not exist in pediatric patients.

Non Responsive



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/s/

GETTIE AUDAIN
07/22/2015



NDA 207233

INFORMATION REQUEST

Iroko Properties Inc.
Attention: Paul M. Kirsch Vice President, Regulatory Affairs
One Kew Place
150 Rouse Blvd
Philadelphia, PA 19112

Dear Mr. Kirsch,

Please refer to your original New Drug Application received Tuesday, December 23, 2014 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vivlodex™ (meloxicam) capsules 5 mg and 10 mg strengths.

We are reviewing your submission and have the following comments. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Thursday, July 30, 2015.

Drug Product

1. Since particle size measurement was performed by (b) (4) (b) (4) provide information on:
 - a) Whether reported particle size measurement is (b) (4) (b) (4)
 - b) (b) (4) (b) (4)
2. (b) (4) (b) (4)

D. Process

1. In DMF 28483 and your application you demonstrate that the process (b) (4) (b) (4)



E. Biopharm

1. [REDACTED] (b) (4)
2. Submit a list of the CMAs and [REDACTED] (b) (4) identified for your proposed product.
3. Provide dissolution data (in tabular and graphical form) showing the ability of the proposed method to discriminate for aberrant batches for the identified CMAs and [REDACTED] (b) (4) such as data showing the discriminating ability toward variations in the properties of [REDACTED] (b) (4).
4. The provided dissolution data do not support the proposed acceptance criterion of $Q \geq [REDACTED] (b) (4) \%$ at [REDACTED] (b) (4) minutes and it is not acceptable. In order to improve the discriminating ability of the proposed dissolution method, implement the following dissolution acceptance criterion for your proposed product and provide the revised specifications table with the updated acceptance criterion for the dissolution test.

$$Q \geq [REDACTED] (b) (4) \% \text{ at } 10 \text{ min}$$

5. Provide dissolution profile comparisons with similarity testing (where applicable) in three different pH media between the following two drug product manufacturing sites: [REDACTED] (b) (4)
6. Meloxicam Capsules 5 mg in blister [REDACTED] (b) (4) (Lot L0402782) failed dissolution acceptance criteria under accelerated stability conditions. Provide data to demonstrate that the dissolution failure was not due to the change of drug substance solid state.
7. Clarify whether the terms [REDACTED] (b) (4) [REDACTED] (b) (4) drug substance only or drug substance and excipient mixture in your dissolution method characterization report.

Sincerely,

Steven

Kinsley -S

Steven Kinsley, Ph.D.

Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Digitally signed by Steven Kinsley -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Steven Kinsley
-S,
0.9.2342.19200300.100.1.1=2001720189
Date: 2015.07.20 14:50:14 -04'00'

Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, July 14, 2015 11:49 AM
To: Paul Kirsch (pkirsch@iroko.com)
Subject: NDA 207233 Info Request

Paul,
Response to the following is due by July 21, 2015:

1. Given the (b) (4) in the formulation of your proposed product, provide rationale for the inclusion and the concentration of SLS used in the dissolution medium.
2. Submit a list of the CMAs and (b) (4) identified for your proposed product.
3. Provide dissolution data (in tabular and graphical form) showing the ability of the proposed method to discriminate for aberrant batches for the identified CMAs and (b) (4) such as data showing the discriminating ability toward variations in the properties of (b) (4) (b) (4)
4. The provided dissolution data do not support the proposed acceptance criterion of $Q \geq (b) (4)\%$ at (b) (4) minutes and it is not acceptable. In order to improve the discriminating ability of the proposed dissolution method, implement the following dissolution acceptance criterion for your proposed product and provide the revised specifications table with the updated acceptance criterion for the dissolution test.

$Q \geq (b) (4)\%$ at 10 min

5. Provide dissolution profile comparisons with similarity testing (where applicable) in three different pH media between the following two drug product manufacturing sites: (b) (4)
6. Meloxicam Capsules 5 mg in blister (b) (4) (Lot L0402782) failed dissolution acceptance criteria under accelerated stability conditions. Provide data to demonstrate that the dissolution failure was not due to the change of drug substance solid state.
7. Clarify whether the terms (b) (4) drug substance only or drug substance and excipient mixture in your dissolution method characterization report.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II

Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

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/s/

ALLISON MEYER
07/14/2015

Meyer, Allison

From: Meyer, Allison
Sent: Friday, June 05, 2015 12:44 PM
To: Paul Kirsch (pkirsch@iroko.com)
Subject: labeling recommendations

The following comments will need to be addressed for your carton/container labeling:

A. Container Labels (all strengths)

1. Revise the established name from [REDACTED] (b) (4) capsules” to the approved established name “(meloxicam) capsules.”
2. Revise the middle digits of the NDC number from sequential digits between the 5 mg and 10 mg strength to non-sequential digits. The similarity of NDC numbers has led to selecting and dispensing of the wrong strength and wrong drug. Health care professionals traditionally use the middle digits to check the correct product, strength, and formulation. Therefore, assignment of sequential numbers (e.g., 6666, 6667, and 6668) for the middle digits is not an effective differentiating feature.ⁱ
3. Ensure the expiration date is presented in a standard format, using three-letter text for the month, two-digit numerals for the day (if included), and four-digit numerals for the year, as follows, MMMYYYY or MMMDDYYYY.ⁱⁱ
4. Relocate the statement, “Attention: Dispense the accompanying Medication Guide to each patient” from the side panel to the principal display panel in accordance with 21 CFR 208.24(d). Remove the manufacturer information and logo from the principal display panel to accommodate this change and since this information is provided on the side panel and is redundant.

B. Physician Sample Blister Label (all strengths)

1. See A.1 through A.3.
2. Consider packaging each capsule in an individual blister instead of the current package size [REDACTED] (b) (4) [REDACTED] to mitigate the risk for overdose errors. We have post-marketing experience of overdose errors where [REDACTED] (b) (4) together.ⁱⁱⁱ If this is implemented, change the net quantity to 1 capsule to reflect this change.

C. Physician Sample Carton Labeling (all strengths)

1. See A.1 through A.3.

D. Physician Sample Box Holder Carton Labeling (all strengths)

1. See A.1.
2. Consider ensuring that the NDC number appears on all drug labels and in other drug labeling, including the label of any prescription drug container furnished to a consumer in accordance with

21 CFR 201.2. If you choose to display the NDC number, see A.2 and ensure it is displayed in accordance with 21 CFR 207.35(b)(3).

3. Ensure the expiration date is present in accordance with 21 CFR 201.17. Additionally, see A.3.
4. Ensure the lot number is present in accordance with 21 CFR 201.18.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

ⁱ Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

ⁱⁱ Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

ⁱⁱⁱ Institute for Safe Medication Practices, Safety Briefs. ISMP Med Safe Alert Acute Care 2002; 7(17):2

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/s/

ALLISON MEYER
06/05/2015

Meyer, Allison

From: Paul Kirsch <pkirsch@iroko.com>
Sent: Wednesday, June 03, 2015 1:07 PM
To: Meyer, Allison
Subject: RE: NDA 207233

Hi Allison,

If you are asking us to make a determination at this time, we plan on utilizing the manufacturing facilities in the following manner:

The primary facility for final dosage form will be [REDACTED] (b) (4) will be the alternate.

[REDACTED] (b) (4) is the only facility for packaging.

Kind regards,

Paul

Paul M. Kirsch
Vice President, Regulatory Affairs
Iroko Pharmaceuticals LLC.
One Kew Place
150 Rouse Boulevard
Philadelphia, PA 19112
(O) +1-267-546-1428
(F) +1-267-546-3004



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From: Meyer, Allison [<mailto:Allison.Meyer@fda.hhs.gov>]
Sent: Wednesday, June 03, 2015 12:04 PM
To: Paul Kirsch
Subject: NDA 207233

Paul, Which facility will be used as the primary for the final dosage form and which is the alternate, between [REDACTED] (b) (4) [REDACTED] (b) (4)

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
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/s/

ALLISON MEYER
06/05/2015

Meyer, Allison

From: Meyer, Allison
Sent: Friday, May 29, 2015 11:49 AM
To: 'Paul Kirsch'
Subject: RE: NDA 207233

Yes the increasing shifts.

From: Paul Kirsch [<mailto:pkirsch@iroko.com>]
Sent: Friday, May 29, 2015 9:58 AM
To: Meyer, Allison
Subject: RE: NDA 207233

Dear Allison,

Just confirming that I received this request.

We will provide this information as soon as possible and certainly by June 5, 2015.

Please confirm that the Reviewer is **only** requesting increasing shifts (normal to high); **not** requesting decreasing shifts (normal to low).

Kind regards,

Paul

Paul M. Kirsch
Vice President, Regulatory Affairs
Iroko Pharmaceuticals LLC.
One Kew Place
150 Rouse Boulevard
Philadelphia, PA 19112
(O) +1-267-546-1428
(F) +1-267-546-3004



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From: Meyer, Allison [<mailto:Allison.Meyer@fda.hhs.gov>]

Sent: Friday, May 29, 2015 8:49 AM

To: Paul Kirsch

Subject: NDA 207233

For both studies MEL 3-12-02 and MEL3-12-03, make a “shift table” that displays the changes in blood pressure that may have taken place over each study. The purpose of these tables is to view the changes in blood pressure that may have taken place at each visit over the study. Such tables may appear as below when complete:

Table 1 MEL3-12-02 blood pressure shift table

Shift from normal to high from Visit 1 to Visit 3 (% of subjects)	Shift from normal to high from Visit 3 to Visit 4 (% of subjects)	Shift from normal to high from Visit 4 to Visit 5 (% of subjects)	Shift from normal to high from Visit 1 to Visit 5 (% of subjects)
---	---	---	---

Systolic
blood
pressure

Diastolic
blood
pressure

Table 2 MEL3-12-03 blood pressure shift table

Shift from normal to high from Baseline to Week 1 (% of subjects)	Shift from normal to high from Week 1 to Week 4 (% of subjects)	Shift from normal to high from Week 4 to Week 8 (% of subjects)	Shift from normal to high from Week 8 to Week 12 (% of subjects)	Shift from normal to high from Week 12 to Week 48 (% of subjects)	Shift from normal to high from Week 48 to Week 52 (% of subjects)
---	---	---	--	---	---

Systolic
blood
pressure

Diastolic
blood
pressure

Response to these is due by June 5, 2015.

Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II

Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

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/s/

ALLISON MEYER
05/29/2015

Meyer, Allison

From: Meyer, Allison
Sent: Thursday, April 23, 2015 10:33 AM
To: 'Paul Kirsch'
Subject: NDA 207233 clinical IR

Paul,

In reviewing your NDA for Vivlodex, we have noticed that many of the laboratory values are reported in units that are different from the units that are specified in the "Criteria for Laboratory Values of Potential Clinical Concern." For example, in the "Criteria for Laboratory Values of Potential Clinical Concern," the units for BUN are in "mg/dl," but in the data sets, the units are in "mmol/L."

Provide the following information or the location of the following information in the NDA:

1. Normal lab values for all laboratories studied in the units in which they have been reported in your NDA.
2. An organized conversion table for the laboratories in the "Criteria for Laboratory Values of Potential Clinical Concern" as converted into the units in which you have reported them in the NDA. For example:

Lab	Low Value		High Value	
glucose	≤55 mg/dl	?? mmol/L	≥200 mg/dl	?? mmol/L

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
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10903 New Hampshire Avenue
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Silver Spring, MD 20993
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301-796-9713 (fax)

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/s/

ALLISON MEYER
04/23/2015

Meyer, Allison

From: Meyer, Allison
Sent: Wednesday, March 11, 2015 11:31 AM
To: Paul Kirsch (pkirsch@iroko.com)
Subject: NDA 207233 clinical IR

The following questions pertain to your submission dated December 23, 2014 in the document titled "ISS Analysis ADAM Dataset adae:"

1. Does the column labeled "AEDECOD" represent preferred terms?
2. Does the column labeled "AETERM" represent verbatim terms?

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

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/s/

ALLISON MEYER
04/23/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207233

INFORMATION REQUEST

Iroko Pharmaceuticals LLC.
Attn: Paul M. Kirsch
Vice President, Regulatory Affairs
One Kew Place
150 Rouse Boulevard
Philadelphia, PA 19112

Dear Mr. Kirsch:

Please refer to your New Drug Application (NDA) dated and received December 23, 2014, submitted pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Vivlodex (meloxicam) Capsules 5 mg and 10 mg.

We are reviewing the CMC section of your submission and have the following comments and information requests. We request a prompt written response by May 4, 2015 in order to continue our evaluation of your NDA.

A. The Manufacturing Process.



(b) (4)

B. The Microbiology

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.

If you have any questions, call Youbang Liu, Regulatory Project Manager, at (301) 796-1926.

Sincerely,

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: 2015.04.13 12:12:55 -04'00'

Ciby J. Abraham, Ph.D.
Application Technical Lead
Branch IV, Division II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



NDA 207233

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Iroko Pharmaceuticals LLC
One Kew Place
150 Rouse Boulevard
Philadelphia, PA 19112

Attention: Paul M. Kirsch
Vice President, Regulatory Affairs

Dear Mr. Kirsch:

Please refer to your New Drug Application (NDA) dated December 23, 2014, received December 23, 2014, submitted pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Vivlodex (meloxicam) Capsules 5 mg and 10 mg.

We also refer to your amendments dated December 29, 2014, and January 23 and 30, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 23, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 11, 2015.

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

Biopharmaceutics

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 *f2* testing in three different media between the following two drug product manufacturing sites: (b) (4)

Chemistry, Manufacturing and Controls (CMC)

4. Clarify if the acceptance criterion 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.

Pharmacology/Toxicology

6. We note that the submitted study entitled “Computational assessment and evaluation of potential genotoxicity of three Meloxicam impurities using CASE Ultra” predicted that the drug product impurity (b) (4) was positive for bacterial mutagenicity and therefore the NDA indicated that this impurity would be kept within the acceptable intake of 1.5 mcg/day in accordance with the ICH M7 guideline: *Assessment and Control of DNA Reactive (Mutagenic) Impurities In Pharmaceuticals to Limit Potential Carcinogenic Risk*. However, the drug product specification for this impurity is NMT (b) (4) %, which could potentially result in daily exposures of (b) (4) mcg/day and (b) (4) mcg/day for the 5 mg and 10 mg tablets, respectively. You must either reduce the drug product specification to NMT 1.5 mcg/day or demonstrate that the impurity is negative in an Ames test.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded

upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

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

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

PROMOTIONAL MATERIAL

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Allison Meyer, Regulatory Project Manager, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Acting Director
Division of Anesthesia, Analgesia,
And Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

RIGOBERTO A ROCA on behalf of SHARON H HERTZ
03/03/2015



NDA 207233

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Iroko Pharmaceuticals, LLC
One Kew Place
150 Rouse Blvd
Philadelphia, PA 19112

ATTENTION: Paul M. Kirsch
Vice President, Regulatory Affairs

Dear Mr. Kirsch:

Please refer to your New Drug Application (NDA), dated and received December 23, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Meloxicam Capsules, 5 mg and 10 mg.

We also refer to your correspondence, dated and received December 29, 2014, requesting review of your proposed proprietary name, Vivlodex.

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

If any of the proposed product characteristics as stated in your December 29, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Lisa Skarupa, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2219. For any other information regarding this application, contact Allison Meyer, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

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

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/s/

TODD D BRIDGES
01/30/2015

Meyer, Allison

From: Meyer, Allison
Sent: Tuesday, January 20, 2015 4:17 PM
To: Paul Kirsch (pkirsch@iroko.com)
Subject: Meloxicam IR

In the materials you have submitted, we are unable to find the following information:

1. A table denoting the number of subjects screened, randomized, those with protocol violations, and those prematurely discontinued by study site.
2. A safety assessment of meloxicam based on all current worldwide knowledge regarding this product, typically located in the ISS.

Submit the above items to us or indicate where they can be found in your submission by 1/23/15.

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia and
Addiction Products
Office of New Drugs II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Rm. 3176
Silver Spring, MD 20993
301-796-1258
301-796-9713 (fax)

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/s/

ALLISON MEYER
01/20/2015



NDA 207233

NDA ACKNOWLEDGMENT

Iroko Pharmaceuticals LLC
One Kew Place
150 Rouse Boulevard
Philadelphia, PA 19112

Attention: Paul M. Kirsch
Vice President, Regulatory Affairs

Dear Mr. Kirsch:

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

Name of Drug Product: Vivlodex (meloxicam) Capsules 5 mg and 10 mg

Date of Application: December 23, 2014

Date of Receipt: December 23, 2014

Our Reference Number: NDA 207233

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 21, 2015, in accordance with 21 CFR 314.101(a).

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

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

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

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

If you have any questions, call me, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia,
And Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ALLISON MEYER
01/09/2015



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

IND 114045

MEETING PRELIMINARY COMMENTS

Iroko Pharmaceuticals, LLC
One Kew Place
150 Rouse Boulevard
Philadelphia, PA 19112

Attention: Paul M. Kirsch
Executive Director, Regulatory Affairs

Dear Mr. Kirsch:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Meloxicam SoluMatrix Capsules.

We also refer to your April 7, 2014, correspondence, received April 8, 2014, requesting a meeting to discuss the submission of a 505(b)(2) NDA for the (b)(4) of osteoarthritis pain.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me, at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA
Meeting Date and Time: July 22, 2014 at 12:00 PM (Eastern time)
Meeting Location: 10903 New Hampshire Avenue
 White Oak Building 22, Conference Room: 1315
 Silver Spring, Maryland 20903
Application Number: 114045
Product Name: Meloxicam SoluMatrix Capsules
Indication: (b) (4) of osteoarthritis pain
Sponsor/Applicant Name: Iroko Pharmaceuticals, LLC

FDA Attendees	Title
Sharon Hertz, MD	Deputy Division Director, DAAAP
Joshua Lloyd, MD	Clinical Team Leader, DAAAP
Pamela Horn, MD	Clinical Reviewer, DAAAP
Yun Xu, PhD	Clinical Pharmacology Team Leader, DAAAP
Suresh Narahariseti, PhD	Clinical Pharmacology Reviewer, DAAAP
Adam Wasserman, PhD	Pharmacology / Toxicology Supervisor, DAAAP
Armaghan Emami, PhD	Pharmacology / Toxicology Reviewer, DAAAP
Janice Derr, PhD	Mathematical Statistics Team Leader
Julia Pinto, PhD	Pharmaceutical Assessment Lead, ONDQA
Allison Meyer	Regulatory Project Manager, DAAAP
Iroko Pharmaceuticals LLC	Title
Paul M. Kirsch	Executive Director, Regulatory Affairs
Goral Patel	Manager, Regulatory Affairs
Clarence L. Young, MD	Chief Medical Officer
Daniel Solorio	Executive Director, Clinical Operations
Alexis Gomez	Director Clinical Operations
David Dickason	Executive Director, Technical Development
Mark Jaros, PhD	Statistical Consultant
Carie Masoner	Regulatory Consultant

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for July 22, 2014, at 12:00 PM (eastern time) between you and the Division of Anesthesia, Analgesia, and Addiction Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these

preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Iroko Pharmaceuticals, LLC plans to file a 505(b)(2) NDA for Meloxicam SoluMatrix Capsules in December 2014. Meloxicam is a nonsteroidal, anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic, and antipyretic properties. The reference listed drug will be Mobic Tablets (NDA 020938). This application will have 5 core clinical trials to support the NDA for the indication of (b) (4) of osteoarthritis pain.

2.0 DISCUSSION

The questions from the June 19, 2014, meeting package are shown below in *italic font*, the preliminary responses are in **bold font**.

Question 1: Does the Division agree that the pivotal efficacy and safety trial MEL3-12-02 and the open-label safety trial MEL3-12-03, in addition to the Phase 1 PK trial MEL1-12-04 are sufficient to an approvable NDA for the treatment of osteoarthritis pain?

FDA Response:

Studies MEL3-12-02 and MEL3-12-03 appear to provide clinical efficacy and safety information that would support filing of a 505(b)(2) NDA in conjunction with data from MEL1-12-04 that is intended to provide a scientific bridge to the Agency's previous findings relevant to your product.

The final to-be-marketed formulation must be used in the PK and clinical studies to support your NDA submission. Otherwise, you must provide adequate bridging information or justification why the study results apply to your final to-be-marketed product.

Question 2: Does the Division agree with the approach that the integrated safety analysis will comprise pooled data only from the Phase 3 (MEL3-12-02 and MEL3-12-03) clinical trials?

FDA Response:

Yes, this appears to be acceptable.

Question 3: Does the Division have any comments on the ISS Statistical Analysis Plan?

FDA Response:

No, we have no comments at this time. During the review cycle, additional analyses may be requested.

Question 4: Does the Division concur with Iroko's proposal of providing a summary of effectiveness in Module 2.7.3 that reviews the efficacy data from the pivotal Phase 3 trial supported by the relevant published literature on the effectiveness of meloxicam?

FDA Response:

Yes, this appears to be an acceptable approach. However, the summary must satisfy the regulatory requirements for approval under 21 CFR 314.50(d)(5)(v) and incorporate how the Agency's previous findings for the reference product support the proposed indication. Note that you must submit a document to Module 5.3.5.3 (Integrated Summary of Effectiveness) that cross references the Summary of Clinical Effectiveness in Module 2.7.3.

Question 5: Does the Division have any comments on the proposed analysis approaches summarized above?

FDA Response:

At the End-of-Phase 2 meeting and in subsequent communications, we expressed the following concerns about the proposed approach:

- A favorable outcome might be assigned to a patient who discontinued due to an adverse event; but we believe that a discontinuation due to an adverse event is an unfavorable outcome.
- Patients who discontinue study drug and do not provide post-discontinuation endpoint data ("unretrieved dropouts") are assumed to be similar to completers; but we do not believe this assumption is plausible.

In the Pre-NDA briefing document, you acknowledged these concerns. You did not change the primary efficacy analysis, but you provided sensitivity analyses that were developed to address these concerns. The briefing document includes the results of these analyses. Our statistical review of the NDA submission will include an evaluation of the primary and sensitivity analyses with respect to these issues.

Question 6: Does the Division agree with Iroko's proposal for which CRFs and case summaries will be included in the NDA?

FDA Response:

Yes, providing case summaries and completed CRFs for subjects with reported deaths or serious adverse events, subjects who withdrew from the trial due to adverse events, subjects who discontinued due to withdrawal of consent, or subjects who indicated "other" as their reason for withdrawal and providing case summaries for subjects who

experienced adverse events of special interest, such as elevated liver function tests and gastrointestinal, cardiovascular, and renal events, is acceptable.

Question 7a: Please confirm that Iroko's initial Pediatric Study Plan requesting a full waiver of pediatric studies for the indication of (b)(4) of osteoarthritis pain is acceptable.

FDA Response:

Refer to the July 2, 2014, letter from the Agency regarding your waiver request for pediatric studies.

Question 7b: Please confirm that a waiver for pediatric studies for the indication of (b)(4) of OA pain is acceptable.

FDA Response:

Yes, this is generally acceptable.

Question 8: Does the Division agree with Iroko's plan to submit only the PK concentration source data for the Phase 1 trials listed above?

FDA Response:

Your proposal, in general, is acceptable.

Question 9: Does the Division agree with Iroko's plan to submit Study QP09C03 as a legacy report?

FDA Response:

Your proposal, in general, is acceptable.

Question 10: Does the Division agree that no additional non clinical safety studies are required to support the safety of Meloxicam SoluMatrix Capsules?

FDA Response:

Based on the information provided in the meeting package, we agree that no additional nonclinical studies are required.

However, we note that due to increased bioavailability with your drug product, your total daily dose is lower than the referenced drug product yet provides comparable exposure levels. Most of the nonclinical data in the referenced drug product labeling includes exposure margins that are based on body surface extrapolations. Exposure margins are necessary to put the nonclinical findings into clinical perspective. Adjusting the body surface area exposure margins based on total daily dose alone would imply a greater safety margin, which would be inaccurate and misleading if the actual exposure with your product is comparable to the referenced drug product. For your eventual product labeling, you must take this into consideration and either propose adequate language that is scientifically accurate, clinically meaningful, and not misleading or provide actual exposure data to revise the safety margins. The latter may

require animal toxicokinetic studies that mimic the dosing regimen employed in the studies cited in the referenced product labeling.

Question 11: Does the Division agree that stability data generated with the development

(b) (4)

FDA Response: Yes, we agree that the stability data generated with the development

(b) (4)

Question 12: Does the Division agree with the approach to only cite reference articles in Section 5.4 of the NDA and alternatively make them available upon request?

FDA Response:

If you contend that these literature articles are not necessary for approval of your application and that your application can rely on referenced NDA applications and the clinical trials you conducted alone, then these reference articles need not be submitted. However, any article that is necessary to support approval of your application must be submitted with the NDA application.

Additional Comment from Division of Medication Error Prevention and Analysis:

The established name for your product is meloxicam, which will make it difficult to distinguish your product from other meloxicam products if a prescription is ordered by the established name instead of the proprietary name. We recognize that you are proposing strengths of 5 mg and 10 mg for your product with a maximum daily dose of 10 mg, which differs from the 7.5 mg and 15 mg strengths that are currently marketed. However, given that a 15 mg dose of meloxicam is achievable with your proposed 5 mg and 10 mg capsules (e.g., three 5 mg capsules or one 5 mg capsule plus one 10 mg capsule) we are concerned that the risk exists for confusion between varying formulations that can result in wrong drug errors. We recommend you conduct a risk analysis and determine how best to mitigate this risk for medication error if your product is marketed (e.g., labeling interventions, marketing plans, education/communication, etc.). Submit this information with your application. Because of the differences in bioavailability between your product and other meloxicam formulations on the market, if the wrong product is dispensed, there would be the potential for increased side effects.

3.0 ADDITIONAL INFORMATION

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

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

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

MANUFACTURING FACILITIES

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

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

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

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

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

Corresponding names and titles of onsite contact:

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

505(b)(2) REGULATORY PATHWAY

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

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

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

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

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

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

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

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>

2. <i>Example: NDA XXXXXX</i> <i>"TRADENAME"</i>	<i>Previous finding of effectiveness for indication X</i>
3. <i>Example: NDA YYYYYY</i> <i>"TRADENAME"</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
4.	

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

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

/s/

ALLISON MEYER
07/16/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

IND 114045

MEETING MINUTES

iCeutica Operations, LLC
c/o Premier Research Group Limited
Center Square West
1500 Market Street, Suite 3500
Philadelphia, PA 19102

Attention: Linda Hibbs
Associate Director, Regulatory Operations

Dear Ms. Hibbs:

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

We also refer to the meeting between representatives of your firm and the FDA on November 13, 2012. The purpose of the meeting was to discuss the development program and future submission of a 505(b)(2).

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

If you have any questions, call me at (301) 796-1258.

Sincerely,

{See appended electronic signature page}

Allison Meyer
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
 CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B, End-of-Phase 2
Meeting Date and Time: November 13, 2012, 10:00 a.m. (Eastern)
Meeting Location: 10903 New Hampshire Avenue
 White Oak Building 22, Conference Room: 1315
 Silver Spring, Maryland 20903
Application Number: IND 114045
Product Name: Meloxicam SoluMatrix Capsules
Indication: (b) (4) of pain of OA
Sponsor/Applicant Name: iCeutica Operations, LLC
Meeting Chair: Ellen Fields, M.D., Clinical Team Leader, DAAAP
Meeting Recorder: Allison Meyer, Sr. Regulatory Project Manager, DAAAP

Industry Representatives	Title
Bill Bosch, Ph.D.	Chief Scientific Officer
Paul Nemeth, Ph.D.	Vice President, Clinical Development and Regulatory Affairs
David A. Dickason	Senior Director, Technical Development
James Foy, Ph.D.	Senior Manager, Regulatory Affairs CMC
Steven Jensen	Vice President, Regulatory Affairs and Quality
Daniel Solorio	Senior Director, Clinical Operations
Clarence Young, M.D.	Chief Medical Officer
Linda Hibbs	Associate Director, Regulatory Operations
(b) (4)	
Florence Vickers, Ph.D., FCP	Director, Regulatory Affairs
(b) (4)	
FDA	Title
Bob A. Rappaport, M.D.	Division Director, DAAAP
Sharon Hertz, M.D.	Deputy Director, DAAAP
Ellen Fields, M.D.	Clinical Team Leader, DAAAP
Jin Chen, M.D., PhD	Medical Officer, DAAAP
Adam Wasserman, Ph.D.	Supervisor, Pharmacology/Toxicology, DAAAP
Craig Bertha, Ph.D.	Product Quality Reviewer, ONDQA
Suresh Naraharansetti, Ph.D.	Clinical Pharmacology Reviewer, Office of Clinical Pharmacology
Dionne Price, Ph.D.	Biostatistics Team Leader, Division of Biometrics II (DBII)
Feng Li, Ph.D.	Biostatistics Reviewer, DBII
Allison Meyer	Sr. Regulatory Project Manager, DAAAP

Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits antipyretic, anti-inflammatory and analgesic properties. The Sponsor would like to confirm the acceptability of proceeding with the 5 mg and 10 mg Meloxicam (b)(4) Capsules dosage strengths to Phase 3 studies, the overall trial design and analysis strategy for the single trial design to support an efficacy claim for (b)(4) of osteoarthritis pain, confirm that the 505(b)(2) pathway is appropriate, and confirm plans for compliance with the Pediatric Research Equity Act (PREA).

The Sponsor's original questions are incorporated below in *italics* followed by the FDA Response in **bold** font. Discussion that took place during the meeting is captured following the question to which it pertains in normal text.

DISCUSSION

Opening Remarks: After brief introductions, the Division asked the Sponsor to clarify the relationship between iCeutica and Iroko. The Sponsor stated that iCeutica was an Australian-owned company that is now based in the U.S. In 2007, iCeutica collaborated with Iroko on three compounds for development, using iCeutica's technology and outsourcing the regulatory and clinical work. The Sponsor stated that both companies share a board chairman.

- 1. Does the Division agree that a 505(b)(2) NDA is the appropriate submission pathway for Meloxicam (b)(4) Capsules?*

FDA Response: Yes, we agree a 505(b)(2) NDA is an appropriate pathway for Meloxicam (b)(4) Capsules.

Discussion: There was no further discussion of this question.

- 2. Does the Division concur with iCeutica's intention to proceed in parallel with the definitive Phase 1 PK trial and pivotal Phase 3 osteoarthritis trial evaluating Meloxicam (b)(4) Capsules at 5 mg and 10 mg dosage strengths without a need for a Phase 2 proof-of-concept trial?*

FDA Response: No, we do not concur with your proposal to proceed in parallel with the definitive Phase 1 PK trial and the Phase 3 osteoarthritis trial. Your proposed formulation for 5 and 10 mg strengths is significantly different than the formulation used in the initial PK study, so the PK parameters (e.g. C_{max}) cannot be predicted based on data from the old formulation. Considering a high C_{max} will lead to safety concerns, a Phase 1 PK study must be conducted prior to initiating the Phase 3 osteoarthritis trial.

Discussion: The Sponsor stated that the formulation for the Phase 3 trial was modified to address the stability concern with the original formulation regarding particle size increase over time. The revised formulation was shown in vitro to maintain a consistent particle

size. The Division stated that there has not been any PK information submitted on the modified formulation. The in vitro dissolution method is not sufficient to discriminate the modified formulation from the original formulation in stability. While this may not be a hold issue, the PK profile of the revised formulation must be defined to support the proper dosing interval, particularly regarding end of dose failure, and safety for the Phase 3 trial. If there is an earlier t_{max} (e.g., left shift of the PK curve), a potential concern is lower plasma concentrations toward the end of the dosing interval that could result in end-of-dose failure and inadequate efficacy for the proposed once daily dosing regimen. The Division suggested that time to rescue medication be included in the Phase 3 protocol as additional support for the dosing interval. If the final formulation has a higher C_{max} than the referenced product Mobic, additional safety data may be needed. The Sponsor agreed to fully characterize the PK of the final-to-be marketed formulation before moving forward with Phase 2 or 3 studies.

The Division confirmed that a Phase 2 dose-ranging study, while recommended, is not required for this program.

Clinical Pharmacology Post-Meeting Note:

The final to-be-marketed product must be used in the clinical pharmacology and Phase 3 clinical studies used to support the NDA submission of the product. Otherwise, you must provide adequate bridging information or justification for why the study results can apply to your final to-be-marketed product.

3. a. Does the Division agree that the proposed definitive Phase 1 PK, pivotal Phase 3 osteoarthritis pain, and safety exposure studies are adequate to support a commercial application for Meloxicam ^{(b)(4)} Capsules?

FDA Response: Overall, the clinical development plan (Phase 1 PK study with the to-be marketed formulation, one Phase 3 efficacy trial, and one Phase 3 open-label safety trial) may be sufficient to support a commercial application for your product depending on the results of the new PK study (also see response to Question 2).

The proposed Phase 3 efficacy trial (MEL3-12-02) is inadequately designed due to your plan to use only some of the questions in the WOMAC pain subscale (See response to Question 4 for details).

Otherwise, based on the synopsis provided for the Phase 3 trial protocol, the design appears generally appropriate. Additional comments may be forthcoming following submission of the final protocol and the Agency's review of it.

Discussion: The Sponsor clarified that they plan to calculate an average score based on 4 or 5 out of 5 questions on the WOMAC Pain subscale, in cases where subjects have only answered 4 of the 5 questions. They plan to ask all 5 questions, but based on prior experience, approximately 5% of patients are expected to only answer 4 out of 5 questions. They will require a minimum of responses to 4 questions for the subscale to be considered valid.

Post-meeting Note from the Sponsor: In Iroko's recently completed Zorvolex (IND 103880) OA Phase 3 trial DIC3-08-05, only 22 out of 1,456 assessments (1.5%) had fewer than five responses provided over the course of the 12 week study.

b. Does the Division concur that the safety database for the open-label safety trial of no less than 300 patients who have received Meloxicam (b)(4) Capsules for six months and no less than 100 patients treated for one year is sufficient?

FDA Response: Yes, the safety database containing at least 600 subjects with at least 300 patients exposed for 6 months and at least 100 patients exposed for 12 months to Meloxicam (b)(4) 10 mg once a day (qd) appears sufficient for the proposed product.

Discussion: There was no further discussion of this question.

4. *Does the Division concur that the mean change from Baseline WOMAC pain subscale score be used as the primary endpoint for the pivotal Phase 3 trial to support an indication for the treatment of osteoarthritis pain?*

FDA Response: We concur that "the mean change from baseline for WOMAC pain subscale score" may be used as the primary endpoint for the Phase 3 trial to support the proposed indication. However, it is not acceptable to rely on only four of five pain questions in the WOMAC Pain questionnaire. The questions of the WOMAC pain subscale must be used as a complete set, as use of only 4 of 5 questions has not been qualified as an instrument.

Discussion: There was no further discussion of this question.

5. *Does the Division concur with iCeutica's proposal to incorporate flare methodology in the Phase 3 osteoarthritis pain study design?*

FDA Response: Yes, the proposed flare approach for the Phase 3 efficacy trial is acceptable for this reformulation of an approved NSAID.

Discussion: There was no further discussion of this question.

6. *Does the Division agree with the proposed methodology for analyzing the primary efficacy endpoint, as described above?*

FDA Response: The appropriateness of the proposed methodology will depend on the causal estimand. The National Academy of Sciences (NAS) released a report on missing data in 2010. The report can be found online at http://www.nap.edu/catalog.php?record_id=12955. You should explicitly specify the causal estimand as recommended in the report.

Your analysis will include data from retrieved dropouts (i.e. patients that discontinue treatment but continue to provide pain assessments). This analysis approach appears to

be consistent with an intent-to-treat estimand. When using an intent-to-treat estimand in a chronic pain setting, concern may arise if the estimate of the treatment effect is overly influenced by the use of effective alternative treatments.

In addition, you propose to use a Mixed Model Repeated Measure (MMRM) approach for those patients that discontinue and for whom you are unable to collect Week 12 data. This analysis strategy may attribute a favorable outcome to a patient discontinuing due to adverse events. However in chronic pain trials, a favorable outcome should not be attributed to a patient that discontinues due to adverse events.

The results of the efficacy analysis with respect to WOMAC function and patient's global impression may be included in the label; therefore, you should include an appropriate strategy to control multiplicity.

You should submit a detailed protocol and address the above concerns. Additional comments may be warranted upon review of the detailed protocol.

Discussion: The Division stated that the appropriateness of the proposed analysis will be evaluated once the causal estimand has been specified. The Division reiterated the general concerns with a MMRM analysis in a chronic pain setting and stated that the analysis plan should address the concern. The Sponsor stated that they plan to utilize an intent-to-treat estimand and to conduct sensitivity analyses.

The Division noted that the WOMAC function and patient's global impression analyses will be included in the Clinical Studies section of the Prescribing Information label. This is intended to provide prescribers with a full picture of the relevant outcomes for the OA population.

7. *Does the Division agree that a waiver for pediatric studies for the indication of osteoarthritis pain management is appropriate?*

FDA Response: Yes, we agree that a waiver request for pediatric studies under PREA is acceptable for the proposed indication.

Discussion: The Division clarified that the Pediatric Research Committee (PeRC) makes these final determinations, however, a full pediatric waiver for OA is typically granted.

8. *Does the Division agree that no additional nonclinical safety studies are required to support the safety of Meloxicam (b) (4) Capsules?*

FDA Response: Assuming that the reformulated product does not produce clinical exposure to meloxicam which exceeds that of the referenced product, we agree that additional nonclinical studies are not required to support the safety of meloxicam for Phase 3 studies or the NDA submission.

However, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety for the NDA submission. Refer to the Guidances for Industry: *Q3A Impurities in New Drug Substances* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073385.pdf> and *Q3B(R2) Impurities in New Drug Products* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073389.pdf>

Discussion: The Division noted that the Sponsor must evaluate impurities to determine if these contain structural alerts for genotoxicity. Impurities that contain structural alerts or are identified as genotoxic or carcinogenic must be controlled using stricter specification criteria. The Division referred the Sponsor to the draft Guidance for Industry: *Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches*.

9. Does the Division have any additional comments to the information provided in this meeting package?

FDA Response:

1. In order to obtain accurate PK data for your product, modify your protocol (MELI-12-04) to exclude any drug (including both prescription and OTC products), herbal supplement (e.g. St John's Wort, etc), dietary supplement (e.g. grape fruit containing products, etc) known to induce or inhibit hepatic drug metabolism within 14 days before planned dosing and during the study.
2. Provide a rationale as to why you plan to pursue the indication "OA pain" instead of "signs and symptoms of OA" which is the indication for Mobic. The results of the WOMAC Function subscale and patient global assessment in addition to the WOMAC pain subscale, will likely appear in the label so that prescribers will understand if the efficacy of your product differs from Mobic.
3. During our review of the original IND submission, we noted that there was a relatively large increase in overall formulation particle size (b)(4) and an apparent concomitant decrease of drug release during dissolution testing. In addition, the magnitude of the changes differed between lots. Therefore, we highly recommend that you include testing for the particle size distribution of the new formulation in stability studies supporting your forthcoming new drug application.
4. The in vitro dissolution method does not seem to be optimal with more than (b)(4)% dissolved at the 10-minute time point. Further development for the dissolution method is needed for the new formulation planned. The development report should include the rationale for the selection of dissolution methodology, such as the apparatus, rotation speed, and media (including selection of surfactants and their concentrations) to show the discriminating ability for identifying the quality problems if any. All the raw data should be included in the report, including the individual value, the mean, the standard deviation and the plots under different conditions.

Discussion: The Sponsor stated that the increase in drug particle size (b) (4) (b) (4) as described in the data included in the original IND submission, was (b) (4) The Sponsor noted that the formulation in the original IND submission consisted of (b) (4) (b) (4) The to-be-marketed formulation includes (b) (4) (b) (4) intended to maintain particle size. While, the Sponsor acknowledged the Division's recommendation to include testing of particle size distribution of the new formulation in stability studies, particle size analysis of the drug product is not possible due to (b) (4)

(b) (4)

POST-Meeting Note: We acknowledge that you plan to use a separate and distinct dissolution method from your planned quality control dissolution method to monitor the drug product formulation particle size distribution during stability studies. This approach was suggested at the meeting by you in response to our concern that your preliminary particle size data (b) (4) (b) (4) If you would like to submit additional information on this planned approach for our evaluation, include this in an amendment to the IND.

ACTION ITEMS

1. The Sponsor will fully characterize the PK of the final to be marketed formulation before moving forward with Phase 2 or 3 studies.
2. The Sponsor will clarify the use of 4 of 5 of the WOMAC Pain questions as part of their protocol.
3. The Sponsor will submit a detailed analysis plan as part of the full protocol.
4. The Sponsor will look for genotoxic impurities and if necessary address according to Agency guidance.

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/s/

ALLISON MEYER
12/03/2012