

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207233Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 207233	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Vivlodex Established/Proper Name: meloxicam Dosage Form: Capsules Strengths: 5 mg and 10 mg		
Applicant: Iroko Pharmaceuticals		
Date of Receipt: 12/23/14		
PDUFA Goal Date: 10/23/15		Action Goal Date (if different):
• Proposed Indication(s): management of osteoarthritis pain		

GENERAL INFORMATION

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

YES NO

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



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

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

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 20938 Mobic Tablets NDA 21530 Mobic Suspension	Non-clinical information, labeling

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

A relative bioavailability study was performed with 15 mg Mobic for comparison in study MEL1-12-04.

RELIANCE ON PUBLISHED LITERATURE

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

YES NO

If “NO,” proceed to question #5.

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

YES NO

If “NO,” proceed to question #5.

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

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

N/A NO YES

RELIANCE ON LISTED DRUG(S)

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

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

YES NO

If "NO," proceed to question #10.

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

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Mobic Tablets	020938	Y

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

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

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

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

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

YES NO

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

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

- b) Approved by the DESI process?

YES NO

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

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

- c) Described in a monograph?

YES NO

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

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

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

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

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

YES NO

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

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

The change from the listed drug is in the dose and dosage form. Vivlodex is offered at 5 and 10 mg capsules, Mobic at 7.5 and 15 mg tablets. Also, there is a minor change in the indication from management of signs and symptoms of osteoarthritis (Mobic) to management of pain of osteoarthritis (Vivlodex)

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

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

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

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period;

(2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

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

YES NO

If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.

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

YES NO

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

YES NO

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

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

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

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

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

YES NO

If "NO", proceed to question #12.

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

YES NO

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

YES NO

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

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

Pharmaceutical alternative(s): NDAs 020938 and 021530 Mobic Tablets and Suspension
And Multiple Generics

PATENT CERTIFICATION/STATEMENTS

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

Listed drug/Patent number(s):

No patents listed proceed to question #14

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

YES NO

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

Listed drug/Patent number(s):

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

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

Patent number(s):

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

Patent number(s):

Expiry date(s):

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

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

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

Patent number(s):

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

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

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

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

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

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

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

Date(s):

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

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

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

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/s/

ALLISON MEYER
10/22/2015

PARINDA JANI
10/22/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: October 09, 2015

To: Sharon Hertz, MD
Acting Director
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

L. Shenee' Toombs, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): VIVLODEX (meloxicam)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 207233

Applicant: Iroko Pharmaceuticals, LLC

1 INTRODUCTION

On December 23, 2014, Iroko Pharmaceuticals, LLC submitted for the Agency's review an original 505(b)(2) New Drug Application (NDA) 207233 for VIVLODEX (meloxicam) capsules. The proposed indication for VIVLODEX (meloxicam) capsules is for management of osteoarthritis pain. The Reference Listed Drug (RLD) for this product is MOBIC (meloxicam) tablets (NDA 020938).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on May 11, 2015, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for VIVLODEX (meloxicam) capsules.

2 MATERIAL REVIEWED

- Draft VIVLODEX (meloxicam) capsules MG received on December 23, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 08, 2015.
- Draft VIVLODEX (meloxicam) capsules Prescribing Information (PI) received on December 23, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on October 08, 2015.
- Draft VIVLODEX (meloxicam) capsules Prescribing Information (PI) received on December 23, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on September 30, 2015.
- Approved MOBIC (meloxicam) MG dated August 03, 2011.

3 REVIEW METHODS

In our collaborative review of the MG we have:

- ensured that the MG is consistent with the Prescribing Information (PI)
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

BARBARA A FULLER
10/09/2015

LATOYA S TOOMBS
10/09/2015

LASHAWN M GRIFFITHS
10/13/2015

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: October 8, 2015

To: Allison Meyer, Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: L. Shenee Toombs, Regulatory Review Officer (OPDP)

CC: Olga Salis, Senior Regulatory Health Project Manager (OPDP)
Michael Wade, Regulatory Health Project Manager (OPDP)

Subject: NDA 207233
OPDP labeling comments for Vivlodex (meloxicam) capsules, for oral use
Labeling Review

OPDP has reviewed the proposed package insert (PI) and carton/container labeling for Vivlodex (meloxicam) capsules, for oral use (Vivlodex) that was submitted for consult on May 11, 2015. Comments on the proposed PI are based on the version sent via email from Allison Meyer (RPM) on September 30, 2015 entitled "11413-draft-labeling-text-0016.doc" and the draft carton/container labeling submitted September 24, 2015.

Comments regarding the PI are provided on the marked version below.

We have no comments on the draft carton/container labeling

Please note that comments on the Medication Guide will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP).

Thank you for the opportunity to comment.

If you have any questions, please contact Shenee' Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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/s/

LATOYA S TOOMBS
10/08/2015

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: August 21, 2015

TO: Allison Meyer, Regulatory Project Manager
Amelia Lockett, M.D., Medical Officer
Ellen Fields, M.D., Team Leader
Division of Analgesia, Anesthesia, and Addiction Products

FROM: John Lee M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H., Team Leader
Susan Thompson, M.D., Team Leader, for
Kassa Ayalew, M.D., M.P.H., Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

APPLICATIONS: NDA 207233

APPLICANT: Iroko Pharmaceuticals, LLC

DRUG: Meloxicam (Vivlodex®)

NME: No

INDICATION: Management of [REDACTED] (b) (4) osteoarthritis

REVIEW CLASSIFICATION: Standard

DARRTS CONSULTATION DATE: February 23, 2015

INSPECTION SUMMARY GOAL DATE: August 23, 2015

REGULATORY ACTION GOAL DATE: October 23, 2015

PDUFA DUE DATE: October 23, 2015

I. BACKGROUND

In this NDA 207233, Iroko Pharmaceutical, LLC (**Iroko**) references Mobic® (Boehringer Ingelheim, NDA 20938) as the reference listed drug in seeking 505(b)(2) approval of Vivlodex® (trade name pending), a new formulation of the non-steroidal anti-inflammatory drug (**NSAID**) meloxicam. Like other NSAIDs, the mechanism of action of meloxicam is mediated by the inhibition of prostaglandin synthetase (cyclooxygenase). To date, the use of meloxicam has been limited by side effects, including thrombosis, bleeding, and gastrointestinal ulcers. Vivlodex® is a submicron formulation of meloxicam engineered to reduce the drug delivery particle size, enhance GI absorption, and reduce NSAID-associated adverse events (**AEs**).

The reference drug Mobic® is a meloxicam formulation approved in the United States (**US**) in 2000 for the management of pain associated with osteoarthritis (**OA**), rheumatoid arthritis, and juvenile rheumatoid arthritis in adult and pediatric patients. For Vivlodex®, Iroko proposes “management of (b) (4) (b) (4) OA” as the clinical indication for use. Of the three new Vivlodex® studies sponsored by Iroko (under IND 114045), the randomized blinded efficacy Study MEL3-12-02 (**Study 02**) and the single-arm open-label safety Study MEL3-12-03 (**Study 03**) were identified for on-site audit at good clinical practice (**GCP**) inspections of two clinical investigator (**CI**) sites with large subject enrollment. The two studies are described below with emphasis on study features important to inspection. In the study titles, Vivlodex® is referred to as Meloxicam SoluMatrix (b) (4).

Study 02

A Phase 3, Multicenter, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Fixed-Dose, Parallel-Group, Efficacy, and Safety Study of Meloxicam SoluMatrix (b) (4) Capsules in Patients with Pain Due to Osteoarthritis of the Knee or Hip

This randomized, double-blind, placebo-controlled study was conducted between March and October of 2013 in 403 subjects with OA randomized at 40 US CI sites. The primary study objective was to compare the analgesic efficacy and safety of Vivlodex® 5 mg and 10 mg relative to placebo in subjects with pain due to OA of the knee or hip. The study consisted of three phases over 12 weeks and six study visits: (1) subject screening Visit 1; (2) baseline evaluation and randomization Visit 2, followed by 12 weeks of blinded treatment Visits 3-5 at Weeks 2, 6, and 12; and (3) follow up evaluation Visit 6 one week after study completion or after discontinuation from study.

Subject Selection

- Age \geq 40 years with OA of hip or knee as the primary diagnosis, and: (1) OA Functional Class I-III, and (2) chronic and current use of NSAIDs and/or acetaminophen to manage OA pain
- Western Ontario and McMaster Universities Osteoarthritis Index (**WOMAC**) pain score \geq 40 mm at baseline, with an OA-associated pain score increase of \geq 15 mm since initial screening
- Rescue medication (acetaminophen, up to 3000 mg per day) prior to baseline visit: allowed during washout, discouraged within 12 hours, and prohibited within six hours
- Body weight \geq 45 kg and body mass index (**BMI**) \leq 40 kg/m²; for women of childbearing potential, using acceptable birth control and not already pregnant or lactating

Treatment Groups and Regimen

- Subject randomization into three treatment groups in equal ratio, for once daily oral dosing of: (1) Vivlodex® 5 mg, (2) Vivlodex® 10 mg, or (3) placebo
- Acetaminophen rescue: 500 mg every four to six hours as needed up to 3000 mg/day, discouraged within 12 hours and prohibited within six hours of visits for Weeks 2, 6, and 12

Major Endpoints and Analyses

Data listings verified at inspection

- Reduction in WOMAC pain score, from baseline (randomization) to: (1) Week 12 (primary endpoint); (2) Weeks 2 and 6 (major secondary endpoints); and (3) the average score for the 12 treatment weeks
- Safety monitoring: (1) serious AEs (**SAEs**) for all subjects at each CI site, including any emergency room visit, hospitalization, or death; and (2) all other AEs (whether or not treatment-related, per CI or sponsor) for those subjects selected for detailed case records review at inspection

Other data, to be verified as applicable per inspectional findings

- Treatment response rates at Weeks 2, 6, and 12 as measured by $\geq 30\%$ and $\geq 50\%$ WOMAC pain score reduction from baseline; treatment response with respect to rescue medication use
- Two telephone assessments (single day, between Weeks 1 and 2) to assess target joint pain (treatment response) just before and two hours after dosing
- Week 12 score for Patient Global Impression of Change (**PGIC**) and Clinical Global Impression of Change (**CGIC**); discontinuations due to lack of efficacy through Week 12
- Safety monitoring: clinical laboratory testing, electrocardiogram (**ECG**), and any special evaluation triggered by an AE (including vital signs and physical examination)

Major Sponsor-Reported Outcomes

- Relative to placebo, a statistically greater WOMAC pain score reduction was observed for Vivlodex[®] (5 mg and 10 mg doses statistically not different) from baseline to: (1) Week 12 (primary endpoint), 5 mg ($p = 0.0005$) and 10 mg ($p = 0.006$); and (2) Week 6, 5 mg ($p = 0.0004$) and 10 mg ($p = 0.008$).
- Fewer subjects required rescue medication with Vivlodex[®] than with placebo (statistically not significant), and the overall (mean daily) rescue medication use was lower with Vivlodex[®] at 10 mg (314 mg, $p = 0.002$) and at 5 mg (326 mg, $p = 0.005$) than with placebo (464 mg).
- PGIC and CGIC improved with Vivlodex[®] treatment. Vivlodex[®] was generally well tolerated with no evidence of significant, dose-dependent, or unexpected AEs, including cardiovascular, GI, or renal AEs.

Study 03

A Multicenter, Open-Label, Safety Study of Meloxicam SoluMatrix[™] Capsules in Subjects with Osteoarthritis of the Knee or Hip

This single-group, open-label, long-term safety study was conducted between March 2013 and June 2014 in 600 subjects with OA at 40 US CI sites. The primary study objective was to evaluate the safety of Vivlodex[®] 10 mg once daily for up to 52 weeks in subjects with pain due to OA of the knee or hip.

Subject Selection

- Age ≥ 40 years with OA of hip or knee as the primary diagnosis requiring chronic (and current) use of NSAIDs and/or acetaminophen to manage the OA pain
- Body weight ≥ 45 kg and BMI ≤ 40 kg/m²; for women of childbearing potential, using acceptable birth control and not already pregnant or nursing

Treatment Groups and Regimen

- Single-group, open-label: Vivlodex[®] 10 mg orally once daily, “occasional” missed dose permitted
- Rescue medication: acetaminophen 500 mg every 4 to 6 hours as needed (maximum 3000 mg/day)

Major Endpoints and Analyses

Data listings verified at inspection

- Primary endpoint (safety): SAEs for all subjects at each CI site, including any emergency room visit, hospitalization, or death
- All other AEs (whether or not considered treatment-related, by CI or sponsor) for those subjects selected for detailed case records review at inspection

Other data to be verified as applicable per inspectional findings

- Clinical laboratory testing, ECG, and concomitant medication use
- Any special evaluation triggered by an AE (including vital signs and physical examination)

Major Sponsor-Reported Outcomes

- One subject died during the study, and a second died after withdrawing from the study (presumably neither was treatment-related). SAEs were reported for 6% of subjects. Severe AEs temporally associated with study medication dosing were observed in 4% of subjects.
- Cardiovascular, GI, hepatic, and renal AEs were of special interest, given the known NSAID safety profile. These AEs were seen in 16% of subjects (most in $\leq 2\%$ of subjects), with hypertension as the most common AE (4% of subjects). No new safety concerns were identified for these organ systems.
- Abnormal laboratory values of potential clinical concern (observed in individual subjects) included alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bilirubin, blood urea nitrogen, creatinine, glucose, and potassium.
- Vivlodex[®] 10 mg once daily appeared to be well tolerated. 13% of subjects withdrew from the study after an AE, most commonly after gastro-esophageal reflux (0.7% of subjects). 5% of subjects withdrew due to lack of efficacy.

II. INSPECTIONS

In auditing the two pivotal Studies 02 and 03 for this NDA, the following two CI sites were identified for on-site inspection, to confirm acceptable study conduct as assessed at NDA review. Each CI site was selected for the largest number of subjects, either randomized (blinded efficacy Study 02, Site 102) or enrolled (open-label safety Study 03, Site 124). For either study, no special concerns about study conduct were identified at NDA review, including protocol adherence and CI conflict of interest.

	Clinical Investigator	Study, Site, Enrollment	Inspection Outcome
1	Enrico G. Jones, M.D. Richard L. Montgomery, M.D. Triad Clinical Trials, LLC 515 College Road, Suite 15 Greensboro, North Carolina	Study 02, Site 102 32 subjects randomized	June 3 - 5, 2015 Pending, preliminary NAI
2	David W. Bouda, M.D. Heartland Clinical Research, Inc. 2201 North 90th Street, Suite 125 Omaha, Nebraska	Study 02, Site 124 26 subjects randomized Study 03, Site 124 50 subjects enrolled	April 17 - May 15, 2015 Pending, preliminary NAI

NAI = no action indicated; Pending = preliminary results based on communication with field investigator

1. Enrico G. Jones, M.D. (Richard L. Montgomery, M.D.)

- a. What was inspected: Form FDA 482 (Notice of Inspection) issued to Richard L. Montgomery, M.D.
- Records review: institutional review board (**IRB**) and sponsor oversight, CI financial disclosure, drug accountability and disposition, and subject case records
 - Subject case records: informed consent, subject screening and eligibility assessment, randomization and efficacy assessment, treatment compliance, AE monitoring, and data verification
 - Data verification: randomization, primary efficacy endpoint, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study 02, Site 102: 37 subjects were screened, 37 were enrolled, 32 were randomized, and 28 completed the study. Case records were reviewed for all subjects, including detailed review for 10 randomized subjects.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared adequate, including informed consent, randomization, efficacy assessment, AE monitoring, protocol deviations reporting, and drug accountability. IRB and sponsor oversight appeared acceptable. Source records were well maintained. All audited endpoint data were verifiable among source records, case report forms (**CRFs**), and NDA data listings.

- c. Assessment of data integrity: The data from this study site appear reliable.

Note: The findings noted above are based on preliminary communication with the field investigator.

2. David W. Bouda, M.D.

a. What was inspected:

- Records review: IRB oversight and sponsor monitoring, CI financial disclosure, drug accountability and disposition, and subject case records
- Subject case records: informed consent, subject screening and eligibility assessment, randomization and efficacy assessment, treatment compliance, AE monitoring, and data verification
- Data verification: randomization, primary efficacy endpoint, AEs, protocol deviations, subject discontinuations, and concomitant medication use

b. General observations and comments:

Study 02, Site 124: 41 subjects were screened, 26 were enrolled, 26 were randomized, and 26 completed the study. Case records were reviewed for all subjects, including detailed review for 10 randomized subjects.

Study 03, Site 124: 55 subjects were screened, 50 were enrolled, and 37 completed the study. Thirteen subjects were withdrawn for AEs and/or protocol non-compliance. Case records were reviewed for all subjects, including detailed review for 10 enrolled subjects.

No significant deficiencies were observed for either study and a Form FDA 483 was not issued. For both studies, the overall study conduct appeared adequate, including informed consent, randomization and efficacy assessment, AE monitoring, protocol deviations reporting, and drug accountability. IRB oversight and sponsor monitoring appeared acceptable. Source records were well maintained. All audited endpoint data were verifiable among source records, CRFs, and NDA data listings.

- c. Assessment of data integrity: The data from this study site appear reliable.

Note: The findings noted above are based on preliminary communication with the field investigator.

III. OVERALL ASSESSMENT AND RECOMMENDATIONS

To support the review of this 505 (b)(2) NDA for Vivlodex[®], the two core pivotal Studies 02 and 03 were audited on-site to confirm adequate study conduct (according to GCP) as assessed at NDA review. Two CI sites were inspected, each selected for its largest number of subjects, either randomized (blinded efficacy Study 02, Site 102) or enrolled (open-label safety Study 03, Site 124).

- Study 02 (403 subjects randomized): At the two CI sites inspected, subject case records were reviewed for a combined total of 58 randomized subjects (14%), including detailed review for 20 subjects (5%).
- Study 03 (600 subjects enrolled): At the single CI site inspected, subject case records were reviewed for 50 subjects (8%), including detailed review for 10 subjects (2%).

A total of three study-sites were audited (both studies audited at inspection of Site 124). No significant deficiencies were observed for all three study-sites, and a Form FDA 483 was not issued at either CI site. Study conduct appeared adequate, including IRB and sponsor oversight of study conduct. All audited data were adequately verifiable among source records, CRFs, and NDA data listings. The data from the three study-sites appear reliable as reported in the NDA.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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/s/

JONG HOON LEE
08/21/2015

JANICE K POHLMAN
08/21/2015

SUSAN D THOMPSON
08/21/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: August 19, 2015
Requesting Office or Division: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number: NDA 207233
Product Name and Strength: Vivlodex (meloxicam) capsules, 5 mg and 10 mg
Submission Date: August 14, 2015
Applicant/Sponsor Name: Iroko Pharmaceuticals, LLC
OSE RCM #: 2015-130
DMEPA Primary Reviewer: Millie Shah, PharmD, BCPS
DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised container labels and carton labeling (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

The Sponsor did not implement our recommendation to revise the middle digits of the NDC number from sequential digits between the 5 mg and 10 mg strength to non-sequential digits. The Sponsor responded to our recommendation that they use the product code as an identifier that is printed on the capsule shell for their products. Therefore, the Sponsor did not revise the middle digits of the NDC number, but rather increased the prominence of the middle digits by increasing their size in comparison to the other digits of the NDC number.

Additionally, the Sponsor did not implement our recommendation to relocate the statement, “Attention: Dispense the accompanying Medication Guide to each patient” from the side panel

¹ Shah M. Label and Labeling Review for Vivlodex (NDA 207233). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 MAY 28. 17 p. OSE RCM No.: 2015-130.

to the principal display panel. The Sponsor responded to our recommendation that they prefer to keep the statement in the same location, but made the statement more prominent and conspicuous by using a different and much brighter color (red).

2 CONCLUSIONS

The revised container labels and carton labeling are acceptable from a medication error perspective.

5 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

MILLIE C BRAHMBHATT
08/19/2015

BRENDA V BORDERS-HEMPHILL
08/19/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 28, 2015
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 207233
Product Name and Strength:	Vivlodex (meloxicam) capsules, 5 mg and 10 mg
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Iroko Pharmaceuticals, LLC
Submission Date:	December 23, 2014
OSE RCM #:	2015-130
DMEPA Primary Reviewer:	Millie Shah, PharmD, BCPS
DMEPA Acting Team Leader:	Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

Iroko Pharmaceuticals, LLC submitted NDA 207233 for Vivlodex (meloxicam) capsules. Thus, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested we evaluate the container labels, carton labeling, and prescribing information for vulnerabilities that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-(N/A)
ISMP Newsletters	D-(N/A)
FDA Adverse Event Reporting System (FAERS)*	E-(N/A)
Labels and Labeling	F
Highlights of Prescribing and Full Prescribing Information	G
Medication Error Risk Mitigation Strategy	H

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container labels, carton labeling, and prescribing information to identify deficiencies that may lead to medication errors and other areas for improvement. Additionally, we evaluated the risk analysis submitted by the Sponsor assessing the risk for medication errors between Vivlodex and other formulations of meloxicam.

Container Labels and Carton Labeling

Our review of the container labels and carton labeling identified areas of improvement to increase clarity and prominence of important information. We note the statement, "Attention: Dispense the accompanying Medication Guide to each patient" is located on the side panel. We recommend relocating this statement to the principal display panel to increase its prominence. We identified the middle digits of the NDC number are sequential between the 5 mg and 10 mg capsule strength. Since health care professionals traditionally use the middle

digits of the NDC number to check the correct product, strength, and formulation, wrong strength errors between the 5 mg and 10 mg strengths may result due to similarity of the middle digits of the NDC numbers. Our review of the physician sample blister label determined (b) (4) Although the label states the mg strength per capsule, the packaging of (b) (4) may be confusing and could lead to medication errors. We have post-marketing experience of overdose errors (b) (4) (b) (4) Thus, we provide recommendations in Section 4.2.

Prescribing Information

Our review of the *How Supplied* section identified the middle digits of the NDC number are sequential between the 5 mg and 10 mg capsule strength. Thus, we provide recommendations in Section 4.1 to mitigate the risk for wrong strength errors.

Medication Error Assessment-Risk for Confusion with Other meloxicam Products

As part of the Pre-NDA Meeting Response (See Appendix H for Pre-NDA Meeting Response), we communicated a concern that, based on the proposed strengths of 5 mg and 10 mg, a medication error could occur with the currently available 15 mg strength of meloxicam. Specifically, because of the differences in bioavailability between Vivlodex and other meloxicam formulations on the market, if Vivlodex is dispensed when meloxicam is intended, there would be the potential for increased side effects. We requested the Sponsor submit a risk analysis and determine how best to mitigate the risk for medication errors at the time of NDA submission.

We reviewed the risk analysis and medication error risk mitigation strategies submitted by the Sponsor (See Appendix H for Medication Error Risk Mitigation Strategy) on December 23, 2014. The Sponsor proposes labeling interventions, statements to be included in marketing materials for health care providers, and development of educational materials for patients. We find the strategy to include statements in marketing materials directed to health care providers and educational materials for patients acceptable from a medication error perspective. As part of the labeling interventions, the Sponsor proposes to include a non-interchangeability statement in the *Dosage and Administration* section of the prescribing information that would alert health care providers to the fact that Vivlodex capsules are not interchangeable with other meloxicam products due to the difference in relative bioavailability. We find the proposed statement acceptable. Additionally, the Sponsor proposes to change the established name from “meloxicam” to (b) (4) as part of the labeling interventions. We communicated the Sponsor’s proposal to change the established name to the Product Quality Reviewer. Per the Product Quality Reviewer, the established name must remain consistent with the approved established name, meloxicam. Thus, we provide recommendations in Sections 4.1 and 4.2 to change the established name to meloxicam on all labels and labeling.

¹ Institute for Safe Medication Practices, Safety Briefs. ISMP Med Safe Alert Acute Care 2002; 7(17):2

We assessed the risk for wrong drug errors between Vivlodex and other formulations of meloxicam. If a prescriber orders meloxicam, the pharmacist would not be able to substitute Vivlodex, since Vivlodex is not interchangeable with meloxicam. Conversely, if a prescriber orders Vivlodex, the pharmacist would not be able to substitute meloxicam, since meloxicam is not interchangeable with Vivlodex. Therefore, the inclusion of the non-interchangeability statement in the prescribing information is sufficient to mitigate the risk of wrong drug errors between Vivlodex and other formulations of meloxicam.

4 CONCLUSION & RECOMMENDATIONS

We conclude the Sponsor can improve the proposed labels and labeling to increase clarity and prominence of important information to promote safe use of this product. In addition, we conclude the Sponsor's proposed non-interchangeability statement in the prescribing information is sufficient to mitigate the risk of wrong drug errors between Vivlodex and other formulations of meloxicam.

If you have further questions or need clarifications, please contact Lisa Skarupa, OSE Project Manager, at 301-796-2219.

4.1 RECOMMENDATIONS FOR THE DIVISION

We have revised the Highlights of Prescribing and the Full Prescribing Information (See Appendix G) and have provided a detailed summary below for review and consideration by DAAAP.

A. Highlights of Prescribing

1. Revise the established name from, [REDACTED] (b) (4) capsules" to the approved established name, "(meloxicam) capsules."

B. Full Prescribing Information

1. See A.1.
2. Revise the middle digits of the NDC number in the *How Supplied* section from sequential digits between the 5 mg and 10 mg strengths 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.²

² 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>

4.2 RECOMMENDATIONS FOR IROKO PHARMACEUTICALS

We recommend the Sponsor implement the following prior to approval of this NDA.

A. Container Labels (all strengths)

1. Revise the established name from (b) (4) 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.³
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.⁴
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 (b) (4) to mitigate the risk for overdose errors. We have post-marketing experience of overdose errors where (b) (4). If this is implemented, change the net quantity to 1 capsule to reflect this change.

³ 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>

⁴ 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>

⁵ Institute for Safe Medication Practices, Safety Briefs. ISMP Med Safe Alert Acute Care 2002; 7(17):2

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.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vivlodex (meloxicam) capsules that Iroko Pharmaceuticals, LLC submitted on December 23, 2014.

Table 2. Relevant Product Information for Vivlodex (meloxicam) capsules	
Initial Approval Date	Not Applicable
Active Ingredient	meloxicam
Indication	management of osteoarthritis pain
Route of Administration	oral
Dosage Form	capsule
Strength	5 mg and 10 mg
Dose and Frequency	5 mg or 10 mg orally once daily
How Supplied/ Container Closure	Bottles of 30 or 90 capsules
Storage	Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F). [See USP Controlled Room Temperature]

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On May 19, 2015, we searched the L:drive and AIMS using the term, Vivlodex, to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any previous label/labeling reviews relevant to this review.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁶ along with postmarket medication error data, we reviewed the following Vivlodex (meloxicam) capsules labels and labeling submitted by Iroko Pharmaceuticals, LLC on December 23, 2014.

- Container label
- Carton labeling
- Professional Sample Blistercards

⁶ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDIX H. MEDICATION ERROR RISK MITIGATION STRATEGY

MEDICATION ERROR RISK MITIGATION STRATEGY FOR VIVLODEX CAPSULES

The following concern was communicated to Iroko as part of the Division's response to the Pre-NDA Meeting for VIVLODEX capsules:

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.

Risk Analysis

Given the proposed VIVLODEX Capsules doses, it is conceivable that a patient may ingest a 5 mg capsule and a 10 mg capsule (or 3 x 5 mg capsules), thinking that they are achieving dosing equivalence to Mobic 15 mg tablets. To assess the risk to patients of taking an inadvertent 15 mg dose of VIVLODEX Capsules, the C_{max} and AUC_{0-inf} of a hypothetical single 15 mg dose of VIVLODEX Capsules was estimated using a statistical examination of the observed PK parameters of 5, 6, 10, and 12 mg single doses of VIVLODEX Capsules. A theoretical single dose of VIVLODEX Capsules 15 mg is estimated to produce a C_{max} comparable to that reported for a single 30 mg dose of orally administered Mobic tablets (1.91 and 1.72 $\mu\text{g/mL}$, respectively), but lower than C_{max} values that have been reported under steady state conditions in fed elderly male and female subjects (Johnson JR, 2014; Türck D, et al, 1996; Mobic US PI, 2012). The AUC_{0-inf} for VIVLODEX Capsules 15 mg, however, is estimated to be significantly lower compared to what is reported for a single 30 mg dose of orally administered Mobic tablets (48.9 and 67.5 $\text{hr}\cdot\mu\text{g/mL}$, respectively) (Johnson JR, 2014; Türck D, et al, 1996).

Data from published clinical trials using meloxicam at doses up to 22.5 mg once daily for up to one year show that rates of GI adverse events either did not differ significantly from placebo or were similar to lower doses of meloxicam (Furst DE, et al, 2002 and Dougados M, et al, 1999). In a 52-week trial of subjects with ankylosing spondylitis, the

percentage of subjects who withdrew from the trial due to adverse events was similar between the meloxicam 22.5 mg treatment group and placebo, and did not reach the level of statistical significance by log rank test (P=0.08) (Dougados M, et al, 1999). Published safety data is not available for patients taking meloxicam doses in excess of 22.5 mg daily.

This information is presented in the Summary of Clinical Safety (2.7.4.6.6 Overdose).

Medication Error Risk Mitigation Strategy

Iroko fully understands the Agency’s concern and agrees that we should utilize all means of communication available to us to mitigate this risk.

Iroko conducted a survey of 76 primary care physicians practicing in the US in order to understand the most effective methods, from the prescribers’ perspective, to prevent the use of VIVLODEX capsules to obtain a 15 mg dose of meloxicam. A summary of this survey and a description of the results are provided in the [Appendix](#).

Based on the results of this survey, Iroko is proposing a multi-faceted approach to mitigate the risk for medication error with VIVLODEX capsules when approved and marketed that includes: labeling interventions, statements to be included in marketing materials for health care providers (HCPs), and development of educational materials for patients.

Labeling Interventions

1. Established name

Iroko strongly believes that the most effective way to prevent a medication error is to differentiate the established name for VIVOLODEX from that of currently available meloxicam products. Iroko is proposing to differentiate the established name (b)(4) (b)(4) “meloxicam”.

All of the proposed container and product labeling is presented with this proposal. The proposed trade and established name is as follows:

Vivlodex™ ((b)(4) meloxicam) capsules

While Iroko’s proposal is supported by the results of the HCP survey, we are open to further discussion with the Division to variations of differentiating the established name for VIVLODEX.

2. Non-Interchangeability Statement

Iroko is also proposing to include a section in the Dosage and Administration section of the prescribing information for VIVLODEX. This will alert HCPs to the fact that VIVLODEX capsules are not interchangeable with other meloxicam products because of the difference in relative bioavailability. The proposed statements are as follows:

2.2 *Non-Interchangeability with Other Formulations of Meloxicam*

VIVLODEX capsules are not interchangeable with other formulations of oral meloxicam even if the total milligram strength is the same. (b) (4)

(b) (4)
(b) (4) *do not substitute similar dosing strengths of other meloxicam products [see Clinical Pharmacology (12.3)].*

(b) (4)

The reference at the end of the first paragraph directs the prescriber to the Clinical Pharmacology section of the Prescribing Information where the pharmacokinetic data describing the difference between VIVLODEX capsules and currently available meloxicam is located.

Statement in Marketing Materials directed to HCPs

Iroko commits to include a statement in all professional promotional materials that would alert HCPs to the fact that 15 mg dose of VIVLODEX Capsules is not equal to a 15 mg dose of other meloxicam drug products.

Educational Materials for Patients

Iroko commits to produce and make available to patients educational materials that would include a statement that would advise them to take their medication as directed and not to exceed a total daily dose of 10 mg for VIVLODEX capsules.

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/s/

MILLIE C BRAHMBHATT
05/28/2015

BRENDA V BORDERS-HEMPHILL
05/28/2015

**Selected Requirements of Prescribing Information
REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: 207233

Application Type: NDA

Name of Drug/Dosage Form: Vivlodex (meloxicam) Capsules

Applicant: Iroko Pharmaceuticals LLC

Receipt Date: December 23, 2014

Goal Date: October 23, 2015

1. Regulatory History and Applicant's Main Proposals

Iroko Pharmaceuticals LLC is submitting a 505(b)(2) new drug application (NDA 207233) to obtain approval to market VIVLODEX Capsules 5mg and 10mg for the proposed indication of management of osteoarthritis pain. This NDA is being submitted via the 505(b)(2) regulatory pathway and therefore will rely on Mobic® Tablets 7.5 mg and 15 mg (Boehringer Ingelheim, NDA020938) for existing safety and efficacy data; along with the results of three core clinical trials conducted by Iroko.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

Selected Requirements of Prescribing Information

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.
Comment: None
- NO** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.
Comment: The length is more than 1/2 page. A waiver request is not submitted.
- Yes** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
Comment: None
- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.
Comment: None
- yes** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.
Comment: none
- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.
Comment: None
- yes** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required

Selected Requirements of Prescribing Information

• Revision Date	Required
------------------------	----------

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment: none

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.
- Comment:** None

Highlights Limitation Statement

- Yes** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.
- Comment:** none

Product Title in Highlights

- YES** 10. Product title must be **bolded**.
- Comment:** None

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.
- Comment:** None

Boxed Warning (BW) in Highlights

- yes** 12. All text in the BW must be **bolded**.
- Comment:** None
- yes** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.
- Comment:** None
- yes** 14. The BW must always have the verbatim statement “***See full prescribing information for complete boxed warning.***” This statement should be centered immediately beneath the heading and appear in *italics*.
- Comment:** None
- yes** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “***See full prescribing information for complete boxed warning.***”).
- Comment:** None

Selected Requirements of Prescribing Information

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment: *New Application*

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment: *None*

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment: *None*

Indications and Usage in Highlights

- yes** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment: *none*

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment: *Single dosage form*

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment: *None*

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment: *None*

Patient Counseling Information Statement in Highlights

- yes** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

Selected Requirements of Prescribing Information

If a product **does not** have FDA-approved patient labeling:

- “See 17 for PATIENT COUNSELING INFORMATION”

If a product **has** FDA-approved patient labeling:

- “See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling”
- “See 17 for PATIENT COUNSELING INFORMATION and Medication Guide”

Comment: *Pateint Counsleing Information Statment is missing.*

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *None*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment: None
- yes** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment: none
- yes** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment: none
- yes** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment: none
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment: None
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment: None
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment: None

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: None

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment: None

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment: *None*

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment: *None*

BOXED WARNING Section in the FPI

- yes** 36. In the BW, all text should be **bolded**.

Comment: *none*

- yes** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment: *None*

CONTRAINDICATIONS Section in the FPI

- yes** 38. If no Contraindications are known, this section must state “None.”

Comment: *none*

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment: *None*

- yes** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment: *Postmarketing Experience Section is not included.*

PATIENT COUNSELING INFORMATION Section in the FPI

- yes** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment: *none*

- yes** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment: *None*

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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
05/13/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 207233 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric
Proprietary Name: Vivlodex Established/Proper Name: meloxicam Dosage Form: capsules Strengths: 5 mg and 10 mg		
Applicant: Iroko Pharmaceuticals Agent for Applicant (if applicable):		
Date of Application: December 23, 2014 Date of Receipt: December 23, 2014 Date clock started after UN:		
PDUFA/BsUFA Goal Date: October 23, 2015		Action Goal Date (if different):
Filing Date: February 21, 2015		Date of Filing Meeting: January 22, 2015
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input checked="" type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): management of osteoarthritis pain		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<i>The application will be a priority review if:</i>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none">• A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)• The product is a Qualified Infectious Disease Product (QIDP)• A Tropical Disease Priority Review Voucher was submitted• A Pediatric Rare Disease Priority Review Voucher was submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): 114045

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:							
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 				<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)]. 				<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>				<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p>				<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes , please list below:							
Application No.		Drug Name		Exclusivity Code		Exclusivity Expiration	
<p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>							
Exclusivity				YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?				<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>							
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?				<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes , # years requested: 3							
<i>Note: An applicant can receive exclusivity without requesting it;</i>							

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ <i>If not, explain (e.g., waiver granted).</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Waiver requested

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

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forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Full waiver
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

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Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Meeting Minutes/SPAs	YES	NO	NA	Comment

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

End-of Phase 2 meeting(s)? Date(s): 12/3/12 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 7/16/14 <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input type="checkbox"/>		Prelim comments sent, meeting canceled by sponsor
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 22, 2015

BACKGROUND: Iroko Pharmaceuticals LLC is submitting a 505(b)(2) new drug application to obtain approval to market VIVLODEX Capsules for the proposed indication of management of osteoarthritis pain. This NDA is being submitted via the 505(b)(2) regulatory pathway and therefore will rely on Mobic® Tablets 7.5 mg and 15 mg (Boehringer Ingelheim, NDA020938) for existing safety and efficacy data; along with the results of three core clinical trials conducted by Iroko.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Allison Meyer	y
	CPMS/TL:	Parinda Jani	n
Cross-Discipline Team Leader (CDTL)	Ellen Fields		y
Division Director/Deputy	Sharon Hertz		y
Office Director/Deputy			
Clinical	Reviewer:	Amelia Lockett	Y
	TL:	Ellen Fields	y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Suresh Naraharisetti/Deep Kwatra	y
	TL:	Yun Xu	y
Biostatistics	Reviewer:	Kate Meaker	y

	TL:	Freda Cooner	y
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Nonclinical (Pharmacology/Toxicology)	Reviewer:	Armaghan Emami	Y
	TL:	Jay Chang	y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) <i>(for protein/peptide products only)</i>	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Ciby Abraham	y
	TL:	Julia Pinto	y
Biopharmaceutics	Reviewer:	Larry Chen	y
	TL:	Sandra Suarez	y
Quality Microbiology	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Jim Schlick	y
	TL:	Vicki Borders-Hemphill	y
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines	Reviewer:		
	TL:		
Other attendees	Dan Mellon, Eric Duffy, Lisa Skarupa		y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO BA study
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIostatistics</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
Comments:	
IMMUNOGENICITY (protein/peptide products only)	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	
PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
Comments:	
New Molecular Entity (NDAs only)	
<ul style="list-style-type: none"> Is the product an NME? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<u>Environmental Assessment</u>	
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
<u>Quality Microbiology</u>	<input checked="" type="checkbox"/> Not Applicable
<ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Sharon Hertz, MD</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60
<input type="checkbox"/>	If priority review:

	<ul style="list-style-type: none"> • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

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
02/25/2015

PARINDA JANI
02/25/2015