CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204768Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # **204768** SUPPL # HFD # **170**

Trade Name **Tivorbex**

Generic Name **Indomethacin**

Applicant Name **Iroko Pharmaceuticals LLC**

Approval Date, If Known **2/24/14**

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2) NDA

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

YES ☒ NO ☐

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

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

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? **3**

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☒ NO ☐

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

Appl No	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N018851	INDOMETHACIN	CAPSULE; ORAL	25MG	INDOMETHACIN	HERITAGE PHARMS INC
N018851	INDOMETHACIN	CAPSULE; ORAL	50MG	INDOMETHACIN	HERITAGE PHARMS INC
N018858	INDOMETHACIN	CAPSULE; ORAL	25MG	INDOMETHACIN	MYLAN
N022536	INDOMETHACIN	INJECTABLE; INJECTION	EQ 1MG BASE/VIAL	INDOMETHACIN	FRESENIUS KABI USA
N018332	INDOMETHACIN	SUSPENSION; ORAL	25MG/5ML	INDOCIN	IROKO PHARMS
N018878	INDOMETHACIN SODIUM	INJECTABLE; INJECTION	EQ 1MG BASE/VIAL	INDOCIN	RECORDATI RARE

2. Combination product.

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

N/A ☒ YES ☐ NO ☐

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

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES ☒ NO ☐

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

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

the application, without reference to the clinical investigation submitted in the application.

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

YES ☒ NO ☐

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

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

YES ☒ NO ☐

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

YES ☐ NO ☒

If yes, explain:

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

YES ☐ NO ☒

If yes, explain:

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

IND3-08-04b, ***A Phase 3, Randomized, Double-Blind, Multiple-Dose, Parallel-Group, Active and Placebo-Controlled Study of Indomethacin Nanoformulation Capsules for the Treatment of Acute Postoperative Pain After Bunionectomy***

IND3-10-06, ***A Phase 3, Randomized, Double-Blind, Multiple-Dose, Parallel-Group, Placebo-Controlled Study of Indomethacin Nanoformulation Capsules for the Treatment of Acute Postoperative Pain After Bunionectomy***

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

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

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

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

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

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

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on: **N/A**

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

IND3-08-04b, ***A Phase 3, Randomized, Double-Blind, Multiple-Dose, Parallel-Group, Active and Placebo-Controlled Study of Indomethacin Nanoformulation Capsules for the Treatment of Acute Postoperative Pain After Bunionectomy***

IND3-10-06, ***A Phase 3, Randomized, Double-Blind, Multiple-Dose, Parallel-Group, Placebo-Controlled Study of Indomethacin Nanoformulation Capsules for the Treatment of Acute Postoperative Pain After Bunionectomy***

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

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

Investigation #1

IND # **101940** YES ☒ NO ☐

Investigation #2

IND # **101940** YES ☒ NO ☐

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

N/A

Investigation #1

YES ☐ NO ☐

Explain: Explain:

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

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Kim Compton, Project Manager, will assistance from Anjelina Pokrovnichka, Medical Officer
Date: 2/21/14

Name of Office/Division Director signing form: Sharon Hertz
Title: Deputy Director, DAAAP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

KIMBERLY A COMPTON
02/24/2014

SHARON H HERTZ
02/24/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 204768	NDA Supplement # n/a	If NDA, Efficacy Supplement Type: n/a
Proprietary Name: Tivorbex Established/Proper Name: indomethacin Dosage Form: capsules		Applicant: Iroko Pharmaceuticals, LLC Agent for Applicant (if applicable):
RPM: Kim Compton		Division: DAAAP

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: 2/24/14

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 2/28/14	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

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

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

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 5
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☒ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ **Verified** ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ **Included**
Documentation of consent/non-consent by officers/employees	☒ **Included**

Action Letters

❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) **AP, 2/24/14**

Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ **Included**
• Original applicant-proposed labeling	☒ **Included**
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)* **NOTE: included at end of PI, not as stand alone document.**	☒ **Medication Guide** ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ **Included**
• Original applicant-proposed labeling	☒ **Included**
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ **Included**
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	**1/9/14** **1/3/14**
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None **7/9/13** DMEPA: ☐ None **1/8/14** DMPP/PLT: ☐ None **1/23/14** OPDP: ☐ None **1/30/14** SEALD: ☒ None **2/20/14** CSS: ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Committee	**6/28/13** ☐ Not a (b)(2) **1/21/14**
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ **Included**
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action

[4] Filing reviews for scientific disciplines should be filed with the respective discipline.

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC **1/15/14** If PeRC review not necessary, explain: _____	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) *(do not include previous action letters, as these are located elsewhere in package)*	**Various**
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	**Various**
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg **11/14/12**
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg **7/2/10**
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None **2/24/14**
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None **2/3/14**
PMR/PMC Development Templates *(indicate total number)*	☐ None **3**
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	**1/15/14; 6/28/13 (filing)**
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	**See Clinical Review dated 1/15/14, page 16**
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None **PMHS Review: 1/29/14; 10/24/13** **Drug Use Review: 10/21/13**
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A

❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested **1/22/14**
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None **1/9/14; 6/21/13 (filing)**
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ **None 1/16/14; 6/20/13 (filing)**
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None **1/20/14; 6/27/13 (filing)**
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ No separate review
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None **Quality: 1/17/14: 6/21/13 (filing)** **Biopharm: 1/15/14; (6/21/13 (filing)**
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)*	☐ Not needed **5/13/13 (filing and documentation that no further micro review needed)**
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	**See Quality Review dated 1/17/14, page 63**
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])*	Date completed: 9/26/13 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ **Not needed (per review)**

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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

/s/

KIMBERLY A COMPTON
02/25/2014

Compton, Kimberly

From: Compton, Kimberly
Sent: Friday, January 24, 2014 11:48 AM
To: Steve Jensen
Cc: Compton, Kimberly
Subject: RE: Tivorbex Request

Great, thanks Steve.

I just received a new request from the clinical team. They are requesting a response by next Friday Jan 31. Please let me know if that is feasible after you have a chance to look at it and discuss with your team.

1. Provide a shift table for blood pressure that shows percent changes from baseline to worst value for both diastolic and systolic blood pressure by treatment group (you may exclude the celecoxib group), and include mean, median, and standard deviations.

2. Provide the number of reports of SAEs and discontinuations that were due to abnormal blood pressure measurements, and for those subjects, provide the time course of blood pressure measurements over the treatment period.

Thanks
Kim

From: Steve Jensen [mailto:sjensen@iroko.com]
Sent: Thursday, January 23, 2014 7:20 PM
To: Compton, Kimberly
Subject: RE: Tivorbex Request

Hi Kim,

Per the request below, the following table includes Iroko's proposed Trial Completion Dates. Note that the dates for Final Protocol Submission, Trial Start Date, and Final Report Submission remain unchanged from those already submitted. This table is extracted from Iroko's updated Proposed Pediatric Study Plan attached (Table 10-1). Please advise if you would like the updated plan submitted as a formal amendment to the NDA.

Clinical Trials	Final Protocol Submission Date	Trial Start Date	Trial Completion Date	Final Report Submission
6 years to < 18 years (Trial 1)	April 1, 2015	October 1, 2015	February 1, 2017	October 2, 2017
2 years to < 6 years (Trial 2)	November 2, 2015	June 1, 2016	October 2, 2017	June 1, 2018
1 year to < 2 years (Trial 3)	June 1, 2018	December 31, 2018	April 30, 2021	December 31, 2021

Best Regards,

Steve

Steve Jensen
Sr. Vice President, Regulatory Affairs & Quality
Iroko Pharmaceuticals, LLC
One Kew Place
150 Rouse Blvd.
Philadelphia, PA 19112
(O) +1-267-546-3019
(F) +1-267-546-3004

IROKO PHARMACEUTICALS, LLC

Please consider the environment before printing this e-mail

From: Compton, Kimberly [mailto:Kimberly.Compton@fda.hhs.gov]
Sent: Wednesday, January 22, 2014 11:37 AM
To: Steve Jensen
Subject: RE: Tivorbex Request

HI Steve,

We are preparing our template for PMR documentation and the template requires us to list agreed upon dates for study completion. For each of the three Peds studies we have dates for protocol submission, study start date and final report submission, but not trial completion date. Could you please provide those?

Thanks
Kim

From: Compton, Kimberly
Sent: Friday, January 17, 2014 3:46 PM
To: sjensen@iroko.com
Subject: FW: Tivorbex Request

Hi Steve,

The team reviewed this and we will accept your proposed timeline as it is consistent with that accepted for Zorvolex.

Thanks
Kim

From: Steve Jensen [mailto:sjensen@iroko.com]
Sent: Thursday, January 16, 2014 8:18 PM
To: Compton, Kimberly
Subject: RE: Tivorbex Request

Dear Kim,

In response to the Information Request below, the timeline included for the Tivorbex pediatric studies was proposed based upon the timeline accepted by FDA (DAAAP) in our recent NDA 204592 (Zorvolex) approved October 18, 2013. The relative timings proposed for Tivorbex are consistent with those approved for Zorvolex assuming Tivorbex approval is received on the PDUFA Action Date of February 28, 2014.

Iroko would certainly target submission of the initial version of the first protocol well in advance of the proposed April 1, 2015 finalization date, however, we understand that FDA is under no obligation to respond with comments under a prescribed time period. We recognize how busy reviewers within the Agency are and we have concerns that comments will be received allowing only a minimum period of time for Iroko to digest those comments, produce a final protocol, and still meet our regulatory obligations.

Based on the reasoning above, Iroko requests that FDA reconsider the Information Request and accept the timeline currently proposed. If this is not acceptable however, Iroko is open to a phone discussion to better understand the timings that would be expected. Additionally, if Iroko had better knowledge of the timing with which the Agency reviewed and commented on PREA protocols, it would increase our understanding of the amount of time likely to be required to finalize the protocol.

Thank you for consideration of our comments, and I look forward to hearing back from you.

Steve

Steve Jensen
Sr. Vice President, Regulatory Affairs & Quality
Iroko Pharmaceuticals, LLC
One Kew Place
150 Rouse Blvd.
Philadelphia, PA 19112

(O) +1-267-546-3019
(F) +1-267-546-3004

IROKO PHARMACEUTICALS, LLC

Please consider the environment before printing this e-mail

From: Compton, Kimberly [mailto:Kimberly.Compton@fda.hhs.gov]
Sent: Wednesday, January 15, 2014 2:06 PM
To: Steve Jensen
Cc: Compton, Kimberly
Subject: Tivorbex Request

HI Steve,

We have the following Information Request regarding your pediatric study requirements:

You have submitted the following timeline for pediatric studies:

Clinical Trials	Final Protocol Submission Date	Trial Start Date	Final Report Submission
6 years to < 18 years (Trial 1)	April 1, 2015	October 1, 2015	October 2, 2017
2 years to < 6 years (Trial 2)	November 2, 2015	June 1, 2016	June 1, 2018
1 year to < 2 years (Trial 3)	June 1, 2018	December 31, 2018	December 31, 2020

The final protocol submission date of April 1, 2015 for the first study is too far in the future, as it does not seem necessary to take more than a year to finalize this protocol.

Therefore, provide a new timeline that includes earlier dates for all protocol submissions, and adjust the study conduct dates and report submissions to align with those dates.

We acknowledge that at least 6 months may be needed to submit a draft of the first protocol and come to agreement on a final version.

Please let me know if you have any questions about our request, and when you think you can provide a response.

Thanks
Kim

Kimberly Compton

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191

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/s/

KIMBERLY A COMPTON
01/24/2014

Compton, Kimberly

From: Compton, Kimberly
Sent: Tuesday, January 21, 2014 4:50 PM
To: sjensen@iroko.com
Cc: Compton, Kimberly
Subject: Tivorbex PI

Hi Steve,

The team has marked up the PI (the MG is still out for review with the patient labeling and OPDP team) with our suggested changes. Please take a look at our changes and notes and discuss with your team (our changes are all shown marked.) Please accept the ones the Iroko will accept and show any additional changes or responses you would like to share with us and send a marked version showing the next iteration of Iroko changes back in a WORD copy via email within 1 week.

Please let me know if you have any questions on our items.

Thanks
Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191
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24 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

KIMBERLY A COMPTON
01/24/2014

PeRC PREA Subcommittee Meeting Minutes
January 15, 2014

PeRC Members Attending:
Lynne Yao
Rosemary Addy
Hari Cheryl Sachs
George Greeley
Robert "Skip" Nelson
Jane Inglese
Wiley Chambers
Tom Smith
Karen Davis-Bruno
Shrikant Pagay
Lily Mulugeta
Dianne Murphy
William J. Rodriguez
Kevin Krudys (Did not review Tiborbex)
Maura O'Leary
Daiva Shetty
Coleen LoCicero
Peter Starke (Did not review Tiborbex)

Agenda

PREA

10:55	NDA	204768	Asmanex HFA (Partial Waiver/Deferral/Plan)	Maintenance treatment of asthma as a prophylactic therapy in patients 12 years of age and older
11:15	NDA	(b) (4)		
11:35	NDA	21345	Arixtra (fondaparinux sodium) PREA PMR Change/Partial Waiver	Prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE): Treatment of acute deep vein thrombosis when administered in conjunction with warfarin sodium Treatment of acute pulmonary embolism when administered in conjunction with warfarin sodium when initial therapy is administered in the hospital.
11:50	NDA	204768	Tivorbex (indomethacin) Partial Waiver/Deferral/Plan	Treatment of mild to moderate acute pain in adults
	NDA	*22-257 & 21-304*	*Valcyte (valganiciclovir hydrochloride) Deferral Extension*	*Prevention of CMV in pediatric kidney and heart transplant patients*

Asmanex HFA Partial Waiver/Deferral/Plan/Appropriately Labeled

- NDA 205641 seeks marketing approval for Asmanex HFA for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older.
- The application has a PDUFA goal date of April 27, 2014.
- The application triggers PREA as directed to a new dosing regimen.
- *PeRC Recommendations:*
    - The PeRC agreed with the Division to grant a partial waiver in patients less than five years of age because the product fails to offer a meaningful therapeutic benefit and a deferral studies in patients 5 to 11 years because studies are underway. The product is appropriately labeled for use in patients 12 years of age and older.

(b) (4)

Arixtra PREA PMR Change/Partial Waiver

NDA 21345 seeks a partial waiver and PREA PMR change to their marketed and approved application for Arixtra (fondapirinux sodium) approval for the Prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), Treatment of acute deep vein thrombosis when administered in conjunction with warfarin sodium, Treatment of acute pulmonary embolism when administered in conjunction with warfarin sodium when initial therapy is administered in the hospital.

- *PeRC Recommendations:*
    - The PeRC agreed with the Division to grant a partial waiver in patients ages birth to less than one year.
    - The PeRC noted that the original PREA requirements date back to 2003-2004, a time at which there were very few products for very limited options for the treatment of DVT in children. The sponsor submitted studies to address these PREA requirements in 2008 but the Division did not agree that the studies were sufficient to fulfill the PREA requirement. In the meantime other products have been approved to treat DVT that do not require administration of warfarin. PREA studies for these products are in progress. Therefore, use of this product in patients less than one year would not be considered to be a public health benefit at this point. Therefore, PeRC agrees with the waiver. In addition, PMHS and Clinical Pharmacology would be available to review any protocols to address this PREA requirement for older children.

Tivorbex Partial Waiver/Deferral/Plan

- NDA 204768 seeks marketing approval of the application for Tivorbex (indomethacin) for the treatment of mild to moderate pain.
- The application has a PDUFA goal date of February 28, 2014.

- The application triggers PREA as directed to a new indication and new dosing regimen.
- *PeRC Recommendations:*
    - The PeRC agreed with the Division to grant a partial waiver in patients birth to less than one year of age because the product does not represent a meaningful therapeutic benefit and will not be used in a substantial number of patients and to the deferral in patients 1 year to less than 17 years because adult studies are ready for approval. The Division provided use data to support a partial waiver in patients less than one year.
    - The PeRC recommends that the timeline for studies be moved up for this product.

Valcyte Deferral Extension

- NDAs 22257 & 21304 was approved on August 13, 2012, for the prevention of cytomegalovirus (CMV) disease and heart transplant patients > 4 months of age at high risk of developing CMV.
- (b) (4)
- *PeRC Recommendations:*

(b) (4)

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/s/

GEORGE E GREELEY
02/03/2014

Compton, Kimberly

From: Compton, Kimberly
Sent: Wednesday, January 15, 2014 2:06 PM
To: sjensen@iroko.com
Cc: Compton, Kimberly
Subject: Tivorbex Request

HI Steve,

We have the following Information Request regarding your pediatric study requirements:

You have submitted the following timeline for pediatric studies:

Clinical Trials	Final Protocol Submission Date	Trial Start Date	Final Report Submission
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Therefore, provide a new timeline that includes earlier dates for all protocol submissions, and adjust the study conduct dates and report submissions to align with those dates.

We acknowledge that at least 6 months may be needed to submit a draft of the first protocol and come to agreement on a final version.

Please let me know if you have any questions about our request, and when you think you can provide a response.

Thanks
Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191

APPEARS THIS WAY ON ORIGINAL

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/s/

KIMBERLY A COMPTON
01/15/2014

Rivera, Luz E (CDER)

From: Steve Jensen <sjensen@iroko.com>
Sent: Monday, January 13, 2014 9:36 AM
To: Rivera, Luz E (CDER)
Subject: RE: NDA 204768

Hi Luz,

I confirm receipt of your email. The requested stability data is being prepared for submission to you via email tomorrow. A formal amendment to the NDA will follow.

Best Regards,

Steve

Steve Jensen
Sr. Vice President, Regulatory Affairs & Quality
Iroko Pharmaceuticals, LLC
One Kew Place
150 Rouse Blvd.
Philadelphia, PA 19112
(O) +1-267-546-3019
(F) +1-267-546-3004

IROKO PHARMACEUTICALS, LLC

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From: Rivera, Luz E (CDER) [mailto:Luz.E.Rivera@fda.hhs.gov]
Sent: Saturday, January 11, 2014 7:44 PM
To: Steve Jensen
Subject: NDA 204768

Good afternoon Mr. Jensen,

We are reviewing your NDA 204768 and request additional information. We request a written response by **Tuesday, January 14, 2014**, in order to continue our evaluation of your NDA.

- Provide updated stability data for the 15, 18, and 21 month time points if available. Note that although you are encouraged to amend the NDA with additional data, and every effort will be made to review the stability

updates, their review will depend on the timeliness of the submission, the extent of submitted data, and the available resources. The expiration dating period would be commensurate with the available and reviewed stability data.

Please submit the information requested by email to me (Luz.E.Rivera@fda.hhs.gov) and officially submit to the application.

Please acknowledge the receipt of this request

Thank you,
Luz E Rivera, Psy.D.
LCDR, US Public Health Service
Regulatory Health Project Manager
FDA/CDER/OPS/ ONDQA
Division of New Drug Quality Assessment III
luz.e.rivera@fda.hhs.gov
301 796 4013

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/s/

LUZ E RIVERA
01/13/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204768

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

ATTENTION: Steve Jensen
Senior Vice President, Regulatory Affairs & Quality

Dear Mr. Jensen:

Please refer to your New Drug Application (NDA) dated and received April 30, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Indomethacin Capsules, 20 mg and 40 mg.

We also refer to your correspondence, dated and received October 18, 2013, requesting review of your proposed proprietary name, Tivorbex. We have completed our review of the proposed proprietary name, Tivorbex and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your October 18, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Lisa Skarupa, Senior Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2219. For any other information regarding this application, contact Kimberly A. Compton, R.Ph., Senior Regulatory Project Manager, in the Office of New Drugs at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
01/09/2014

Compton, Kimberly

From: Compton, Kimberly
Sent: Monday, November 25, 2013 2:31 PM
To: sjensen@iroko.com
Cc: Compton, Kimberly
Subject: Pediatric Study Plan (PSP) for N 204-768

HI Steve,

I have the following from the clinical team who just took a look at the PSP for Tivorbex:

> We have received your revised pediatric plan, and agree with the proposed types of studies for the oldest two age groups. However, while an open-label (OL) study in the youngest age group will provide safety and PK data, it will not be adequate to assess efficacy. We are willing to work out the details of the protocol design with you in the future and as data is obtained in the older age groups, but at this time we cannot agree to an OL efficacy study in this age group.
>
> Revise the pediatric plan to include a double-blind efficacy assessment of pain in pediatric patients ages 1 to less than 2 years. Wording can be as follows:
>
> > A pharmacokinetic, safety, and efficacy study or studies of an age-appropriate formulation of Tivorbex in pediatric patients 1 year to less than 2 years of age with acute pain.

Please let me know if you have any questions.

Thanks and Happy Thanksgiving,

Kim

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/s/

KIMBERLY A COMPTON
11/25/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

From: Donna Snyder, MD, Medical Officer
Pediatric and Maternal Health Staff (PMHS)

Through: Hari Cheryl Sachs, MD, Team Leader
Lynne Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff (PMHS)

To: Division of Analgesia, Anesthesia and Addictive Products (DAAAP)

Products: Diclofenac (Zorvolex®), NDA 204592
Indomethacin (b) (4) NDA 204768

Consult Request: The Division requested a response for the following question:

"Please provide input on the appropriate lower age limit for PREA PMR studies of NSAIDs indicated for acute pain. We also refer to the meeting minutes for the Sept. 4, 2013, PeRC meeting where partial waiver/deferral plan for Zorvolex was discussed with the Division.

Applicant Iroko Pharmaceuticals is requesting [a] waiver for pediatric [patients] age 0 to 12 months. The Division agrees with their request on the grounds that drug would be ineffective or unsafe in this age group because pharmacokinetic pathways for the drug's metabolism are not fully developed in this age group. PeRC did not agree with the Division on waiver justification. The PeRC noted that it may not be worth the "risk" to study this product for this population but that other products metabolized by CYP2C9 may be important to be studied in the 0 to 6 month population. PeRC granted [a] partial waiver in age group birth to less than one year because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients of this age and is

not likely to be used in a substantial number of pediatric patients in this age group. There was concern expressed by the Division and some members of the PeRC that there may not be adequate existing therapies for the treatment of mild to moderate pain in patients 0 to 6 months of age."

Materials Reviewed:

- Medical Review for Diclofenac (Zorvolex®) dated September 17, 2013 (DARRTS Reference ID: 3375013)
- Pediatric Review Committee Meeting Minutes from September 4, 2013 (DARRTS Reference ID: 3377309)
- Pre-NDA Meeting Package for (b) (4) (indomethacin) from September 13, 2012
- Type B, Pre-NDA Meeting Minutes dated November 14, 2012, (DARRTS Reference ID: 3216872)
- Indomethacin capsule, tablet and suspension labeling from Drugs @ FDA, accessed October 3, 2013
- Indomethacin for injection labeling from Drugs @ FDA, accessed October 3, 2013
- PMHS Diclofenac Consult dated July 29, 2013, (DARRTS Reference ID: 3348913)
- (b) (4)
- (b) (4)
- Ofirmev® (IV acetaminophen, NDA 22450) approval letter dated November 2, 2010, (DARRTS Reference ID: 2858778)
- Caldolor® (IV ibuprofen, NDA 22348) approval letter dated June 11, 2009, from Drugs @ FDA
- Dilantin® (phenytoin) labeling from Drugs@FDA
- Postmarketing Requirements for Nucynta (tapentadol, NDA 22304) from fda.gov
- Morphine Sulfate Oral Solution, 10 mg/5 mL and 20 mg/5 mL (NDA 22-195) and Morphine Sulfate Tablets, 15 mg and 30 mg (NDA 22-207) approval letter from Drugs@FDA

Background and Regulatory History:

DAAAP would like guidance on the lower age limit and rationale for a full or partial waiver of pediatric studies for NSAIDS with a particular focus on two products that are currently under review, Zorvolex® (diclofenac) and (b) (4) (indomethacin).

ZORVOLEX® (DICLOFENAC)

Zorvolex® (diclofenac) is (b) (4) a non-steroidal anti-inflammatory Drug (NSAID). The sponsor is Iroko Pharmaceuticals, LLC. The NDA is currently under review by DAAAP. The proposed indication is the treatment of mild to moderate acute pain in adults. No studies have been conducted in pediatric patients. Since the drug is ready for approval for adults, the sponsor requested a deferral of studies in pediatric patients 1 year to 17 years of age and a waiver of studies in

pediatric patients less than 1 year of age.

Diclofenac is approved in a number of formulations:

- Voltaren® (diclofenac sodium) 25, 50, and 75 mg Delayed Release Tablets (NDA 19201, approved in 1988)
- Votaren® (diclofenac sodium) 0.1% Ophthalmic Solution (NDA 20037, approved in 1991)
- Cataflam® (diclofenac potassium) 25 and 50 mg Immediate Release Tablets (NDA 20142, approved in 1993)
- Voltaren-XR® (diclofenac sodium) 100 mg Extended Release Tablets (NDA 20254, approved in 1996)
- Arthrotec® (diclofenac sodium/misoprostol) 50mg/.2mg, 75 mg/0.2 mg Delayed Release Tablets (NDA 20607, approved in 1997)
- Solaraze® (diclofenac sodium) 3% Gel (NDA 21005, approved in 2000)
- Flector® (diclofenac epolamine) 1.3% patch (NDA 21234, approved in 2007)
- Voltaren® (diclofenac sodium) 1% Gel (NDA 22122, approved in 2007)
- Zipsor®(diclofenac potassium) 25 mg capsules (NDA 022202, approved 2009)

There are also generic versions of some of the diclofenac products available. ***None of these products are approved for use in pediatrics.***

(b) (4)

(b) (4)

Iroko Pharmaceuticals discussed the pediatric plan for Zorvolex® with DAAAP in November 2010. DAAAP provided preliminary feedback at the meeting and determined that efficacy could be extrapolated for pediatric patients 2 years of age for acute pain and older but that the pharmacokinetics (PK) and safety of the drug would need to be studied. For patients less than 2 years of age, a PK, safety and efficacy study would likely be required. For patients under 1 year of age, a partial waiver may be possible due to the immaturity of the enzymes required to metabolize diclofenac. The rationale for the waiver would be that the product would be unsafe in that pediatric age group.

DAAAP met with the Pediatric Review Committee (PeRC) on September 4, 2013 to discuss a partial waiver and deferral plan for Zorvolex® for the treatment of acute pain. The sponsor has proposed deferring the following pediatric studies:

- An open-label PK and safety study or studies of an age appropriate formulation of diclofenac in pediatric patients 6 to < 18 years of age with acute pain.
- An open-label PK and safety study or studies of an age appropriate formulation of diclofenac in pediatric patients 2 to < 6 years of age with acute pain.
- A PK, safety, and efficacy study or studies of an age appropriate formulation of diclofenac in pediatric patients 1 to < 2 years of age with acute pain.

PeRC agreed that studies should be deferred and that a partial waiver could be granted for patients less than 1 year of age. However PeRC did not agree that a partial waiver should be granted on the grounds that the drug would be unsafe in the pediatric population under 1 year. The PeRC acknowledged that, in the past, a waiver had been issued in the less than 1 year old age range because the pharmacokinetic pathways (CYP2C9) for the drug's metabolism are not fully developed in this age group. However, PeRC noted that use of this rationale for not studying the product may set a precedent for the study of other NSAIDs where information may be needed in the birth to 1 year age range. PeRC suggested that if a waiver were to be granted for pediatric patients less than 1 year of age, the rationale should be that the product does not represent a meaningful benefit over existing therapies and that the product is unlikely to be used in a substantial number of patients in this age group. DAAAP is consulting PMHS for advice on the appropriate rationale and age for a waiver in light of PeRC's recommendations.

(b) (4) (INDOMETHACIN)

(b) (4) is a submicron particle formulation of indomethacin that is being developed for the treatment of mild to moderate acute pain. The sponsor is also Iroko Pharmaceuticals, LLC. There are several approved formulations of indomethacin, including generics that are marketed; below are the Reference Listed Drugs (RLD) for each formulation:

- Indocin (indomethacin) oral suspension 25 mg/5 ml (NDA 018332, approved 1985)

- Indocin (indomethacin sodium) injection 1 mg single dose vial (NDA 018878, approved 1985)
- Indomethacin 1 mg single dose vial (NDA 022536, approved 2010)
- Indomethacin extended release oral capsule 75 mg (ANDA 074464, approved 1998)
- Indomethacin oral capsule 50 mg (ANDA 070624, approved 1985)
- Indomethacin suppository 50 mg (ANDA 073314, approved 1992)

Currently indomethacin is approved in adults and children over 14 years of age in tablet, capsule and suppository for:

- Moderate to severe rheumatoid arthritis including acute flares of chronic disease
- Moderate to severe ankylosing spondylitis
- Moderate to severe osteoarthritis
- Acute painful shoulder (bursitis and/or tendinitis)
- Acute gouty arthritis

The extended release capsule is approved for all the indications above except for gout in adults and pediatric patients over 14 years of age. There are no outstanding PREA requirements for any of these products (since they were approved before the enactment of PREA) and no Written Requests have been issued.

Indomethacin is approved in an IV form, "to close a hemodynamically significant patent ductus arteriosus in premature infants weighing between 500 and 1750 g when after 48 hours usual medical management is ineffective." There are no approved adult indications.

The sponsor met with DAAAP on June 8, 2010, for an end of Phase 2 meeting and discussed the pediatric plan (b) (4) (b) (4) DAAAP provided preliminary feedback at the meeting on the pediatric plan. DAAAP stated that studies could be conducted for the proposed indication of acute pain in pediatric patients (b) (4) However, if the sponsor determined that it would be unsafe to use the product under a certain age, then the sponsor could submit justification. DAAAP encouraged the sponsor to start pediatric studies before submission of their NDA; however the sponsor indicated that they planned to submit a pediatric plan with submission of the NDA.

On October 23, 2012, the sponsor met with DAAAP to discuss the submission of an NDA under the 505(b)(2) pathway. The sponsor filed the NDA on April 30, 2013, and submitted a pediatric plan. The sponsor has requested a partial waiver for pediatric patients (b) (4) and a deferral of studies in patients (b) (4) IMS data on the projected number of unique patients who were prescribed indomethacin in calendar year 2011 for the entire pediatric age range were provided to support their partial waiver request.

DAAAP would like guidance on the lower age limit and rationale for a full or partial waiver of pediatric studies for NSAIDS (using diclofenac and indomethacin as examples) for the indication of acute pain.

PMHS Discussion:
The criteria for a full or partial waiver under the Pediatric Research and Equity Act (PREA) are the following:

1. Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed).

2. The product would be ineffective or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information must be included in labeling.

3. The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

In addition, a partial waiver can be granted if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

Necessary studies are impossible or highly impracticable
The indication that is proposed for both of these products is treatment of mild to moderate acute pain. Pediatric patients commonly experience acute pain through acute medical procedures, illness and injuries.[1] Studies should be possible across all age spectrums and have been required for other products used to treat acute pain. Examples of drugs that are indicated in adults for acute pain and are being studied across all pediatric age ranges for acute pain are Ofirmev® (IV acetaminophen), Caldolor® (IV ibuprofen), Nucynta® (tapentadol) and morphine sulfate oral solution and tablets.

The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
Note: both arms of this criterion must be met
Diclofenac is used routinely for acute pain in children. A Cochran review from 2011 explored the use of diclofenac for acute pain in pediatric patients.[2] The review included

[1] Committee on Psychosocial Aspects of Child and Family Health and task Force on Pain in Infants, Children, and Adolescents. The Assessment and Management of Acute Pain in Infants, Children, and Adolescents. Pediatrics: 2001; 108; 793-797.
[2] Standing, J, Savage, I, Pritchard, D and Waddington, M. Diclofenac for acute pain in children. The Cochrane Database of Systematic Reviews 2009. Issue 4. Art. No.: CD005538. DOI: 10.1002/14651858.CD005538.pub2

74 trials and data on 3616 participants. The review concluded that diclofenac may reduce the occurrence of nausea and vomiting when used in the peri-operative period and that the optimum dose for use in children needs to be determined. Studies included patients down to 4 months of age but the majority of patients were over the age of 1 year. A prospective review of use in UK hospitals determined that diclofenac was widely used for treating acute pain in pediatric patients and that the safety profile was similar to that of adults. Diclofenac was used more frequently in older children when compared to groups treated with other medications for pain. The authors postulate that because diclofenac is renally excreted, concerns about the maturation of renal function in the youngest patients may have resulted in avoidance of use in that population.[3,4] However, the authors also note that the lack of a pediatric formulation made dosing in patients under the age of 6 years of age more difficult. Another study surveyed anesthesiologists in Great Britain and Ireland on use of NSAIDs in infants and found that diclofenac was the NSAID used most commonly intra-operatively (78%) and ibuprofen was most likely to be used post-operatively (73%). The specific age ranges for each specific NSAIDs were not provided, but the article did state that nearly 48% of responders prescribed NSAIDs for infants less than 6 months of age and 80% of responders used NSAIDS in infants less than 1 year of age.[5]

Literature suggests that diclofenac is used in pediatric patients under 1 year but the exact frequency of use in the youngest pediatric patients is unclear. Because diclofenac has been approved in a variety of formulations since 1988, use data may help define the population using the product and indicate where study information would be of public health benefit. If the use data confirms that diclofenac is unlikely to be used in patients less than 1 year of age for acute pain (as proposed at the PeRC meeting), then an argument may be made that studies in patients under age 1 would not represent a meaningful benefit over existing therapies for pediatric patients and would not be used in a substantial number of patients. If use data does show that the product is likely to be used pediatric patients less than 1 year of age, then diclofenac should be studied in that pediatric population.

In contrast, indomethacin is approved for use in neonates to close a patent ductus arteriosus (PDA) but is not approved for treatment of acute pain. Indomethacin may prevent the occurrence of intra-ventricular hemorrhage in pre-term infants when compared to other agents used for PDA closure, such as ibuprofen.[6] Indomethacin may be used off-label in patients with Juvenile Idiopathic Arthritis (JIA)[7] and to treat certain

[3] Standing, J. et al. Prospective Observational Study of Adverse Drug reactions to Diclofenac in Children. Br J Clin Pharmacol: 2009. 68(2); 243-251.
[4] Kokki, H. Nonsteroidal Anti-Inflammatory Drugs for Postoperative Pain: A Focus on Children. Pediatr Drugs 2003; 5 (2): 103-123.
[5] Eustace, N and O'Hare, B. Use of nonsteroidal anti-inflammatory drugs in infants. A survey of members of the Association of Paediatric Anaesthetists of Great Britain and Ireland. Paediatr Anaesth. 2007 May;17(5):464-9.
[6] Ohlsson, A., R. Walia, and S.S. Shah. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev, 2010(4): p. CD003481.
[7] Hugel, B. et al. Treatment Preferences in juvenile idiopathic arthritis - a comparative analysis in two health care systems. Pediatric Rheumatology: 2013. 11:3.

uncommon headache disorders such as paroxysmal hemicrania and hemicrania continua.[8] The American Academy of Pediatrics (AAP) Committee on Pediatric Emergency Medicine and Section on Anesthesiology and Pain Medicine does not include indomethacin as a recommended treatment for acute pain in pediatric patients in an emergency room setting.[9] An extensive literature review did not support use in pediatrics for the acute pain indication proposed by the sponsor.

The IMS data provided by the sponsor also appears to support their partial waiver request. (b) (4)

PMHS would recommend that DAAAP perform a use review to independently evaluate the use of indomethacin in patients (b) (4) 0 to less than 1 year of age. Indomethacin has been approved since 1985 in a variety of formulations, including formulations that can be given to infants. If use data confirm the sponsor's data that indomethacin is unlikely to be used in the pediatric population (b) (4) for acute pain, there may be no public health benefit to performing studies. Indomethacin would then meet both arms of the criterion that are needed for a partial pediatric waiver. (b) (4)

<u>The product would be ineffective or unsafe in one or more of the pediatric group(s) for which a waiver is being requested</u>

DAAAP has issued a waiver in the past for diclofenac products on the grounds that the product may be unsafe to use in pediatric patients less than 1 year of age because of the immaturity of the enzymes needed to metabolize that product. Both diclofenac and indomethacin are metabolized primarily through the CYP2C9 pathway.[10,11] Newborns acquire expression CYP2C9 by about 10 days of life with continued maturation thereafter through the first year of life.[12] However, several drugs metabolized through this pathway are approved or are being studied for use in infants less than one year of age. Examples include phenytoin, fosphenytoin, and intravenous ibuprofen (Caldolor®). Phenytoin is approved in pediatric patients and intravenous ibuprofen has a PREA requirement down to birth. (b) (4) Use of these drugs in very young infants is anticipated and collection of PK data is critical to inform use.

[8] Summ, O. and Evers, S. Mechanism of Action of Indomethacin in Indomethacin-Responsive Headaches. Curr Pain Headache Rep (2013) 17:327
[9] Fein, J.A., et al., Relief of pain and anxiety in pediatric patients in emergency medical systems. Pediatrics, 2012. 130(5): p. e1391-405.
[10] Davies, N. and Anderson, K. Clinical Pharmacokinetics of Diclofenac, Therapeutic Insights and Pitfalls. Clin. Pharmacokinetics: 1997. 33 (3): 184-213.
[11] Nakajima, M et al. Cytochrome P4502C9 Catalyzes Indomethacin 0-demethylation in Human Live Microsomes. Drug Metablism and Disposition: 1998. 26 (3); 261-266.
[12] Sevasti, B et al. Developmental Expression of Human Hepatic CYP2C9 and CYP2C19. Journal of Pharmacology and Experimental Therapeutics: 2004. 308 (3): 965-974.

Maturation of renal function is of concern in very young infants; glomerular filtration rate and tubular secretion are both immature at birth but reach adult capacity sometime during the later part of the first year of life.[13] NSAIDs are excreted through the kidney and are known to affect renal function, likely due to the effect on renal prostaglandin synthesis.[14] Thus, as long as there would be a public health benefit for studying a particular NSAID in the pediatric population, studies should proceed as long as careful monitoring of fluid and renal status occurs. Requiring inclusion of a Data Safety Monitoring Board may also help ensure that studies are ethically performed in the pediatric population.

(b) (4)

This rationale alone would not be sufficient to issue a waiver (b) (4)

Inability to make age-appropriate formulation:
The sponsor is aware that they must use an age appropriate formulation in pediatric studies. The sponsor has not requested a partial waiver for diclofenac for this reason. (b) (4)

For indomethacin, the sponsor has requested a partial waiver on the grounds that development of a pediatric formulation with the same pharmacokinetic profile is not viable. However, indomethacin in IV and oral solution formulations are available, although not approved in children, and could be used in pediatric studies if the studies would be of a public health benefit.

If ultimately, the sponsor cannot produce an appropriate pediatric formulation, the partial waiver will only include those age ranges that would require a different formulation and

[13] Kearns, G et al. Developmental Pharmacology - Drug Disposition, Action, and Therapy in Infants and Children. N Engl J Med 349; 12; 1157-1167.
[14] Ibis [4].

the information on the sponsor's attempts to produce an appropriate pediatric formulation will be posted publically on the FDA website.

Conclusion:
PMHS agrees that studies should **not** be waived in the pediatric population because the pharmacokinetic pathways for the drug's metabolism are not fully developed in pediatric patients under 1 year (b) (4) Both diclofenac and indomethacin are metabolized primarily through the CYP2C9 pathway. However, several drugs metabolized through this pathway are approved or are being studied for use in infants less than one year of age. The need for a waiver should be based on whether there is a public health benefit to performing the studies in the pediatric population. However, the determination for a partial waiver is product specific and cannot be generalized across the entire class of NSAIDs. If substantial use is demonstrated in the case of diclofenac and indomethacin, then studies are particularly critical in the pediatric population where the product is expected to be used to inform dosing and to evaluate the adverse event profile in that specific age group.

In the case of diclofenac, although the sponsor has requested a partial waiver on the grounds that use would be unsafe, the Division and PeRC agreed that use was likely below the age of one year. PMHS found literature suggesting that the product is used in pediatric patients under 1 year, though the frequency of use compared to other NSAIDs in this age group was not clear. A review of use data may help further define the pediatric populations that are using the product and help determine if a partial waiver in the pediatric population is justified.

In contrast, a literature review did not suggest that indomethacin is typically used for the treatment of acute pain in the pediatric population. The sponsor submitted data that determined that use of indomethacin is low across the entire pediatric population and has requested a waiver of studies in pediatric patients (b) (4) Thus, indomethacin may qualify for a partial waiver in this age group because the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested. PMHS recommends that DAAAP confirm that use of indomethacin in the pediatric population is low before agreeing on a pediatric study plan for this product.

The Division is reminded that PMHS and PeRC are separate. Generally, the PeRC often provides recommendations that are consistent with advice provided from PMHS. Nevertheless, PMHS cannot make recommendations on behalf of the PeRC.

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/s/

DONNA L SNYDER
10/24/2013

LYNNE P YAO
10/24/2013

Compton, Kimberly

From: Compton, Kimberly
Sent: Friday, October 11, 2013 6:52 PM
To: sjensen@iroko.com
Cc: Compton, Kimberly
Subject: N 204768 C&C Requests

Hi Steve,

Our team has completed their review of the submitted carton and container labeling for N 204768. They are listed below.

Please review and let me know if you have any questions on our requests and when you think Iroko will be able to submit revised labels.

A. Regarding all the Container Labels and Carton Labeling (30 count, 90 count, and physician samples - 20 mg and 40 mg strengths)

1. Revise the presentation of the proprietary name so it appears in title case rather than all capital letters to improve readability.

2. Revise the established name to read "(indomethacin) capsules". Additionally, ensure that the entirety of the name appears on one line underneath the proprietary name.

3. (b) (4)

4. Revise the color of the line graphic that appears underneath the strength statement so that each strength has a distinct underline color. Using the same colored line on the different strengths diminishes the differentiation of these labels. Alternatively, the line could be deleted, the entire strength can be placed in a different colored box, and the strength can be color blocked.

B. Regarding the bottle Container Labels (30 count and 90 count - 20 mg and 40 mg strengths)

1. Ensure that the image of the capsule on the principal display panel of bottle labels represents the actual capsule and its true size, color and imprint. Ensure that the capsule image does not compete in size or prominence with the proprietary name and strength information.

2. Remove the statement "See package insert for dosage information" from the principal display panel or relocate it to the side panel.

(b) (4)

(b) (4)

I will archive a copy of this request in our system to document the request.

Thanks
Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191
Please consider the environment before printing this e-mail. If you decide to print, please make double-sided copies.

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/s/

KIMBERLY A COMPTON
10/11/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204768

INFORMATION REQUEST

Iroko Pharmaceuticals, LLC
Attention: Steven Jensen
Senior Vice President, Regulatory Affairs & Quality
One Kew Place, 150 Rouse Boulevard
Philadelphia, PA 19112

Dear Mr. Jensen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act for Indomethacin Capsules, 20 mg and 40 mg.

We are reviewing the Chemistry, Manufacturing and Control and Biopharmaceutics sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Submit the actual reference standard information to the drug substance section of the NDA (Section 3.2.S.5).
2. Your registration stability data do not support the NMT (b) (4) acceptance limit for total impurities you proposed for the drug product. Tighten the acceptance limit to be reflective of the actual data.
3. Using HPLC retention time alone as the identification test for the drug product is not sufficiently specific to the API. Add an additional orthogonal identification test to your drug product specifications, for example, the UV spectrum acquired using diode array in impurity analysis.
4. Provide an actual copy of each test method used in your release and stability testing, clearly identify each method with a unique method ID and version number. Revise the drug product specification tables to include these method identifications.
5. Clarify if the drug product container closure system components meet the respective CFR sections of indirect food additive regulations. If yes, provide a table that correlates the individual components with the relevant CFR sections.
6. As stated in 21 CFR 314.81, commit to immediately discuss with the Agency any aberrations of the drug product from its approved specifications and to withdraw the affected lots from the market as warranted.
7. Your proposed dissolution method is not (b) (4) appropriate. We recommend that you change this method (b) (4)

8. Explain the discrepancy [redacted] as depicted in Figure 5-1 of the dissolution method report.
9. Using the recommended pH [redacted] method, provide full dissolution profiles (5, 10, 15, 20, 30, 45, 60, and 75 minute time points; individual, mean, SD, profiles, tables and figures) for the phase 3 clinical and registration batches. Start collecting stability data using the revised dissolution method as soon as possible (next stability time point).

If you have any questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796-4013.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
10/03/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 204768

PROPRIETARY NAME REQUEST WITHDRAWN

Iroko Pharmaceuticals, LLC
c/o Carie Masoner
2290 Shimmering Bay Ln.
Cincinnati, OH 45244

ATTENTION: Carie Masoner
Senior Regulatory Consultant

Dear Ms. Masoner:

Please refer to your New Drug Application (NDA) dated and received, April 30, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Indomethacin Capsules, 20 mg and 40 mg.

We also refer to the August 19, 2013, telephone conference held between Iroko Pharmaceuticals and FDA concerning the proposed proprietary name (b) (4)

We acknowledge receipt of your September 4, 2013 correspondence on September 5, 2013, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4) This proposed proprietary name request is considered withdrawn as of September 5, 2013.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, a new request for a proposed proprietary name review should be submitted. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Vaishali Jarral, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4248. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Kimberly Compton, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

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

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/s/

CAROL A HOLQUIST
09/11/2013

MEMORANDUM of TELECONFERENCE

MEETING DATE: August 19, 2013
TIME: 2:30 pm to 3:00 pm EDT
LOCATION: Conference room 4266, Building 22
APPLICATION: NDA 204768
DRUG NAME: (b) (4) (indomethacin submicron particle) capsules
TYPE OF MEETING: Teleconference
MEETING CHAIRS: Jamie Wilkins Parker, Team Leader, DMEPA
Vaishali Jarral, OSE Project Management

FDA ATTENDEES: Vicky Borders-Hemphill, Safety Evaluator, DMEPA
Kellie Taylor, Deputy Director, DMEPA

SPONSOR ATTENDEES:

Steve Jensen	Sr. Vice President, Regulatory Affairs & Quality
Ariyapadi N. Krishnaraj	Senior Vice President, Marketing and Managed Markets
Juliana Schwarz-Rocha	Senior Manager, Regulatory Affairs
Carie Masoner	Senior Regulatory Consultant
(b) (4)	

BACKGROUND:
Iroko Pharmaceuticals, LLC (Iroko) submitted a 505(b)(2) NDA 204768 on April 30, 2013 for indomethacin capsules. Iroko has submitted a request for proprietary name review (b) (4) to NDA 204768 on June 28, 2013 (PDUFA date September 26, 2013).

MEETING OBJECTIVES:
The purpose of the call was to let Sponsor know that DMEPA has completed their preliminary review of the name and finds it unacceptable (b) (4)

DMEPA CONCERNS WITH THE PROPOSED NAME:
(b) (4)

REGULATORY OPTIONS:
Following two options were present to the sponsor:

1. Wait for DMEPA to complete our review (b) (4) by our OSE PDUFA goal date of September 26, 2013 and issue a formal denial.

2. Withdraw the proposed name [redacted] and submit an alternate name for review or consider resubmitting the name with a different spelling that retains the phonetics of the name [redacted]

DISCUSSION:
Iroko acknowledged FDA's concern but did not commit to any regulatory options mentioned above. Instead Iroko requested for more time so that they can discuss the options further prior to making any commitment to FDA. FDA agreed to their proposal.

ACTION ITEMS:

1. Iroko will contact FDA within a day or two to commit to one of the regulatory options that were present to them during the tcon.

2. FDA will provide Iroko a link [redacted]

ADDENDUM:

After the teleconference, the following communication (via electronic mail) was held between FDA and [redacted]

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/s/

VAISHALI JARRAL
09/05/2013

Compton, Kimberly

From: Compton, Kimberly
Sent: Thursday, August 08, 2013 4:03 PM
To: Caroline J Masoner
Cc: Compton, Kimberly
Subject: RE: FW: an IR for NDA 204-768 (b) (4) - RESPONSE REQUESTED

HI Carie,

Yes, we have a response from the stats team today:

> Thank you for the description of the revised ADEA datasets (named ADEA2.xtp) for Studies IND3-08-04b and IND3-10-06 that we received on 8/7/13 by email. The proposed additions to the ADEA datasets for two phase 3 studies are acceptable.
>
> However, we have the following additional request: We request that the ADEA2 datasets also include pain intensity and pain relief recorded immediately before the first rescue use. The reason for this additional request is that both phase 3 study protocols state that pain intensity and pain relief would be assessed immediately before the first dose of rescue analgesia if administered before the 8-hour time point. Therefore, we request that those pain assessments be included in the ADEA2 datasets. You can add one column for pain intensity and one column for pain relief in the ADEA2 datasets. We believe that the ADEA2 datasets, with the additional data columns for pain intensity and pain relief as described above, will fully address our information request.

Thanks
Kim

From: Caroline J Masoner [mailto:cmasoner@csc.com]
Sent: Thursday, August 08, 2013 12:02 PM
To: Compton, Kimberly
Subject: RE: FW: an IR for NDA 204-768 (b) (4) - RESPONSE REQUESTED

Hi Kim, any response from the team? We are working on revising the data sets with the anticipation that the review team will agree with our approach. Thanks!

CARIE MASONER
Sr. Regulatory Consultant
CSC
GBS | o: +1-513-533-0561 | m: (b) (6) | cmasoner@csc.com | www.csc.com

"Compton, Kimberly" ---08/07/2013 11:27:34 AM---Hi Carie, It has gone to the team.

From: "Compton, Kimberly" <Kimberly.Compton@fda.hhs.gov>
To: Caroline J Masoner/USA/CSC@CSC
Date: 08/07/2013 11:27 AM
Subject: RE: FW: an IR for NDA 204-768 (b) (4) - RESPONSE REQUESTED

Hi Carie,

It has gone to the team.

Thanks
Kim

From: Caroline J Masoner [mailto:cmasoner@csc.com]
Sent: Wednesday, August 07, 2013 8:49 AM
To: Compton, Kimberly
Subject: RE: FW: an IR for NDA 204-768 (b) (4) - RESPONSE REQUESTED

Hi Kim,

I inadvertently left off the draft specifications for the ADEA2 datasets. Can you please forward to the team? Thank you!

(See attached file: ADEA2_Draft_Specifications.xlsx)
CARIE MASONER
Sr. Regulatory Consultant
CSC
GBS | o: +1-513-533-0561 | m: (b) (6) | cmasoner@csc.com | www.csc.com

"Compton, Kimberly" ---08/06/2013 06:52:00 PM---Hi Carie, I sent this to the team to ask if it meets our needs and will let you know their reply onc

From: "Compton, Kimberly" <Kimberly.Compton@fda.hhs.gov>
To: Caroline J Masoner/USA/CSC@CSC
Date: 08/06/2013 06:52 PM
Subject: RE: FW: an IR for NDA 204-768 (b) (4) RESPONSE REQUESTED

Hi Carie,

I sent this to the team to ask if it meets our needs and will let you know their reply once I have it.

Thanks
Kim

From: Caroline J Masoner [mailto:cmasoner@csc.com]
Sent: Tuesday, August 06, 2013 4:29 PM
To: Compton, Kimberly
Subject: Re: FW: an IR for NDA 204-768 (b) (4) - RESPONSE REQUESTED

HI Kim,

Could you please forward the following to the Stats Group for their agreement to our planned response to the IR.

In response to the Division's email dated 02-Aug-2013 requesting additional information to facilitate its review of the NDA for (b) (4) Capsules, Iroko intends to submit revised ADEA datasets for studies IND3-08-04b and IND3-10-06 containing additional variables as specified by the reviewers. Details of the intended additions are provided below:

- ***Date/Time for each rescue use***
  Currently, only the date/time of the FIRST rescue is captured in the ADEA dataset as this was the only variable used in efficacy analyses (FRESDTM). The information for all other rescue doses are currently captured in the ADCM datasets (records where CMCAT="RESCUE MEDICATIONS"). We propose to add 12 variables (columns) to the ADEA (named ADEA2.xpt) to capture the date/time for each subsequent instance of rescue taken by a subject after first rescue. These are RES2DTM – RES13DTM in the draft specifications attached (Date/time of first rescue is left unchanged from the original dataset). The type of rescue medication used will not be added to ADEA but will remain available in ADCM.

- ***For each pain assessment, there should be one variable to indicate whether the pain assessment is within a 4-hour window from the previous rescue use***
  Using the variables FRESDTM, RES2DTM, etc. as defined above – one flag will be assigned to capture whether a pain assessment is within 4 hours following any rescue medication start date/time. See RES4HFL in the attached draft specifications. Previous sensitivity analyses performed looked at only assessments within the 4 hours of the FIRST instance of rescue.

- ***For each pain assessment, there should be one variable to indicate whether the pain assessment is within a 6-hour window from the previous rescue use***
  Using the variables FRESDTM, RES2DTM, etc. as defined above – one flag will be assigned to capture whether a pain assessment is within 6 hours following any rescue medication start date/time. See RES6HFL in the attached draft specifications.

- ***For each pain assessment, there should be one variable to indicate whether the pain assessment takes place immediately after the first rescue use. Pain intensity and pain relief recorded immediately before the first rescue use should also be included.***
  Variables will be added to ADEA to identify the last non-missing assessment prior to first rescue, and the first non-missing assessment after first rescue. These flag variables are added as PRRESFL (Prior to Rescue) and PTRESFL (Post Rescue) as outlined in the attached specifications.

It is not intended for the revised dataset to replace the existing ADEA dataset from the original submission. Rather, the ADEA2 dataset will be a stand-alone SAS xpt files (one per trial named ADEA2.xpt) that will contain all original variables from ADEA along with the new specified variables. An associated spec document containing the derivations for the new variables will also be included. The revised datasets and the spec document for the ADEA2 datasets will be submitted no later than Thursday, August 15, as requested. No new ADaM database will be submitted.

Does the Division agree that submission of revised datasets as described above will adequately address the reviewer's questions?

CARIE MASONER
Sr. Regulatory Consultant
CSC
GBS | o: +1-513-533-0561 | m: (b) (6) | cmasoner@csc.com | www.csc.com

"Compton, Kimberly" ---08/02/2013 05:04:09 PM---HI Carie, The stats group has a request for N 204-768:

From: "Compton, Kimberly" <Kimberly.Compton@fda.hhs.gov>
To: Caroline J Masoner/USA/CSC@CSC
Cc: "Compton, Kimberly" <Kimberly.Compton@fda.hhs.gov>
Date: 08/02/2013 05:04 PM
Subject: FW: an IR for NDA 204-768 (b) (4)

HI Carie,

The stats group has a request for N 204-768:

> In Study IND3-08-04b and IND3-10-06, there are high proportions of subjects using rescue medications. Some subjects used the rescue medications more than 1 time. For example, in Study IND3-08-04b, subject 003-091 in the (b) (4) 40mg TID group had a total of 5 rescue uses within 48 hours (Vicodin, Vicodin, Oxycocet, Oxycocet and Vicodin). However, only Date/Time of the first rescue use was included in the submitted efficacy assessment dataset ADEA. To facilitate ease of review of the impact of the use of rescue medications on the efficacy of (b) (4) the dataset ADEA in both Phase 3 studies should include the following information:
>
> - Date/Time for each rescue use
> - For each pain assessment, there should be one variable to indicate whether the pain assessment is within a 4-hour window from the previous rescue use
> - For each pain assessment, there should be one variable to indicate whether the pain assessment is within a 6-hour window from the previous rescue use
> - For each pain assessment, there should be one variable to indicate whether the pain assessment takes place immediately after the first rescue use. Pain intensity and pain relief recorded immediately before the first rescue use should also be included.
>
> To facilitate our ongoing review of this submission, we request the datasets, along with associated documentation, no later than August 15, 2013.

Please let us know if you have any questions.

Thanks
Kim

Kimberly Compton

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191

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/s/

KIMBERLY A COMPTON
08/08/2013

Compton, Kimberly

From: Compton, Kimberly
Sent: Friday, August 02, 2013 5:04 PM
To: cmasoner@csc.com
Cc: Compton, Kimberly
Subject: FW: an IR for NDA 204-768 (b) (4)

HI Carie,

The stats group has a request for N 204-768:

In Study IND3-08-04b and IND3-10-06, there are high proportions of subjects using rescue medications. Some subjects used the rescue medications more than 1 time. For example, in Study IND3-08-04b, subject 003-091 in the (b) (4) 40mg TID group had a total of 5 rescue uses within 48 hours (Vicodin, Vicodin, Oxycocet, Oxycocet and Vicodin). However, only Date/Time of the first rescue use was included in the submitted efficacy assessment dataset ADEA. To facilitate ease of review of the impact of the use of rescue medications on the efficacy of (b) (4) the dataset ADEA in both Phase 3 studies should include the following information:

- Date/Time for each rescue use
- For each pain assessment, there should be one variable to indicate whether the pain assessment is within a 4-hour window from the previous rescue use
- For each pain assessment, there should be one variable to indicate whether the pain assessment is within a 6-hour window from the previous rescue use
- For each pain assessment, there should be one variable to indicate whether the pain assessment takes place immediately after the first rescue use. Pain intensity and pain relief recorded immediately before the first rescue use should also be included.

To facilitate our ongoing review of this submission, we request the datasets, along with associated documentation, no later than August 15, 2013.

Please let us know if you have any questions.

Thanks
Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191

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/s/

KIMBERLY A COMPTON
08/05/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204768

FILING COMMUNICATION

Iroko Pharmaceuticals, LLC
c/o CSC
Suite 100
575 E. Swedesford Rd.
Wayne, PA 19087

Attention: Caroline J. Masoner
Sr. Regulatory Consultant and US Agent

Dear Ms. Masoner:

Please refer to your New Drug Application (NDA) dated April 30, 2013, received April 30, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Indomethacin capsules.

We also refer to your amendment dated June 4, 2013.

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

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by February 1, 2013.

We request that you submit the following information:

1. Provide dissolution profile data (*individual, mean, SD, profiles, tables and figures*) using the proposed dissolution method for the clinical batches with the commercial formulation and registration batches.

2. Clarify whether there is quality control testing of the drug substance upon receipt from [redacted] (b) (4) and prior to use in the manufacture of the drug product. Provide in-house acceptance criteria for quality control testing and validated analytical methods used for the testing of the drug substance prior to use in the manufacture of the drug product

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. White space must be present before each major heading in HL.
2. Product title in HL must be **bolded.**
3. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. The statement, [redacted] (b) (4) is listed in the FPI, but not in HLs.

We request that you resubmit labeling that addresses these issues by July 28, 2013. The resubmitted labeling will be used for further labeling discussions.

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

PROMOTIONAL MATERIAL

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult us. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We also acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, contact Kimberly A. Compton, R.Ph., Senior Regulatory Project Manager, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MATTHEW W SULLIVAN
07/12/2013

Compton, Kimberly

From: Compton, Kimberly
Sent: Monday, May 20, 2013 2:58 PM
To: cmasoner@csc.com
Cc: Compton, Kimberly
Subject: Item for [redacted] (b) (4) (N 204768)

Hello Carie,

The Chemistry team noted the following issue when reviewing your NDA for filing:

> There is little or no information to review in the Drug Substance portion of your NDA. As per ICH M4Q, provide data and information in Module 3.2.S that includes all sections 2.1, 2.2, 2.3, 2.4, 2.5, 2,6 and 2.7. Each section must contain information for review or a reference to an appropriate Drug Master File (DMF). Further, specifications, batch data, and stability data for the drug substance batches used in the clinical drug product and any validation or commercial batches must be included in the NDA in order for this NDA to be fileable from a CMC perspective.

Please amend your NDA application to append it with this information within 14 days of the date of this request so we may continue to review it for filing acceptability.

Please let me know if you have any questions about our request.

Thanks
Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
301-796-1191
Please consider the environment before printing this e-mail. If you decide to print, please make double-sided copies.

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/s/

KIMBERLY A COMPTON
05/21/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204768

NDA ACKNOWLEDGMENT

Iroko Pharmaceuticals, LLC
c/o CSC
575 E. Swedesford Rd.
Suite 100
Wayne, PA 19087

Attention: Caroline J. Masoner
Sr. Regulatory Consultant and US Agent

Dear Ms. Masoner:

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

Name of Drug Product: Indomethacin capsules

Date of Application: April 30, 2013

Date of Receipt: April 30, 2013

Our Reference Number: NDA 204768

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 29, 2013, in accordance with 21 CFR 314.101(a).

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

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

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

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

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

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

If you have any questions, call me at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, R.Ph.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

KIMBERLY A COMPTON
05/09/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 101940

MEETING MINUTES

Premier Research Group
On behalf of Iroko Pharmaceuticals, LLC
Centre Square West
1500 Market Street, Suite 3500
Philadelphia, PA 19102

Attention: Linda Hibbs
Associate Director, Regulatory Operations

Dear Ms. Hibbs:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Indomethacin Nanoformulation Capsules, 20 mg and 40 mg.

We also refer to the meeting between representatives of your firm and the FDA on October 23, 2012. The purpose of the meeting was to discuss the content and format of the Iroko's New Drug Application (NDA) to be submitted via the 505(b)(1) regulatory pathway.

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

If you have any questions, call me at (301) 796-4085.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: October 23, 2012, 12:00 to 1:00 pm
Meeting Location: WO, Bldg. 22, Conf. Rm. 1417

Application Number: IND 101940
Product Name: Indomethacin Nanoformulation Capsules

Indication: Treatment of mild to moderate acute pain
Sponsor/Applicant Name: Iroko Pharmaceuticals, LLC

Meeting Chair: Sharon Hertz, M.D. Deputy Director, Division of Anesthesia, Analgesia and Addiction Products (DAAAP)
Meeting Recorder: Swati Patwardhan, Regulatory Project Manager, DAAAP

FDA ATTENDEES:

FDA	Title
Bob A. Rappaport, M.D. (on phone)	Director, DAAAP
Sharon Hertz, M.D.	Deputy Director/Clinical Team Leader, DAAAP
Steven Galati, M.D	Medical Officer, DAAAP
Adam Wasserman, Ph.D.	Supervisory Pharmacology/Toxicology, DAAAP
Zengjun (Alex) Xu, Ph.D.	Pharmacology/Toxicology Reviewer, DAAAP
Yun Xu, Ph.D.	Team Leader, Division of Clinical Pharmacology II (DCP2)
Suresh Naraharisetti, Ph.D.	Clinical Pharmacology Reviewer, DCP2
Danae Christodoulou, Ph.D.	CMC Lead, ONDQA
Elsbeth Chikhale, Ph.D.	Biopharmaceutics Reviewer, ONDQA
Feng Li, Ph.D.	Biometrics Reviewer, Division of Biometrics II (DB2)
Swati Patwardhan	Regulatory Project Manager, DAAAP
Industry Representatives	**Title**
David A. Dickason	Senior Director, Technical Development (Iroko)
James Foy	Senior Manager, Regulatory Affairs CMC (Iroko)
Steven Jensen	Vice President, Regulatory Affairs & Quality (Iroko)
Juliana Schwarz-Rocha	Senior Manager, Regulatory Affairs (Iroko)
Daniel Solorio	Senior Director, Clinical Operations (Iroko)
Clarence Young, MD	Chief Medical Officer (Iroko)
Michelle Wilson, PhD	Principal Regulatory Strategist (CSC)
Linda Hibbs	Associate Director, Regulatory Operations (Premier Research)

Industry Representatives	Title
Florence Vickers, PhD, FCP	Director, Regulatory Affairs, Early Development & Phase I Clinical Study Regulatory Strategy Specialist (Premier Research)
(b) (4)	Consultant Statistician (b) (4)

1. BACKGROUND

i. On behalf of Iroko Pharmaceuticals, Premier Research Group submitted a Pre- NDA meeting request on August 1, 2012, which was received on August 2, 2012.

ii. Indomethacin, a nonsteroidal anti-inflammatory drug (NSAID), inhibits prostaglandin synthesis.

iii. The objective of the Pre-NDA meeting was to determine if the development program for the Indomethacin Capsule is adequate to support the filing of an NDA via the 505(b)(1) route. Even though Iroko proposes to submit the NDA via the 505(b)(1) route, they intend to reference Indocin® IR (currently discontinued), which they have acquired from Merck.

iv. The meeting request was granted and the briefing package was received on September 14, 2012.

2. DISCUSSION

Preliminary responses were sent to Iroko on October 22, 2012.

Following introductions, the discussion focused on the preliminary comments for Questions 1, 3, 4, and 5. In addition, a brief update was provided by Iroko on their analyses of the second Phase 3 study (IND3-10-06). The Phase 3 topline results (provided via email on October 22, 2012, by the Sponsor) are included in Attachment A.

The Sponsor's questions are italicized and the Division's preliminary responses are bolded text. The Sponsor's response to the Division's preliminary comments (received October 22, 2012) and the Discussion are in regular font.

Content

1. *During the End of Phase 2 Meeting discussions (Meeting Minutes dated July 2, 2010), the Division confirmed that "the drug product to be relied upon as the listed drug for submitting a 505(b)(2) application must be a product approved under an NDA application." Following these discussions, Iroko has modified its strategy and intends to submit* (b) (4) *as a 505(b)(1) application. The clinical package consists of two pivotal Phase 3 trials which will be put forward as the clinical basis of approval. Iroko intends to also reference and rely upon the findings of the review of the discontinued Indocin® IR Capsules application (NDA 016059; discontinued for reasons not related to safety or efficacy) which Iroko acquired from the original sponsor Merck.*

   Finally, for biolinking purposes Iroko is conducting a definitive comparative PK bioavailability study using the Phase 3 / to-be-marketed formulation against the ANDA designated reference drug indomethacin oral capsules (Mylan Pharmaceuticals, Inc., ANDA 070624).

   Does the FDA agree that a 505(b)(1) NDA submission is the appropriate regulatory pathway for (b) (4) *Capsules 20 mg and 40 mg and that the proposed strategy for reference products is acceptable?*

   FDA Response:

   We note that you have changed your regulatory strategy discussed in previous meetings to the 505(b)(1) pathway. A 505(b)(1) application, or "stand-alone NDA," describes an application that contains full reports of investigations of safety and effectiveness that were conducted by or for the applicant or for which the applicant has a right of reference or use. Accordingly, you should submit preclinical and clinical studies in order to support labeling of your product. The Agency is discussing whether you will need to submit all required data to support your proposed product under a 505(b)(1) pathway, and we will let you know once that decision has been made.

   If reference to literature is necessary to fulfill the requirements of your NDA application, your application may be deemed a 505(b)(2) application. An application that relies on literature that names an approved drug product is considered a (b)(2) application and requires patent certification and notification to the relied upon drug.

   You proposed to rely upon the findings of the discontinued Indocin® IR Capsule application (NDA 016059), and conduct a definitive comparative PK bioavailability study using your Phase 3, to-be-marketed formulation compared to the ANDA designated reference listed drug, indomethacin oral capsules (Mylan Pharmaceuticals, Inc., ANDA 070624). This approach is acceptable provided NDA

016059 was not discontinued due to safety and/or effectiveness reasons, and NDA 016059 was the reference listed drug (RLD) for ANDA 070624 approval.

Also, see our response to Question 3 and Question 4.

Response sent by Sponsor via email on October 22, 2012: The response contained below pertains to the Division's responses to Questions #1, #3, and #4.

As confirmed at the End of Phase 2 Meeting, Iroko has acquired the Indocin product (NDA 016059) and plans to cross-reference the nonclinical and clinical studies supporting FDA's determination of safety and efficacy of Indocin. Iroko is able to confirm that NDA 016059 was removed from the market for reasons not related to safety or efficacy. Additionally, Iroko intends to summarize literature reports of any new studies that were conducted. Per the Division's guidance, for any referenced literature studies that name a marketed product, Iroko will include the appropriate patent certification.

Iroko wishes to discuss further with the FDA requirements for the 505(b)(1) versus 505(b)(2) pathway. The 505(b)(1) pathway proposed in the Information Package supporting the Pre-NDA Meeting was determined based upon the End of Phase 2 Meeting discussion and the Division's comments that a 505(b)(2) NDA is not able to cross-reference a 505(j) application, even when designated as the Reference Listed Drug. Iroko's intention is to cross-reference NDA 016059 and also summarize the literature to address the specific items raised in Questions #1, #3, and #4. Iroko seeks the Division's clarification of the more appropriate submission pathway that is consistent with this approach.

Discussion:
The Sponsor noted that the Indocin approved under NDA 016059 was not discontinued for safety or efficacy reasons. They further stated that for biolinking purpose, Iroko is conducting PK studies against Mylan Pharmaceutical's Indomethacin (ANDA 070624), which is a reference listed drug per the Orange Book. Iroko has also conducted two replicate pivotal Phase 3 clinical trials. Iroko agreed to provide all the available reports and summaries for the nonclinical studies conducted by Merck. In addition, if any gap is identified, they agreed to address it through a literature search. Iroko further referenced the EOP2 meeting and the discussion regarding whether this NDA should be a 505(j), 505(b1), or a 505(b2) application. They wanted to know what approach Iroko should take to submit this application, which they plan to submit in February of 2013.

The Division responded that, in order to update the labeling language, submission of the nonclinical studies supporting labeling would be necessary, and noted that the nonclinical studies were originally conducted in the1960s and may not be adequate based on current standards. The Sponsor stated that the nonclinical information described in the label may not be the result of traditional studies. The Division stated that since Indocin was approved in 1960, was marketed for quite a while, and the current

product does not represent a greater risk to the public, Iroko may not be required to do studies to fill gaps in the application even if Iroko submits a 505(b)(1) application. The Division further stated that the final decision is being discussed with upper management and the Division will do their best to convey the outcome of the decision as a post-meeting note in the meeting minutes.

Post Meeting Note: We note your submission submitted November 5, 2012, in which you stated, "It is now Iroko's intention to submit the upcoming (b) (4) application as a 505(b)(2) NDA, as Iroko is no longer the Indocin sponsor and does not have right of reference." Therefore, you may rely on the Agency's prior findings for Indocin, as appropriate, and are not required to conduct the additional studies that may have been required for a 505(b)(1) application.

Chemistry, Manufacturing, and Controls

2. *The proposed release specifications for the drug product as well as the in-process specifications are included in Section 2.10.3.2 of the meeting information package.*

   Does the Division have any comments to the drug product in-process and release specifications?

   FDA Response:

   The proposed testing attributes appear reasonable. Specification limits will be assessed upon NDA review, based on ICHQ6A, ICHQ3A(R) and ICH Q3B(R). Your proposal to omit routine microbiological testing will be assessed upon NDA review based on sufficient rationale and available data such as microbiological control of the manufacturing environment, microbiological control of the drug product components, and the results of historical testing on the drug product.

   Provide the chemical structures (b) (4) in the NDA. Refer to non-clinical comments in response to Question 3, below regarding the control strategy of these impurities during NDA review.

   Regarding dissolution, the proposed USP test may not be the optimal dissolution method for your drug product. Include data in your dissolution method development report addressing our comments previously communicated during the EOP2 meeting (pg. 24 of 108 of the meeting package) and include this report with complete data in your NDA submission. Also, when constructing the dissolution profiles for the bio- and stability batches, include an additional time point at 15 minutes (i.e., 10, 15, 20, 30, 45, and 60 minutes).

   Based on the provided dissolution data (b) (4) your proposed dissolution acceptance criterion of Q= (b) (4) at (b) (4) minutes does not seem appropriate. However, setting the dissolution

acceptance criterion is a review issue under the NDA and is based on the overall profile from the bio-batches and registration batches, using the optimal dissolution method for your drug product.

Response sent by Sponsor via email on October 22, 2012: The Division's comments are clear. Iroko intends to include within the NDA appropriate data following the Division's guidance above. No further discussion is requested.

Discussion:
There was no further discussion during the meeting.

Nonclinical

3. *The End of Phase 2 Meeting Minutes of July 2, 2010, established that the total systemic exposure* (b) (4) *being developed by Iroko* (b) (4) *and therefore no additional nonclinical safety studies would be required to support the safety of indomethacin for the NDA. Furthermore, no impurity or degradation product in the Phase 3 / to-be-marketed formulation used in the Phase 3 studies exceeds ICH qualification thresholds.*

   Does the Division agree that the results of the nonclinical study (1609-001) in conjunction with the existing safety data in the public domain are adequate to support marketing authorization?

   FDA Response:

   No, we do not agree. To submit your drug product as a 505 (b)(1) application, you are required to submit nonclinical safety studies which are required based on the ICH M3(R2) guidance or, alternatively, cross-reference nonclinical studies that were included in NDA 016059. If you choose to cross-reference nonclinical studies from NDA 016059, we recommended submission of the study reports of those nonclinical studies, in order to help us determine whether the toxicology information in the label needs to be updated.

   We acknowledge your conduct of in silico evaluations of the genotoxic potential of known indomethacin-related substances. You must submit the in silico analysis reports you completed for the Division's review and include the structure of the each impurity in the report to allow us to conduct an analysis to confirm your evaluation. If we do not concur that the weight of evidence for each impurity indicates an absence of genotoxic potential, you must conduct genotoxicity studies to qualify the impurity. If the level of the impurity is below the ICHQ3A threshold for qualification, an Ames assay would be sufficient. If the level is above the Q3A threshold, then the addition of a clastogenicity assay would be required to demonstrate safety.

Response sent by Sponsor via email on October 22, 2012: In response to the first paragraph above, Iroko is able to provide the entire legacy nonclinical toxicology section of cross-referenced NDA 016059. Additionally, please refer to the Sponsor Response to Question #1.

In regard to the in silico report, Iroko confirms that the in silico analysis report is scheduled for inclusion in the NDA and includes the structure of each impurity to allow analysis and confirmation of our evaluation.

Discussion:
Refer to the discussion for Question 1.

Clinical

4. *Iroko intends to include the results of five clinical trials conducted in the US using (b) (4) Capsules in support of an indication for the treatment of mild to moderate acute pain. Iroko's clinical program supporting the NDA consists of one PK study (IND1-08-01) and one Phase 2 proof-of-concept dental impaction pain model study (IND2-08-03) using the non-optimized drug product formulation and process (POC Formulation). Following product optimization, Iroko initiated the conduct of a definitive PK study (IND1-12-07) and two pivotal Phase 3 efficacy trials (IND3-08-04b and IND3-10-06) using the Phase 3 / to-be-marketed formulation and process. The definitive Phase 1 study is a PK comparative bioavailability biolinking study against the ANDA indomethacin capsule reference drug (Mylan Pharmaceuticals, Inc., ANDA 070624). The two pivotal Phase 3 efficacy trials are replicate, placebo-controlled bunionectomy post-operative pain trials for which the Division has already confirmed agreement with the study design and primary endpoint within the context of the Special Protocol Assessment (SPA) for protocol IND3-08-04a (S-0002).*

   Does the Division concur that positive results from the two pivotal Phase 3 studies and the definitive PK characterization study of the Phase 3 / to-be-marketed formulation are adequate to support the filing of a 505 (b)(1) NDA for (b) (4) Capsules for the treatment of mild to moderate acute pain?

   FDA Response:

   Positive results from the two pivotal Phase 3 studies and the definitive PK characterization study of the Phase 3 / to-be-marketed formulation are adequate to support the filing your NDA the treatment of mild to moderate acute pain as long as you also provide the following information:

   - **An evaluation of the food effect using your final to-be-marketed product.**

- **The dose-proportionality data for the two proposed strengths (20 mg and 40 mg). This may be addressed using PK data from a study comparing the 20 mg and 40 mg strengths, or you may request a biowaiver for the 20 mg strength in your NDA submission. If you choose to request a biowaiver for the 20 mg strength, you must show that the composition of the 20 mg and 40 mg drug products is proportionally similar and show that the dissolution profiles are similar.**

In addition, we note that the AUC in your first PK study was substantially lower than the reference product under both fasted and fed conditions and your PK curve was shifted to the left. If your definitive PK study shows similar data, it is important that you have clinical data supporting the proposed dosing interval of every 8 hours and an analysis of time to rescue with your individual study reports.

Additional Clinical Pharmacology Comments:

Include the following information in the clinical pharmacology section in your NDA submission to support the labeling of your product:

1. **Absorption, Distribution, Metabolism and Elimination of your product**
2. **PK and dosing recommendation in special populations (effect of age, gender, hepatic and renal impairment, etc.)**
3. **Drug-drug interaction potential and QT prolongation assessment**

Response sent by Sponsor via email on October 22, 2012: Please refer to the Sponsor Response to Question #1.

Discussion:
Regarding the evaluation of the food effect with the to-be-marketed product, Iroko responded that studies have been done with and without food as suggested by the Division.

In response to Additional Clinical Pharmacology Comments, Iroko stated that information related to Absorption, Distribution, Metabolism, and Elimination of indomethacin is readily available in the literature and will be provided with the NDA. Iroko requested a clarification of the PK and dosing recommendations in special populations, and the drug interaction and QT prolongation assessment. The Division stated that these requirements will depend upon whether the submission is a 505(b)(1) or a 505(b)(2) application. Usually these studies are needed for a 505(b)(1) application. Refer to the discussion under Question 1 and the Post Meeting Note.

The Division acknowledged that the total systemic exposure of the indomethacin developed by Iroko is less than that of the referenced drug, and Iroko has not performed studies in specific populations. However, supporting information for labeling in specific

populations, particularly for the geriatric population, could be provided based on a literature review.

The Division added that evaluation of the food effect and dose proportionality data for the two strengths with the final to-be-marketed formulation will be required regardless of whether Iroko plans to submit the application by the 505(b)(1) or 505(b)(2) pathway.

5. *Iroko plans to provide a Summary of Effectiveness that reviews the effectiveness data from the Phase 2 and Phase 3 pivotal studies in Module 2.7.3. Iroko does not intend to perform a metaanalysis of pooled integrated efficacy data across the Phase 2 and Phase 3 pivotal studies since the majority of subjects enrolled in these studies are relatively young and female; and its unlikely that a subgroup analysis of efficacy will be meaningful based on the size of racial and ethnic subgroups. Iroko will summarize the results of the Phase 2 and Phase 3 studies individually as described in the Integrated Summary of Effectiveness (ISE), Draft Guidance for Industry (August, 2008).*
Does the Division agree with Iroko's proposal for preparation of the ISE for inclusion in the (b) (4) *NDA as described above?*

FDA Response:

The proposal to not pool efficacy data across the Phase 2 and Phase 3 studies for the purpose of summarizing the evidence of efficacy is acceptable. The ISE should not recapitulate detailed results of single studies, which are described in individual study reports, but instead should provide a comprehensive, detailed, in-depth analysis of the efficacy results in aggregate, with a clear rationale for the methods used in the analysis. Studies should be presented briefly while noting critical design and analytic features as well as important differences between studies (e.g., population, dose, duration, endpoints).

The background and overview section of the ISE should clearly outline why the studies, in aggregate, demonstrate the claimed effects. This demonstration is particularly important if the results are inconsistent or marginal.

Response sent by Sponsor via email on October 22, 2012: Iroko understands the Division's response to not pool efficacy data across the Phase 2 and Phase 3 studies, however, we wish to clarify that we intend to provide only a summary of efficacy within eCTD section 2.7.3 Summary of Clinical Efficacy. Section 2.7.3 will follow the guidance provided in the FDA Draft Guidance for Industry *Integrated Summary of Effectiveness* (August 2008). A pooled analysis of the replicate Phase 3 studies will not be included and no formal ISE will be included in eCTD section 5.3.5.3. Does the Division agree with this approach?

Discussion:

The Division was in agreement with Iroko's approach stating that the ISE is not for pooling data unless it is pre-agreed for specific reasons. The Division indicated a preference that the ISE and ISS be included in Module 5, and a shorter overview be included in Section 2.7. If the ISE is provided in Section 2.7 (space permitting), then it should be cross referenced to Section 5.3.

6. *For the Integrated Summary of Safety (ISS) Iroko intends to provide an integrated analysis of pooled safety data from the two pivotal Phase 3 studies. Results of the two Phase 1 and one Phase 2 studies will be presented individually in the ISS since these three single dose studies were comprised of relatively young and healthy subjects.*

   Does the Division agree with the approach that the Integrated Summary of Safety will comprise data from each of the individual Phase 1 and Phase 2 studies and analysis of pooled safety data from the two pivotal studies?

   FDA Response:

   Yes, we agree with your approach of pooling the two pivotal Phase 3 studies for the Integrated Summary of Safety and not including the Phase 1 and 2 studies, which used a different product formulation or were single-dose studies.

   Response sent by Sponsor via email on October 22, 2012: The Division's response is clear. No further discussion is necessary.

   Discussion:
   There was no further discussion.

7. *Iroko plans to submit completed Case Report Forms (CRFs) and case summaries only for patients with reported deaths, SAEs, and discontinuations due to adverse events.*

   Does the Division agree that CRFs and case summaries will be included only for patients with reported deaths, SAEs, and discontinuations due to adverse events?

   FDA Response:

   Yes, we agree that CRF's and case summaries must be included for patients with reported deaths, SAEs, and discontinuations due to adverse events regardless of whether the investigator determines the outcome was drug related. Also, patients that discontinue for other reasons must be further investigated to determine whether the discontinuation may have been a masked adverse event.

   Response sent by Sponsor via email on October 22, 2012: The Division's response is clear. No further discussion is necessary.

Discussion:
There was no further discussion.

8. *Iroko is currently working with experts in the design of clinical programs and studies in children to develop a pediatric plan that satisfies the requirements of the Pediatric Research Equity Act. Iroko intends to submit the Pediatric Plan to the IND in advance of the scheduled NDA submission. The comprehensive plan will include requests for waivers or deferrals, types of studies to be conducted, and a timeline consisting of the date of final protocol submission to the Division and the date of final study report submission.*

   Does the Division agree with Iroko's plan to submit the Pediatric Plan in advance of NDA submission?

   FDA Response:

   As described in the EOP2 meeting, you must develop an age appropriate formulation to dose the younger age patients. If you think it would be unsafe to use this drug in patients under a particular age you must submit supporting scientific justification. In the spirit of the Pediatric Research Equity Act (PREA), it is preferable if you commence pediatric studies during development in adults, and if possible, submit completed studies with your NDA. The studies should inform appropriate dose, dose interval, pharmacokinetics, efficacy, and safety in different pediatric age strata. You should conduct pediatric studies during the development cycle and not wait until after approval of the NDA to initiate pediatric studies. However, approval of an NDA would not be withheld if pediatric studies were not complete at the time of the submission.

   Response sent by Sponsor via email on October 22, 2012: The Division's response is clear. Please note that Iroko is presently finalizing our pediatric plan for submission to IND 101940. No further discussion is necessary.

   Discussion:
   There was no further discussion.

9. *Iroko does not intend to include a formal Risk Evaluation Management Strategy (REMS) in the NDA for the acute use of* (b) (4) *Capsules. A Medication Guide that accompanies class labeling for NSAIDs is appropriate for the acute use of* (b) (4) *Capsules in the treatment of mild to moderate pain. Therefore, Iroko intends to include a Medication Guide with the product labeling.*

Does the Division concur with Iroko's plan to not include formal REMS in the NDA for the acute use of (b) (4) *Capsules as outlined above?*

FDA Response:

Yes, we concur with your intention to include a Medication Guide with the product labeling.

Response sent by Sponsor via email on October 22, 2012: The Division's response is clear. No further discussion is necessary.

Discussion:
There was no further discussion.

Data Format

10. *Following the Center for Drug Evaluation and Research (CDER) common data standard issues document updated in December 2011, Iroko plans to submit the clinical trial datasets for the Phase 2 and Phase 3 efficacy studies in SDTM format. All SDTM datasets will be provided as SAS Version 5 Transport (.XPT) files. SDTM datasets will be provided following the SDTM version 1.2/SDTM Implementation Guide (IG) v. 3.1.2. ADaM analysis datasets will be provided for the Phase 2 and Phase 3 studies following ADaM 2.1/ADaM IG v.1. Iroko intends to submit Define documents for both SDTM and ADaM (separately) as Define.xml files.*

    a. *Does the Division agree with Iroko's data submission plans?*

        FDA Response:

        The proposed data submission plan appears acceptable. We emphasize that traceability is an important factor in the submission of data. Reviewers should be able to navigate from CRFs to tabulation data to analysis data.

    b. *Iroko plans to submit all clinical study reports (CSRs) as modular (granular) reports in compliance with ICH E3 guideline. Does the Division concur?*

        FDA Response:

        The proposed plan appears acceptable.

Response sent by Sponsor via email on October 22, 2012: The Division's response is clear. No further discussion is necessary.

Discussion:

There was no further discussion.

11. *For the Phase 1 PK studies, in addition to the tables, listings, and figures included in the final study report (including demographic, PK, adverse event [AE] and concomitant medications), Iroko intends to provide the individual subject concentration source data in SAS (.XPT) format. The non-PK source data will not be provided.*

    Does the Division agree with Iroko's plan to submit only the PK concentration source data for the Phase 1 studies?

    FDA Response:

    Your proposal to submit the tables, listings, and figures (including demographic, PK, adverse event (AE) and concomitant medications) in the final study report and the individual subject concentration source data in SAS (.XPT) format is acceptable.

    Response sent by Sponsor via email on October 22, 2012: The Division's response is clear. No further discussion is necessary.

    Discussion:
    There was no further discussion.

Regulatory

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

    FDA Response:
    Refer below to Section 2 Additional General Comments and Attachment 1.

    Response sent by Sponsor via email on October 22, 2012: The Division's response is clear. No further discussion is necessary.

    Discussion:
    There was no further discussion.

3. ACTION ITEMS

a. Iroko agreed to gather any additional data (from Merck) regarding nonclinical studies and submit in the application.

b. The Division agreed to provide an outcome on upper management's decision on whether the application should be a 505(b)(1) or 505(b)(2). If any additional studies are needed, the Division will inform Iroko accordingly.

4. ATTACHMENTS AND HANDOUTS

Attachment A

APPEARS THIS WAY ON ORIGINAL

(b) (4) (indomethacin submicron particle) Capsules
Topline Results: Phase 3 Study IND3-10-06

Summary

Iroko Pharmaceuticals, LLC (Iroko) is seeking agreement to utilize the analyses recommended in the Division's Advice/Information Request Letter - 14 August 2012 (Advice Letter) to support submission of an NDA based on the findings of clinical efficacy for (b) (4) Capsules 20 mg and 40 mg for the treatment of mild to moderate acute pain.

The Meeting Information Package to support the Type B Pre-NDA Meeting to be held on 23 October 2012 (b) (4) included analyses for study IND3-08-04b, the first of two pivotal trials in patients with post-operative pain following bunionectomy surgery.

The analyses of the second Phase 3 study (IND3-10-06) are now available, portions of which are included in this document. Additionally, analyses of the primary endpoint as recommended in the Advice Letter were considered and results of these analyses are included in this document.

The new analyses for the two (b) (4) Phase 3 studies support the finding of clinical efficacy for (b) (4) 40 mg twice and three times daily and 20 mg three times daily in patients with mild to moderate acute pain following bunionectomy.

Iroko is providing the topline results of the second Phase 3 study to the Division and intends to briefly discuss at the Type B Pre-NDA Meeting on 23 October 2012.

Background

Iroko is seeking an indication for the treatment of mild to moderate acute pain for (b) (4) (indomethacin submicron particle) Capsules based on the results of two replicate Phase 3 studies (IND3-08-04b; IND3-10-06) in patients with post-operative pain following bunionectomy surgery.

The Statistical Analysis Plan (SAP) defined topline results for study IND3-08-04b were included in the Type B Pre-NDA Meeting Information Package (Serial Number 0020 / 13 September 2012).

Topline data from the second pivotal study (IND3-10-06) are now available.

Study IND3-10-06 was a randomized, double-blind, multiple-dose, placebo-controlled study that evaluated (b) (4) Capsules 40 mg twice and three times daily and 20 mg three times daily. In contrast to study IND3-08-04b, a celecoxib treatment arm was not included in this study.

In response to the Advice Letter recommendation to consider using strategies described in the National Academy of Sciences (NAS) Report "The Prevention and Treatment of Missing Data in

Clinical Trials (2010)" to limit imputation of missing data, additional analyses of the primary efficacy parameter have been performed for both Phase 3 studies.

Since the initial Phase 3 study (IND3-08-04b) was already unblinded at the time of receipt of the Advice Letter, for that study, the analyses were conducted post-hoc. The results for these new analyses were similar to the results included in the Pre-NDA Meeting Information Package.

In the second study (IND3-10-06), since last patient last visit had been achieved prior to receiving the Advice Letter, the study protocol was not amended to include the additional analyses recommended by the Division. The study SAP was finalized *prior to* unblinding to include methods intended to address the recommendations contained in the Advice Letter.

Methods

Key elements of these additional analyses were based on considerations provided in the Advice Letter. In order to limit the use of imputed data for subjects that received rescue medication, only pain scores within 4 hours following receipt of rescue medication were imputed using the baseline observation carried forward (BOCF) technique. In addition, Mixed Model Repeated Measures (MMRM) methods that utilized all available data from all subjects to derive an estimate of pain intensity scores for subjects following study withdrawal, rather than "imputing" a score for individual patients, were also utilized. The MMRM analysis is one of the strategies recommended in the NAS report to limit imputation of missing data.

While the primary endpoint was the Summed Pain Intensity Differences measured by Visual Analog Scale (VAS SPID) over 0-48 hours, the outcome variable used in the MMRM analysis was the change from baseline in VAS Pain Intensity scores. Within the MMRM analysis, the treatment differences in the VAS SPID-48 were calculated as the time weighted average of VAS PID Least Squares Mean estimates at each time point based on a MMRM model and included hour-by-treatment interaction as the main effect and baseline pain intensity as a covariate with no intercept. A compound symmetry covariance matrix was used to model the within-subject correlation.

To further investigate the effect of BOCF imputation following the receipt of rescue medication on the results of the primary analysis, the original protocol-defined ANCOVA analysis was repeated wherein BOCF imputation was limited to the four hours following receipt of rescue medication. This approach reduced the amount of imputed data by more than two-thirds across all treatment groups.

IND3-10-06 Efficacy Analysis

The primary efficacy parameter was the sum of pain intensity differences measured by Visual Analog Scale 0-48 hours following study enrollment (VAS SPID-48), see Table 1.

Table 1: Study IND3-10-06 Primary Efficacy Parameter (VAS SPID-48) Analysis Results

	(b) (4) CAPSULES			Placebo (N = 95)
	40 mg TID (N = 95)	40 mg BID (N = 92)	20 mg TID (N = 91)	
ANCOVA using BOCF for all assessments after rescue medication[a]				
Least Squares Mean	592.14	629.22	346.66	278.38
SE	105.119	106.822	107.351	105.245
95% CI	(385.43, 798.85)	(419.16, 839.28)	(135.56, 557.75)	(71.43, 485.34)
P value for difference vs placebo	0.036	0.020	0.650	-
MMRM - BOCF up to 4 hours after rescue medication[b]				
Least Squares Mean	2235.78	2276.22	2100.08	1767.78
SE	73.377	74.609	75.021	73.631
95% CI	(2091.59, 2379.97)	(2129.60, 2422.83)	(1952.65, 2247.50)	(1623.09, 1912.47)
P value for difference vs placebo	<0.001	<0.001	0.002	-
ANCOVA-BOCF up to 4 hours after rescue medication[c]				
Least Squares Mean	2249.50	2302.11	2099.96	1766.75
SE	80.303	82.064	82.481	81.273
95% CI	(2091.58, 2407.42)	(2140.72, 2463.49)	(1937.76, 2262.17)	(1606.92, 1926.57)
P value for difference vs placebo	<0.001	<0.001	0.004	-

Abbreviations: BID=twice daily ; TID=three times daily; SE = Standard Error; BOCF = baseline observation carried forward; CI = confidence interval
Data source:
[a] CSR IND3-10-06 Table 14.2.1.1 – Protocol defined primary analysis
[b] CSR IND3-10-06 Table 14.2.1.7
[c] CSR IND3-10-06 Post-hoc Table 14.2.1.8 - Model 1

In the protocol-defined ANCOVA analyses, statistically significant differences versus placebo in the Least Squares Means for VAS SPID-48 were demonstrated for (b) (4) Capsules 40 mg twice and three times daily arms.

Although the mean VAS SPID-48 score (346.7) for the (b) (4) Capsules 20 mg three times daily group was similar to the score observed in the earlier study IND3-08-04b (380.5), unlike the previous study, the difference versus placebo did not achieve statistical significance due to a higher placebo response.

In the MMRM analysis of the primary efficacy parameter (IND3-10-06), significant differences compared with placebo were demonstrated for all (b) (4) treatment groups including the 20 mg three times daily treatment arm (Table 1).

For the ANCOVA analysis that limited imputation to 4 hours following receipt of rescue medication, all (b) (4) treatment groups demonstrated statistically significant differences compared with placebo.

The overall completion rate for this study was 97.6%.

Assessment

Using the algorithm to limit imputation of individual subject data following receipt of rescue medication, in consideration of the Division's Advice Letter, (b) (4) Capsule efficacy has been demonstrated for all three treatment groups studied – 40 mg twice and three times daily and 20 mg three times daily in two well controlled studies. This approach to the analysis of the primary efficacy parameter resulted in a reduction in the amount of imputed data following rescue medication by more than two-thirds in study IND3-10-06 as well as in study IND3-08-04b.

Analyses using both ANCOVA and MMRM methodology, with similar approaches to limit imputation of data, gave similar results for both studies, indicating that the key factor contributing to the outcome of these analyses was the reduction in imputed data in subjects following receipt of rescue medication.

Post-hoc analysis of secondary efficacy parameters using the algorithm to limit imputed data provided results that were consistent with the analysis of the primary efficacy parameter across all treatment groups in both Phase 3 studies.

In the original protocol-defined primary analysis for both studies, baseline pain intensity scores were carried forward for all remaining assessments following individual subject receipt of rescue medication or study withdrawal due to lack of efficacy or an adverse event. In the Advice Letter, the Division acknowledged that this approach to the handling of missing data was in accordance with previous comments by the Division and represented the current best thinking regarding the handling of missing data at that time. As acknowledged in recent reviews, solid scientific rationale is lacking to support the general application of this approach to the handling of missing data suggesting the need for alternative strategies to limit the imputation of individual subject data (NAS Report 2010; Little RJ, 2012).

The new analyses for the two (b) (4) Phase 3 studies support the finding of clinical efficacy for (b) (4) 40 mg twice and three times daily and 20 mg three times daily in patients with mild to moderate acute pain following bunionectomy.

Question: ***Based on the information provided, does the Division agree that the analyses performed in response to the Advice Letter are sufficient to support clinical efficacy for*** (b) (4) ***Capsules 20 mg and 40 mg in the NDA [treatment of mild to moderate acute pain]?***

References:

1. National Research Council. (2010). The Prevention and Treatment of Missing Data in Clinical Trials. Panel on Handling Missing Data in Clinical Trials. Committee on National Statistics, Division of Behavioral and Social Sciences and Education. Washington DC, The National Academies Press
2. Little RJ, D'Agostino R, Cohen MI, et al. The Prevention and Treatment of Missing Data in Clinical Trials. N Engl J Med 2012; 367:1355-60

Discussion:
Iroko provided a brief overview on the analysis/results of the second Phase 3 study taking into consideration the recommendations provided by the Division, in the August 14, 2012 Advice letter. The Division acknowledged Iroko's consideration of the NAS report on missing data as well as the Division's previous advice and recommended Iroko include the additional analyses conducted with justification in the NDA application. The Division stated that whether the efficacy data are sufficient for supporting the proposed indication will be determined during the NDA review process.

Iroko agreed to submit the requested information in the NDA.

Attachment 1:

Additional Comments for Pre-NDA Stage of Drug Development

Attachment 1:
Additional Comments for Pre-NDA Stage of Drug Development

Nonclinical Comments

1. Include a detailed discussion of the nonclinical information in the published literature in your NDA submission and specifically address how the information within the published domain impacts the safety assessment of your drug product. Include this discussion in Module 2 of the submission. Include copies of all referenced citations in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.

2. We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 draft guidance for industry, *Applications Covered by Section 505(b)(2)*, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

   In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408, available at http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf).

   Note that you may only rely on the Agency's finding of safety and/or effectiveness as it is reflected in the approved labeling for the listed drug(s). You may not reference data in the Summary Basis of Approval or other FDA reviews obtained via the Freedom of Information Act or publically posted on the CDER website to support any aspect of your development program or proposed labeling of your drug product. Reviews are summary data only and do not represent the Agency's previous finding of safety and effectiveness.

   If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). Establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also

must establish that reliance on the studies described in the literature is scientifically appropriate.

3. The nonclinical information in your proposed drug product label must include relevant exposure margins with adequate justification for how these margins were obtained. If you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product label.

4. New excipients in your drug must be adequately qualified for safety. Studies must be submitted to the IND in accordance as per the following guidance for industry, *Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients*.

   As noted in the document cited above, "the phrase ***new excipients*** means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently **proposed level of exposure**, **duration of exposure**, or **route of administration**." (emphasis added).

5. Any impurity or degradation product that exceeds ICH qualification thresholds must be adequately qualified for safety as described in ICHQ3A(R2) and ICHQ3B(R2) guidances at the time of NDA submission.

   Adequate qualification would include:

   a. Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies; e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

   b. Repeat dose toxicology of appropriate duration to support the proposed indication.

6. Genotoxic, carcinogenic or impurities that contain a structural alert for genotoxicity must be either reduced to NMT 1.5 mcg/day in the drug substance and drug product or adequate safety qualification must be provided. For an impurity with a structural alert for mutagenicity, adequate safety qualification requires a negative in vitro bacterial reverse mutation assay (Ames assay) ideally with the isolated impurity, tested up to the appropriate top concentration of the assay as outlined in ICHS2A guidance document titled "Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals." Should the Ames assay produce positive or equivocal results, the

impurity specification must be set at NMT 1.5 mcg/day, or otherwise justified. Justification for a positive or equivocal Ames assay may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.

7. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product, and how these levels compare to ICHQ3A and Q3B qualification thresholds along with a determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification threshold should be adequately justified for safety from a toxicological perspective.

8. The NDA submission must contain information on potential leachables and extractables from the drug container closure system and/or drug product formulation as outlined in the FDA Guidance for Industry titled "Container Closure Systems for Packaging Human Drugs and Biologics." The evaluation of extractables and leachables from the drug container closure system or from a transdermal patch product must include specific assessments for residual monomers, solvents, polymerizers, etc.). Based on identified leachables provide a toxicological evaluation to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these impurities may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, consult the FDA Guidance documents "Container Closure Systems for Packaging Human Drugs and Biologics" and "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation." Additional methodology and considerations have also been described in the PQRI leachables/extractables recommendations to the FDA, which can be found at http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf.

9. Failure to submit adequate impurity qualification, justification for the safety of new excipient use, or an extractable leachable safety assessment at the time of NDA submission can result in a Refusal-to-File or other adverse action.

Chemistry, Manufacturing and Control (CMC) Comments

1. Include a well documented Pharmaceutical Development Report as per the ICH-Q8 guideline and highlight how critical quality attributes and critical process parameters are identified and controlled.

2. Include at least 12 months of real time data and 6 months of accelerated data in the NDA. Alternatively, submit an appropriate amount of satisfactory stability data to cover the proposed expiry dating.

5. Provide summary stability data on a parameter-by-parameter basis (instead of only on a batch to batch basis), and in addition, provide graphical plots of critical parameters and trending parameters. The graphical plots should indicate the proposed acceptance criteria, and they should include both mean and individual data points.

The Abuse Potential section of the NDA is submitted in the eCTD as follows:

Module 1: Administrative Information and Prescribing Information
1.11.4 Multiple Module Information Amendment
This section should contain:

- A summary, interpretation and discussion of abuse potential data provided in the NDA.
- A link to a table of contents that provides additional links to all studies (nonclinical and clinical) and references related to the assessment of abuse potential.
- A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA.

Module 2: Summaries
2.4 Nonclinical Overview
This section should include a brief statement outlining the nonclinical studies performed to assess abuse potential.

2.5 Clinical Overview
This section should include a brief statement outlining the clinical studies performed to assess abuse potential.

Module 3: Quality
3.2.P.1 Description and Composition of the Drug Product
This section should describe any additional studies performed to examine the extraction of the drug substance under various conditions (solvents, pH, or mechanical manipulation).

3.2.P.2 Description and Composition of the Drug Product
This section should describe the development of any components of the drug product that were included to address accidental or intentional misuse.

Module 4: Nonclinical Study Reports

4.2.1 Pharmacology

4.2.1.1 Primary Pharmacodynamics
These sections should contain study reports (*in vitro* and *in vivo*) describing the binding profile of the parent drug and all active metabolites.

4.2.3.7.4 Dependence
This section should include:

- A complete discussion of the nonclinical data related to abuse potential.
- Complete study reports of all preclinical abuse potential studies.

Module 5: Clinical Study Reports
5.3.5.4 Other Study Reports
This section should contain complete study reports of all clinical abuse potential studies.

5.3.6.1 Reports of Postmarketing Experience
This section should include information to all postmarketing experience with abuse, misuse, overdose, and diversion related to this product

General Clinical Comments

The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP 6010.3R).

To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template, including:

1. Section 2.6 Other Relevant Background Information - Important regulatory actions in other countries or important information contained in foreign labeling.
2. Section 4.4 – Clinical Pharmacology- Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.
3. Section 7.5.1 Dose Dependency for Adverse Events
4. Section 7.5.2 Time Dependency for Adverse Events
5. Section 7.5.3 Drug-Demographic Interactions
6. Section 7.5.4 Drug-Disease Interactions
7. Section 7.5.5 Drug-Drug Interactions
8. Section 7.6.4 – Overdose, Drug Abuse Potential, Withdrawal and Rebound

Sites for Inspection

To assist the clinical reviewer in selecting sites for inspection, include a table in the NDA that has the following columns for each of the completed Phase 3 clinical trials:

1. Site number
2. Principle investigator
3. Location: City State, Country
4. Number of subjects screened
5. Number of subjects randomized
6. Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites
7. Number of protocol violations (Major, minor, definition)

Pediatric Plan

You must submit a pediatric plan with the NDA submission regarding studies in pediatric patients to be conducted to fulfill the requirements of the Pediatric Research Equity Act (PREA). The plan must include the studies to be conducted; a timeline for the studies that states for each study, the date of final protocol submission, date of study start, date of study completion, and date of final study report to be submitted to the Agency; requests for waivers and deferrals with justifications; and, where possible, protocol synopses of the proposed studies.

Common PLR Labeling Errors

Highlights:

1. Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3. The highlights limitation statement must read as follows: 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]. [See 21 CFR 201.57(a)(1)]

4. The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]

5. The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).

6. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions)

7. For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].

8. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

   "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

9. Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.

10. Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).

11. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)]

12. Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble]

13. The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]

14. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be

left blank at the time of submission and will be edited to the month/year of application or supplement approval.

15. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

Contents (Table of Contents):

16. The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]

17. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]

18. Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.

19. Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.

20. When a subsection is omitted, the numbering does not change. [See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

    8.1 Pregnancy
    8.3 Nursing Mothers (not 8.2)
    8.4 Pediatric Use (not 8.3)
    8.5 Geriatric Use (not 8.4)

21. When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of the Contents:

    "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI):

22. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).

23. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

24. Do not refer to adverse reactions as "adverse events." Refer to the guidance for industry, *Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format*, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

25. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]

26. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]

27. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)].

28. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA-Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.

29. Since SPL Release 4 validation does not permit the inclusion of the Medication Guide as a subsection, the Medication Guide or Patient Package Insert should not be a subsection under the Patient Counseling Information section. Include at the end of the Patient Counseling Information section without numbering as a subsection.

30. The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.

31. Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.

32. If the "Rx only" statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. See

guidance for industry, *Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements*. The same applies to PPI and MG.

33. For fictitious examples of labeling in the new format, refer to http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

34. For a list of error-prone abbreviations, symbols, and dose designations, refer to the Institute of Safe Medication Practices' website, http://www.ismp.org/Tools/abbreviationslist.pdf

SPL Submission

Structured product labeling (SPL) must be submitted representing the content of your proposed labeling. By regulation [21 CFR 314.50(l), 314.94(d), and 601.14(b); guidance for industry, *Providing Regulatory Submissions in Electronic Format — Content of Labeling*, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm], you are required to submit to FDA prescribing and product information (i.e., the package insert) in SPL format. FDA will work closely with applicants during the review cycle to correct all SPL deficiencies before approval. Please email spl@fda.hhs.gov for individual assistance.

Integrated Summary of Effectiveness

Please refer to the guidance for industry, *Integrated Summary of Effectiveness*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf

Please refer to guidance for industry, *Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document*, available at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf

CDER Data Standards Reference Guide/Checklist

The following resources are intended to assist submitters in the preparation and submission of standardized study data to CDER.

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

Dataset Comments

1. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.

   The integrated safety dataset that must include the following fields/variables:

   a. A unique patient identifier
   b. Study/protocol number
   c. Patient's treatment assignment
   d. Demographic characteristics, including gender, chronological age (not date of birth), and race
   e. Dosing at time of adverse event
   f. Dosing prior to event (if different)
   g. Duration of event (or start and stop dates)
   h. Days on study drug at time of event
   i. Outcome of event (e.g., ongoing, resolved, led to discontinuation)
   j. Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
   k. Marker for serious adverse events
   l. Verbatim term

2. The adverse event dataset must include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset must also include the verbatim term taken from the case report form.

3. See the attached mock adverse event data set that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables must appear and does not address other content that is usually contained in the adverse event data set.

4. In the adverse event data set, provide a variable that gives the numeric MedDRA code for each lower level term.

5. The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it

is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.

6. Provide a detailed description for how verbatim terms were coded to lower level terms according to the *ICH MedDRA Term Selection: Points to Consider* document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.

7. Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.

8. The spelling and capitalization of MedDRA terms must match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.

9. For the concomitant medication dataset, you must use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.

10. For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result must be in numeric format.

11. Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.

12. Across all datasets, the same coding must be used for common variables, e.g. "PBO" for the placebo group. Datasets must not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable must be included in the datasets.

13. All datasets must contain the following variables/fields (in the same format and coding):
    a. Each subject must have one unique ID across the entire NDA
    b. Study number

c. Treatment assignment

d. Demographic characteristics (age, race, gender, etc.)

14. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities must be provided. A listing must be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups are not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values must include assessments of changes from baseline to worst value, not simply the last value.

15. Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.

16. For patients listed as discontinued to due "investigator decision," "sponsor request," "withdrew consent," or "other," the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.

17. With reference to the table on the following page, note that the HLGT and HLT level terms are from the primary MedDRA mapping only. There is no need to provide HLT or HLGT terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data.

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HLGT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 3 (SOC3)	Secondary System Organ Class 4 (SOC4)
01-701-1015	1	701	1015	MedDRA version 8.0	redness around application site	10003058	Application site redness	Application site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders		

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

/s/

SWATI A PATWARDHAN
11/14/2012