CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204768Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 204768
Product Name: Tivorbex (indomethacin) capsules

PMR/PMC Description: An open-label pharmacokinetic and safety study of an age appropriate formulation of indomethacin in pediatric patients 6 to < 17 years of age with acute mild or moderate pain.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	4/1/2015
Study/Trial Completion:	2/1/2017
Final Report Submission:	10/2/2017
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Studies in adults are completed and product is ready for approval

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Reference ID: 3458620

The goal of the study is to describe the pharmacokinetics and safety of Tivorbex in this age group.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Pharmacokinetics and safety study in pediatric patients ages six to less than 17 years. This study can be open label.

Reference ID: 3458620

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
PK and safety study

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

Reference ID: 3458620

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Reference ID: 3458620

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
02/21/2014

JUDITH A RACOOSIN
02/21/2014

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title[1]	**TIVORBEX (indomethacin) Capsules for oral use**
Applicant	Iroko Pharmaceuticals, LLC
Application/Supplement Number	NDA 204768
Type of Application	Original
Indication(s)	For treatment of mild to moderate acute pain in adults
Office/Division	ODEII/DAAAP
Division Project Manager	Kimberly Compton
Date FDA Received Application	April 30, 2013
Goal Date	February 28, 2014
Date PI Received by SEALD	February 20, 2014
SEALD Review Date	February 20, 2014
SEALD Labeling Reviewer	Abimbola Adebowale
Acting SEALD Division Director	Sandra Kweder

[1] Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word "must" denotes that the item is a regulatory requirement, while the word "should" denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item **(deficiency)**.
- **YES:** The PI meets the requirement for this item **(not a deficiency)**.
- **N/A**: This item does not apply to the specific PI under review (**not applicable**).

Highlights

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

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period:**
  - *For efficacy supplements:* If a waiver was previously granted, select "YES" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "NO" because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of-Cycle Period:**
  - Select "**YES"** in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

NO 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
Comment: *There is no horizontal line separating the HL from the TOC. Insert.*

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

NO 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *There is no white space before the Patent Counseling Information Statement and Revision Date headings in HL. Insert white space before both headings.*

There is white space between the HL heading and the HL Limitation Statement in HL. Delete the white space because there must be no white space between the HL heading and HL Limitation Statement.

Reference ID: 3457886

There is white space between the Product Title and Initial U.S. Approval in HL. Delete the white space because there must be no white space between the product title and the Initial U.S. Approval.

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

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

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Reference ID: 3457886

Selected Requirements of Prescribing Information

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

YES 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

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

Comment:

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

Comment:

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

Comment:

Selected Requirements of Prescribing Information

Indications and Usage in Highlights

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

Comment:

Dosage Forms and Strengths in Highlights

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

Comment:

Contraindications in Highlights

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

Comment:

Adverse Reactions in Highlights

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

Comment:

Patient Counseling Information Statement in Highlights

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

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

- **"See 17 for PATIENT COUNSELING INFORMATION"**

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

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

NO 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment: *The bolded revision date at the end of HL is not right justified and it is written as "Revised: [02/2014]" instead of "Revised: 2/2014." Right justify the revision date and correct the format.*

Reference ID: 3457886

Contents: Table of Contents (TOC)

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

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

NO 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment: *The subsection heading "17.7 Effects During Pregnancy" in the TOC does not match the subsection heading "17.7 Fetal Toxicity" in the FPI. Match the TOC and FPI subsection headings.*

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation

Reference ID: 3457886

is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

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

Comment:

NO 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"[see Warnings and Precautions (5.2)]"*.

Comment: *In subsection 12.3 "Pharmacokinetics", the cross-reference currently written as "*[See *Warnings and Precautions* ***(Error! Reference source not found.)]*** *" should read as "[see Warnings and Precautions* ***(Error! Reference source not found.)]*** *" as shown above.*

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

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Reference ID: 3457886

Selected Requirements of Prescribing Information

FPI Heading

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

Comment:

BOXED WARNING Section in the FPI

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

Comment:

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

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

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

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

Comment:

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

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

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING

INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Reference ID: 3457886

Appendix A: Format of the Highlights and Table of Contents

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

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

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
- [text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

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

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

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

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

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

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

Reference ID: 3457886

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

/s/

ABIMBOLA O ADEBOWALE
02/20/2014

ERIC R BRODSKY
02/20/2014
I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, acting SEALD Division Director.

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 204768
Product Name: Tivorbex (indomethacin) capsules

PMR/PMC Description: A pharmacokinetic, safety, and efficacy study of an age appropriate formulation of indomethacin in pediatric patients 1 to < 2 years of age with acute mild or moderate pain.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	6/1/2018
	Study/Trial Completion:	4/30/2021
	Final Report Submission:	12/31/2020
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☒ Other

   Studies in adults are completed and ready for approval. Need safety and PK data from older pediatric age groups prior to studying this age group.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Reference ID: 3453728

The goal of this study is to obtain efficacy, safety, and PK data in pediatric patients ages 1 to <2 years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This trial is to be an adequate and well-controlled trial in pediatric patients ages 1 to < 2 years of age.

Reference ID: 3453728

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
adequate and well controlled clinical trial to determine efficacy, safety and PK

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

Reference ID: 3453728

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Reference ID: 3453728

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
02/13/2014

JUDITH A RACOOSIN
02/21/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 204768
Product Name: Tivorbex (indomethacin) capsules

PMR/PMC Description: An open-label pharmacokinetic and safety study of an age appropriate formulation of indomethacin in pediatric patients 2 to < 6 years of age with acute mild or moderate pain.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	11/2/2015
Study/Trial Completion:	10/2/2017
Final Report Submission:	6/1/2018
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Studies in adults are completed and product is ready for approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the study is to describe the pharmacokinetics and safety of Tivorbex in this age group.

Reference ID: 3453727

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Pharmacokinetics and safety study in pediatric patients ages two to less than six years. This can be an open label study.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Reference ID: 3453727

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☒ Other
PK and safety study

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

---

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

Reference ID: 3453727

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
02/12/2014

JUDITH A RACOOSIN
02/13/2014

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

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

Memorandum

Date: January 30, 2014

To: Kimberly Compton, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

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

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

Subject: NDA 204768
OPDP labeling comments for Tivorbex (indomethacin) Capsules for oral use
Labeling Review

OPDP has reviewed the proposed package insert (PI) and carton/container labeling for Tivorbex (indomethacin) Capsules for oral use (Tivorbex) that was submitted for consult on June 21, 2013. Comments on the proposed PI are based on the version sent via email from Kimberly Compton (RPM) on January 16, 2014 entitled "N 204-768 PI and MG from EDR--USE FOR EDITS.doc

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

We have no comments on the draft carton/container labeling accessed from the following EDR location, \\CDSESUB1\EVSPROD\NDA204768\204768.enx

Thank you for the opportunity to comment.

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

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

---

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

/s/

LATOYA S TOOMBS
01/30/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff Memorandum

Date: January 27, 2014

From: Miriam Dinatale, D.O., Medical Officer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP, Team Leader
Pediatric and Maternal Health Staff

Lynne P. Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff

To: Bob Rappaport, Director, DAAAP

Drug: Tivorbex (indomethacin) capsules

NDA: 204768

Applicant: Iroko Pharmaceuticals

Subject: Pregnancy and Lactation labeling

Materials Reviewed: Proposed Tivorbex product labeling, literature provided by sponsor, Lactmed

Consult Question:
"The sponsor has proposed to include language that indomethacin appears in breast milk in their proposed labeling for this NDA. We believe all breast milk data and nursing mothers' language is to be consulted to PMHS. Please also assist with pregnancy labeling."

INTRODUCTION

On April 30, 2013, Iroko Pharmaceuticals, LLC submitted a 505(b)(2) New Drug Application (NDA 204768) to obtain approval to market Tivorbex (indomethacin) Capsules for the proposed indication of the treatment of mild to moderate acute pain. The Referenced Listed Drug (RLD) is Indocin, NDA 016059, which was discontinued for reasons not related to safety or efficacy. Iroko Pharmaceuticals, LLC is relying on FDA's findings of safety and efficacy for Indocin, as well as published literature, and the results of 5 clinical trials conducted by Iroko.

The Division of Anesthesia, Analgesia and Addiction Products (DAAAP) consulted the Pediatric and Maternal Health Staff (PMHS)-Maternal Health Team (MHT) on October 28, 2013, to provide input for appropriate labeling of the pregnancy and nursing mothers subsections of Tivorbex labeling. See Appendix A for the applicant's proposed pregnancy and nursing mothers labeling.

BACKGROUND

Indomethacin, initially approved in the U.S. on June 10, 1965, is a non-steroidal anti-inflammatory drug (NSAID) that exhibits antipyretic, analgesic and anti-inflammatory properties. *In vitro*, indomethacin is a potent inhibitor of prostaglandin synthesis. It is indicated for the treatment of moderate to severe rheumatoid arthritis, osteoarthritis, acute gouty arthritis, ankylosing spondylitis, and acute painful shoulder. Indomethacin is also approved for the closure of patent ductus arteriosus in neonates.[1]

In the third trimester of pregnancy, prostaglandin synthetase inhibitors can cause closure of the fetal ductus arteriosus with resultant pulmonary hypertension. Therefore, use during pregnancy (particularly after 30 weeks) should be avoided.

In December, 2007, the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) consulted PMHS-MHT to revise the Pregnancy and Nursing Mothers subsections of the NSAID class labeling. This review provides labeling recommendations on the sponsor's proposed indomethacin labeling based on NSAID class labeling and available published data on indomethacin use during pregnancy and lactation.[2]

REVIEW OF DATA

The following is a summary of published data on indomethacin use during pregnancy and lactation. Some of the published literature was submitted by the applicant for review; however, PMHS-MHT also conducted a literature review of the existing reproductive risk and lactation databases for current evidence-based pregnancy and lactation information. MicroMedex Reproductive Risk Information was used to search for available pregnancy use data and the Drugs and Lactation Database (LactMed)[3] was searched for available lactation data. LactMed is a National Library of Medicine (NLM) searchable database with information on drugs and lactation. LactMed provides information, when available, on

[1] Brunton, Laurence. *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th ed*. The McGraw-Hill Companies. 2011.
[2] Maternal Health Team Review on Pregnancy and Lactation Labeling for Diclofenac NDA 22-165), 4/7/2009
[3] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT

maternal levels of drug in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered, and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Relevant pregnancy and lactation data from available published studies will be recommended for inclusion in the indomethacin Pregnancy and Nursing Mothers subsections of labeling.

1. Published data regarding indomethacin during pregnancy:
Animal studies have suggested that early in pregnancy, placental passage of indomethacin is minimal. In rats, indomethacin does not cross the placenta until close to parturition. Most rodent studies have not shown an increase in the frequency in malformations in offspring of mice and rats treated during the first trimester of pregnancy with doses of indomethacin up to 100 times what is used clinically. Data available on first trimester exposure of indomethacin during human pregnancy does not demonstrate malformations in the fetus.[4]

In the second half of pregnancy, indomethacin crosses the placenta and reaches concentrations in the fetus that are equal to that of the mother. Because indomethacin is a potent inhibitor of prostaglandin synthesis, it has been used as a tocolytic agent since 1974.[5] When used between 28 and 32 weeks, it is more effective than placebo and other tocolytics in delaying delivery for at least 48 hours. Even though maternal side effects are minimal, neonatal side effects are multiple and increase when this drug is used beyond 32 weeks of gestation. The possible adverse effects in the neonate include premature closure of the ductus arteriosus, intraventricular hemorrhage (IVH), Necrotizing Entercolitis (NEC), and respiratory distress syndrome (RDS). If indomethacin is used, it is recommended that it be used 48 hours or less and at the lowest possible dose to allow time for corticosteroid treatment but minimize neonatal complications. Monitoring for oligohydramnios via amniotic fluid index (AFI) by ultrasound and patent ductus arteriosus (PDA) by fetal echocardiography is advisable in women receiving indomethacin. In addition, infants who were exposed to indomethacin shortly before birth should be monitored for possible IVH, NEC and RDS.[6]

In one study serial fetal echocardiograms were done on 13 pregnant women in premature labor who had received indomethacin ranging from 100 to 175mg per day for a maximum of 75 hours. The gestational ages of the fetuses ranged from 26.5 to 31 weeks. Ductal constriction was noted in 7 of the 14 fetuses which led to discontinuation of indomethacin. In all seven fetuses affected, ductal constriction resolved by the time they were reevaluated 24 hours after indomethacin was discontinued.[7]

---

[4] Norton, Mary. Teratogen Update: Fetal Effects of Indomethacin Administration During Pregnancy. Teratology. 1997; 56: 282-292
[5] Norton, Mary. Teratogen Update: Fetal Effects of Indomethacin Administration During Pregnancy. Teratology. 1997; 56: 282-292
[6] Abou-Ghannam et al. Indomethacin in Pregnancy: Applications and Safety. American Journal of Perinatology. 2012; 29:175-186
[7] Moise, Kenneth et al. Indomethacin in the Treatment of Premature Labor: Effects on the Fetal Ductus Arteriosus. The New England Journal of Medicine. 2010; 327-331.

2. Published data regarding Indomethacin during lactation:
Three published articles describe data on the use of indomethacin in lactating women. These studies are summarized below.

In a study by T.H. Lebedevs et al, which was submitted by the sponsor in the NDA submission, the presence of indomethacin in breast milk and exposure of infants was studied in 16 women and 7 nursing infants. All women received indomethacin for at least 48 hours prior to sampling, with daily doses ranging between 75 mg orally and 300 mg rectally daily (0.94 to 4.29 mg/kg daily) in the postpartum period. With one exception, the women were less than 10 days postpartum. One patient was 10 months postpartum. Blood samples were taken from the mother at the same time. Blood samples were also obtained from seven nursing infants for assay of indomethacin. In 11 women, indomethacin was undetectable (<20 mcg/L) in breast milk. The median breast milk: plasma ratio in seven patients with measurable drug concentrations in both breast milk and plasma was 0.37. The total infant dose ranged from 0.07% to 0.98% (median of 0.18%) of the weight adjusted[8] maternal dose. Plasma samples were obtained in seven infants. In six of these infants, indomethacin concentrations were below the sensitivity of the assay (<20 mcg/L). One infant had plasma indomethacin concentration of 47 mcg/L, which is also a low value since it is not much higher than the sensitivity of the assay.[9] Overall, the study did not list normal values for indomethacin concentrations in infants, so it is difficult to interpret these levels.

In a study by L.Beaulac-Baillargeaon and G. Allard, eight women donated milk on days 4, 12 and 26 postpartum for an *in vitro* measurement of protein binding and lipid partitioning of indomethacin in milk. The indomethacin M/P ratio was less than 0.01 irrespective of the fat content, protein content, and milk pH. The authors calculated that a breastfed infant would receive about 0.5% of the maternal weight-adjusted dosage or about 3% of the neonatal dose used to treat patent ductus arteriosus with a maternal dosage of 75 mg daily.[10]

In one case report by Eeg-Olofsson et al, a breastfeeding mother had been taking daily doses of indomethacin that increased to 200 mg from the fourth to the sixth day postpartum. On the same day that indomethacin was stopped, the infant had a generalized seizure, followed by another seizure the next day. No metabolic findings could account for the convulsions and no indomethacin levels were measured in the mother or infant. [11]

Reviewer comments
Although small amounts of indomethacin pass into breast milk, there were no adverse effects reported in infants in a study done by Lebedevs et al. There is one case report by Eeg-Olofsson et al that suggests that indomethacin may have caused a seizure in one infant.

---

[8] *Weight adjusted*: This is a standard term used in lactation studies for estimating the infant dose and is included in the current draft lactation guidance. % Maternal Dosage = (Infant Dosage (mg/kg/day)/Maternal dosage (mg/kg/day)) x 100.
[9] TH Lebedevs et al. Excretion of indomethacin in breast milk. *Br J Clin Pharmacol*. 1991; 32 (6): 751-754.
[10] L.Beaulac-Baillargeaon & G. Allard. Distribution of indomethacin in human milk and estimation of its milk to plasma ratio in vitro. Br J Clin Pharmacol. 1993; 36: 413-416.
[11] Eeg-Olofsson O, Malmros I, Elwin CE, Steen B. Convulsions in a breast-fed infant after maternal indomethacin. *Lancet*. 1978; 2 (8082):215

However, there were no samples taken from the breast milk or infant plasma to suggest indomethacin as the cause, making it difficult to draw conclusions from this case report.

The only concern is that neonate drug metabolism is immature compared to that of adults. In adults, indomethacin undergoes O-demethylation and N-deacylation to inactive metabolites and only a small percentage of a dose is excreted unchanged in the urine.[12] *The neonate's duodenum has higher levels of B-glucuronidase, an enzyme that unconjugates drugs, such as indomethacin, that the liver has metabolized via glucuronyl conjugation. These drugs reenter the blood via the enterohepatic circulation and must be remetabolized in the liver. This increases the half-life and prolongs activity of indomethacin.* [13]

Therefore, breast fed infants have the potential to accumulate the indomethacin they receive from their mother's milk. If a lactating woman decides to continue breast feeding while on indomethacin, the infant should be closely monitored for possible adverse effects. This reviewer disagrees with the conclusion reached by the sponsor that indomethacin should not be used in nursing mothers and proposes the recommendations noted in the "Nursing Mothers" section of the label.

DISCUSSION
PREGNANCY AND NURSING MOTHERS LABELING

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing Mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. A brief description of an available pregnancy exposure registry or pregnancy surveillance program that monitors or evaluates pregnancy outcomes with exposure of a drug during pregnancy should be placed in the pregnancy subsection. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in human milk is noted and presented in the label, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

PMHS-MHT notes that pregnancy categories will be eliminated with the publication of the PLLR and replaced with clinically relevant information to assist prescribers with benefit/risk decision making for using a drug during pregnancy.

---

[12] TH Lebedevs et al. Excretion of indomethacin in breast milk. Br J Clin Pharmacol. 1991; 32 (6): 751-754
[13] Blackburn, Susan. *Maternal, Fetal and Neonatal Physiology: A Clinical Perspective, 4th Ed*. Elsevier Saundars, 2013.

CONCLUSIONS

Pregnant and breastfeeding women are commonly exposed to NSAIDS. As with other NSAIDS, indomethacin should not be used after 30 weeks of pregnancy due to an increased risk of premature closure of the ductus arteriosus in the fetus. Limited human data on the use of indomethacin during lactation is available in published literature and these studies show that indomethacin is present in breast milk in low concentrations. However, none of the available literature suggests that breastfeeding be discontinued with maternal indomethacin use. The pregnancy subsection of Tivorbex labeling was structured in the spirit of the proposed PLLR, while complying with current labeling regulations. The nursing mothers subsection of the Tivorbex labeling was revised to comply with current labeling recommendations, as well as incorporating the benefit/risk statement from the proposed PLLR.

PMHS-MHT TIVORBEX (INDOMETHACIN) CAPSULE LABELING

PMHS-MHT recommends the following revision to the Pregnancy and Nursing Mothers sections of Tivorbex (indomethacin) Capsule Labeling. These recommendations were discussed at a labeling meeting with DAAAP on December 5, 2013. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.

HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

5 WARNINGS AND PRECAUTIONS

5.10 Pregnancy Fetal Toxicity

Starting at 30 weeks gestation, TIVORBEX and other NSAIDs, should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur *[see Use in Specific Populations (8.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Category C prior to 30 weeks gestation
Category D starting at 30 weeks gestation

Risk Summary

There are no adequate and well controlled studies of TIVORBEX in pregnant women. Starting at 30 weeks gestation, TIVORBEX, and other NSAIDs, should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. TIVORBEX can cause fetal harm when administered starting at 30 weeks gestation. If the drug is used during this time period in pregnancy, the patient should be apprised of the potential hazard to the fetus. Prior to 30 weeks gestation, TIVORBEX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In (b) (4) animal reproduction studies (b) (4) retarded fetal ossification was observed with administration of indomethacin to mice and rats

during organogenesis at doses 0.16 and 0.32 times, respectively, the maximum recommended dose (MRHD).

Clinical Considerations

Fetal and Neonatal Adverse Reactions

The known effects of indomethacin and other NSAIDS on the human fetus during the third trimester of pregnancy include: constriction of the ductus arteriosus, tricuspid incompetence, and pulmonary hypertension; non-closure of the ductus arteriosus postnatally which may be resistant to medical management; myocardial degenerative changes, platelet dysfunction with resultant bleeding, intracranial bleeding, renal dysfunction or failure, renal injury/dysgenesis which may result in prolonged or permanent renal failure, oligohydramnios, gastrointestinal bleeding or perforation, and increased risk of necrotizing enterocolitis.

Labor or Delivery

The effects of TIVORBEX on labor and delivery in pregnant women are unknown. In rat studies, maternal exposure to NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, increased the incidence of dystocia, delayed parturition, and decreased pup survival.

Reviewer Comment: This information was moved here from [redacted] (b) (4) *the proposed PLLR.*

Data

Animal data

Reproductive studies were conducted in mice and rats at dosages of 0.5, 1.0, 2.0, and 4.0 mg/kg/day. Except for retarded fetal ossification at 4 mg/kg/day (0.16 times [mice] and 0.32 times [rats] the maximum recommended human dose [MRHD] on a mg/m^2 basis, respectively) considered secondary to the decreased average fetal weights, no increase in fetal malformations was observed as compared with control groups. Other studies in mice reported in the literature using higher doses (5 to 15 mg/kg/day, 0.20 to 0.60 times MRHD on a mg/m2 basis) have described maternal toxicity and death, increased fetal resorptions, and fetal malformations. Comparable studies in rodents using high doses of aspirin have shown similar maternal and fetal effects.

Maternal indomethacin administration of 4.0 mg/kg/day during the last 3 days of gestation was associated with an increased incidence of neuronal necrosis in the diencephalon in the live-born fetuses however no increase in neuronal necrosis was observed at 2.0 mg/kg/day as compared to the control groups. Administration of 0.5 or 4.0 mg/kg/day to offspring during the first 3 days of life did not cause an increase in neuronal necrosis at either dose level.

8.3 Nursing Mothers

Based on available published data, indomethacin may be present in human milk. In one study, levels of indomethacin in breast milk were below the sensitivity of the assay (<20 mcg/L) in 11 of 15 women using doses ranging from 75 mg orally to 300 mg rectally daily (0.94 to 4.29 mg/kg daily) in the postpartum period. Based on these levels, the average [redacted] (b) (4) present in breast milk was estimated to be 0.27% of the maternal weight-adjusted dose. In another study indomethacin levels were measured in the donated breast milk of 8 postpartum

women using doses of 75 mg daily and the results were used to calculate an infant daily dose. The estimated infant dose of indomethacin through breast milk was less than 30 μg/day or 4.5 μg/ kg/day assuming breast milk intake of 150 ml/kg/day. This is 0.5% of the maternal weight-adjusted dosage or about 3% of the neonatal dose for treatment of patent ductus arteriosus. The developmental and health benefits of human milk feeding should be considered along with the mother's clinical need for TIVORBEX and any potential adverse effects on the human milk-fed child from the drug or from the underlying maternal condition. Exercise caution when TIVORBEX is administered to a nursing woman.

Reviewer Comment: The statement ***"****The developmental and health benefits of human milk feeding should be considered along with the mother's clinical need for TIVORBEX and any potential adverse effects on the human milk-fed child from the drug or from the underlying maternal condition" is* (b) (4) *from the proposed PLLR. The regulatory statement "Exercise caution when TIVORBEX is administered to a nursing woman" is still required under the current Nursing Mothers labeling regulations.*

17 PATIENT COUNSELING INFORMATION

17.7 Fetal Toxicity

Inform pregnant women to avoid use of TIVOREX and other NSAIDs starting at 30 weeks gestation, *[see Warnings and Precautions (5.10) and Use in Specific Populations (8.1)]*.

APPENDIX A – Applicant's Proposed Pregnancy and Nursing Mothers Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

———USE IN SPECIFIC POPULATIONS———

- Pregnancy: (b) (4)

(b) (4)

5 (b) (4)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4)

(b) (4)

[redacted]

17 PATIENT COUNSELING INFORMATION

17.7 (b) (4) [redacted]

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

/s/

MIRIAM C DINATALE
01/27/2014

JEANINE A BEST
01/27/2014

LYNNE P YAO
01/29/2014

505(b)(2) ASSESSMENT

Application Information		
NDA # 204768	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Tivorbex Established/Proper Name: indomethacin Dosage Form: capsules Strengths: 20 mg and 40 mg		
Applicant: Iroko Pharmaceuticals, LLC Agent for Applicant (if applicable): CSC		
Date of Receipt: 4/30/13		
PDUFA Goal Date: 2/28/14	Action Goal Date (if different):	
RPM: Kim Compton		
Proposed Indication(s): nonsteroidal anti-inflammatory drug (NSAID) indicated for treatment of mild to moderate acute pain in adults		

GENERAL INFORMATION

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

YES ☐ NO ☒

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

Reference ID: 3441840

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

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

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
N 016059 Indocin	**FDA's previous finding of safety and effectiveness (clinical and nonclinical)**

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

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

The approved brand-name indomethacin product (Indocin, N 016059) has been discontinued from the market, so the applicant used an approved generic to conduct bridging studies (ANDA 070624, Indomethacin by Mylan). The Applicant conducted a relative BA study with ANDA 070624 to establish a biolink.

RELIANCE ON PUBLISHED LITERATURE

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

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

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

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*

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

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

YES ☐ NO ☐

Reference ID: 3441840

RELIANCE ON LISTED DRUG(S)

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

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

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

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

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Indocin 25 and 50 mg capsules	**N 016059**	**Y**

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

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

N/A ☒ YES ☐ NO ☐

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

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

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

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

YES ☐ NO ☒

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

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

b) Approved by the DESI process?

YES ☐ NO ☒

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

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

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

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

Reference ID: 3441840

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☒ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing: **Indocin (N 016059), has not been marketed since 2003 and is listed in the DC'd section of the Orange Book.**

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

YES ☐ NO ☒

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

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

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

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

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

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

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

YES ☐ NO ☒

Reference ID: 3441840

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

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

YES ☐ NO ☐

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

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

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

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

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

YES ☒ NO ☐
*If "**NO**", proceed to question #12.*

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

YES ☐ NO ☒

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

N/A ☐ YES ☒ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all*

Reference ID: 3441840

of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): **N 018851 (Heritage) and N 018858 (Mylan), are oral indomethacin products listed in the active section of the Orange Book. In addition, there are many approved ANDAs for indomethacin oral capsules in the Orange Book. The firm conducted bridging studies to a 070624.**

PATENT CERTIFICATION/STATEMENTS

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

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

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

YES ☐ NO ☐

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

Listed drug/Patent number(s):

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

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s): no unexpired patents

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

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

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

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

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

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

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

Reference ID: 3441840

approval

APPEARS THIS WAY ON ORIGINAL

Reference ID: 3441840

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
01/24/2014

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

PATIENT LABELING REVIEW

Date:	January 23, 2014
To:	Bob A. Rappaport, M.D. Director **Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nathan Caulk, MS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Focused Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	TIVORBEX (indomethacin)
Dosage Form and Route:	Capsules, for oral use
Application Type/Number:	NDA 204-768
Applicant:	Iroko Pharmaceuticals, LLC

1 INTRODUCTION

On April 30, 2013, Iroko Pharmaceuticals, LLC submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 204-768 for TIVORBEX (indomethacin) Capsules. The purpose of this submission is to seek approval for the proposed indication for the treatment of mild to moderate acute pain in adults.

This focused review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on June 21, 2013 for DMPP to provide a focused review of the Applicant's proposed Medication Guide (MG) for TIVORBEX (indomethacin) Capsules.

2 MATERIAL REVIEWED

- Draft TIVORBEX (indomethacin) Capsules MG received on April 30, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on January 17, 2014.
- Draft TIVORBEX (indomethacin) Capsules Prescribing Information (PI) received on April 30, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on January 17, 2014.
- Approved ZORVOLEX (diclofenac) comparator labeling dated October 18, 2013.

3 REVIEW METHODS

In our focused review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- ensured that the MG is consistent with class labeling for NSAID products
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

---

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

/s/

NATHAN P CAULK
01/23/2014

BARBARA A FULLER
01/23/2014

LASHAWN M GRIFFITHS
01/23/2014

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: January 20, 2014

TO: Anjelina Pokrovnichka, M.D., Medical Reviewer
Ellen Fields, M.D., Medical Team Leader
Kim Compton, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

FROM: Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 204768

APPLICANT: Iroko Pharmaceuticals, LLC

DRUG: Indomethacin submicron particle (Tivorbex™)*
**The originally proposed proprietary name for the commercial product has been changed.*

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Treatment of mild to moderate acute pain

CONSULTATION REQUEST DATE: June 26, 2013
CLINICAL INSPECTION SUMMARY GOAL DATE: January 27, 2014
DIVISION ACTION GOAL DATE: February 28, 2014
PDUFA DATE: February 28, 2014

I. BACKGROUND

Iroko Pharmaceuticals, LLC (Iroko) is seeking approval of indomethacin submicron particle capsules (Tivorbex™) for treatment of mild to moderate acute pain. The application is a 505(b)(2) new drug application that relies on Indocin® 25 mg and 50 mg capsules application (iCeutica Operations, LLC, NDA 016059 - discontinued for reasons not related to safety or efficacy) for existing safety and efficacy data along with results of five clinical trials conducted by Iroko. The results of the following two pivotal trials were requested for inspection:

- **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

The first subject was screened February 13, 2012, and the last subject completed the study June 12, 2012. A total of 606 potential subjects were screened, 462 subjects were randomized into the trial and 450 subjects completed the trial. This multicenter study included four U.S. sites.

Subjects had to be classified as P1 to P2 in the American Society of Anesthesiologists (ASA) Physical Status Classification System and had to have undergone primary, unilateral, first metatarsal bunionectomy (osteotomy and internal fixation) with no additional collateral procedures.

The primary objective was to evaluate the analgesic efficacy of indomethacin submicron particle capsules (also referred to as Indomethacin Nanoformulation Capsules) compared with placebo in subjects with acute postoperative pain after bunionectomy. The primary efficacy endpoint was the Visual Analogue Scale (VAS) summed pain intensity difference (VAS SPID) (calculated as time-weighted averages) over 0 to 48 hours (VAS SPID-48) after Time 0.

The secondary objectives were the following:

- To evaluate the safety of Indomethacin Nanoformulation Capsules compared with placebo in subjects with acute postoperative pain after bunionectomy.
- To evaluate the time to onset of analgesia for Indomethacin Nanoformulation Capsules compared with the standard formulation of celecoxib.

- **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

The first subject was screened May 21, 2012 and the last subject completed the study August 29, 2012. A total of 516 potential subjects were screened, 373 subjects were randomized into the trial and 364 subjects completed the trial. This multicenter study included four U.S. sites.

This study was identical to the previous trial IND3-08-04b except that once pain intensity entry criteria were met, subjects were randomly assigned in a 1:1:1:1: ratio to receive oral doses of one of the four following treatments administered in a QID regimen containing active and/or dummy doses:

- Indomethacin Nanoformulation Capsules 40 mg TID (one dummy dose)
- Indomethacin Nanoformulation Capsules 40 mg BID (two dummy doses)
- Indomethacin Nanoformulation Capsules 20 mg TID (one dummy dose)
- Placebo capsules QID

The primary objective of this trial was to evaluate the analgesic efficacy of Indomethacin Nanoformulation Capsules compared with placebo in subjects with acute postoperative pain after bunionectomy.

The secondary objective of this trial was to evaluate the safety of Indomethacin Nanoformulation Capsules compared with placebo in subjects with acute postoperative pain after bunionectomy.

Iroko was responsible for the authorization, release and shipment of study drug and comparator medication to sites. Iroko contracted (b) (4) for the receipt, evaluation, and monitoring of safety information and Iroko was responsible for final evaluations and decisions in the review of adverse events and safety information. Iroko transferred all other responsibilities of both trials to the contract research organization (CRO) Premier Research Group Limited. Premier Research is headquartered in London, England and maintains two clinical research sites in the United States: Phoenix, AZ and Austin, TX. At the time the studies were conducted, a third location in Salt Lake City, UT was also operated by Premier Research. The Salt Lake City site was closed in December 2012 and is no longer operational. Randomization of subjects was generated by Premier via a computer software system called IVRS (Interactive Voice Response System). (b) (4) Institutional Review Board (b) (4) was used for both studies.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 204768 in accordance with Compliance Program 7348.811 and 7348.810. General instructions were also provided with this assignment.

Upon closure of the Salt Lake City facility all records from the site were transferred and are presently housed at the Premier Research site in Austin, TX (3200 Red River, Suite 300). Premier shipped the records to the former site in Salt Lake City (the space has not been sublet) and met the inspectors at that address for the audit. The FDA-482 was presented to the clinical investigator at his private office and then everyone moved to the closed Premier clinic for the record review. The clinical investigator was on call for any interviews or questions and was

present for the summation.

II. RESULTS (by Site):

Name of CI/ Site #	Protocol # and # of Subjects Randomized	Inspection Date	Preliminary Classification
Kyle Patrick, DO Site 003	IND3-08-04b 88 subjects IND3-10-06 73 subjects	September 25-27, 2013	NAI
Francis J. Clark, DPM Site 002	IND3-08-04b 126 subjects	November 04-12, 2013	NAI
Jason B. Dickerson, DPM Site 002	IND3-10-06 105 subjects	November 07-14,2013	NAI
Premier Research Group	Contract Research Organization	September 25-October 3, 2013	NAI

Key to Classifications

NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations; data unreliable.
Pending = Preliminary classification based on information in 483, preliminary communication with the field, and review of EIR; final classification is pending.

1. Kyle Patrick, DO

Premier Research Group Limited
20414 North 27th Ave, Suite 200
Phoenix, AZ 85027

a. **What was inspected:** Inspection included the review of informed consent forms for 100% of the patients enrolled, inclusion/exclusion criteria, adverse events (AEs), concomitant medications, source documents, case report forms (CRFs), Institutional Review Board (IRB) approvals and communications, monitoring logs, 1572's, training and test article accountability. For study IND3-08-04b, 30 subject records were reviewed. Complete source documentation verification was performed for the following subjects: 005 and 021 (40 mg TID); 006 (40 mg BID); 027 (20 mg TID); 008 (Celecoxib 200 mg) and 112 (Placebo). For study IND3-10-06, 24 subject records were reviewed. Complete source documentation verification was performed for the following

subjects: 042 and 079 (40 mg TID); 016 and 075 (40 mg BID); 027 (20 mg TID), 054 (Placebo).

b. General observations/commentary: For study IND3-08-04b, 119 subjects were screened, 88 subjects were enrolled and 87 subjects completed the study. The study began at the site on February 15, 2012 and completed on June 6, 2012. For study IND3-10-06, 116 subjects were screened, 73 subjects were enrolled, and 72 subjects completed the study. The study began at the site on May 23, 2012 and completed on August 29, 2012.

All subjects spoke fluent English and were consented in English. All subjects signed the consent forms prior to the start of the study. No discrepancies were noted. All subjects had their surgery performed at the site by the sub-investigators who were also licensed podiatrists. Prior to dosing, the subjects would be blindfolded. The test article drug and/or placebo would be dispensed from an envelope right into the mouth of the subject. The subjects never saw or touched the drug/placebo. All AE's were accounted for and there were no discrepancies. The drug accountability forms for both studies (IND3-08-04b and IND3-10-06) were reviewed. All test articles (drug and placebo) were accurately reconciled. Remaining product was returned to the sponsor (Iroko). No discrepancies were noted.

The Visual Analogue Scale (VAS) pain intensity actual time points Baseline (0) and 48 hours for all selected subjects were compared against the source documentation (for both studies). The primary endpoint was verifiable. A smaller number of subjects (for both studies) were chosen and data verified for every time point (15, 30 and 45 minutes and 1, 1.5, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 32, 40, 48 hours) from the listings and compared against the source documentation. There were no discrepancies.

At the conclusion of the inspection, no Form FDA 483, Inspectional Observations, was issued.

c. Assessment of data integrity: The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

2. Francis J. Clark, DPM
Premier Research Group Limited
3995 South 700 East, Suite 250
Salt Lake City, UT 84107

Post inspectional address: 3584 West 9000 South, Suite 301, West Jordan, UT 84088.

a. What was inspected: Inspection included the review of informed consent

forms for 100% of the subjects, inclusion/exclusion criteria, adverse events, concomitant medications, source documents, case report forms (CRFs), Institutional Review Board (IRB) approvals and communications, monitoring logs, 1572's, training, curriculum vitaes, financial disclosure forms, and test article accountability. There were 48 subject source records reviewed.

General observations/commentary: There were 160 subjects screened at the site, 126 subjects enrolled, and 122 subjects that completed the study. No instances were noted whereby subjects did not meet eligibility criteria. Upon a review of records, no issues regarding protocol-specific blinding/randomization procedures were identified. Test article accountability/disposition was documented adequately. Test article reconciliation showed no issues of concern. The Visual Analogue Scale (VAS) was compared at all of the time points for one third of the total number of subjects, randomly selected from the beginning, middle, and end of the study period. The primary endpoint was verifiable. There was only one instance in which a VAS was identified as being transcribed incorrectly. This was the baseline VAS for Subject 016; the source document identifies the baseline VAS as 86, but the case report form identifies the VAS as 85. A random subset of secondary efficacy endpoints was evaluated during the review of subject files. No discrepancies were noted during this review. No deficiencies were noted regarding adverse/serious adverse event reporting. No concerns regarding randomization were identified during a review of records at this site.

At the conclusion of the inspection, no Form FDA 483, Inspectional Observations, was issued. Issues presented as discussion items included: maintaining all study-related records together (study related x-rays were not readily available), one instance of transcription error from source document to case report form (as discussed earlier), and ensuring the institutional review board was aware of the blindfolding procedures utilized in this study.

c. Assessment of data integrity: The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

3. Jason B. Dickerson, DPM
Premier Research Group Limited
3995 South 700 East, Suite 250
Salt Lake City, UT 84107

Post inspectional address: 5872 South 900 East, Suite 150, Salt Lake City, UT 84121

a. What was inspected: Informed consent was reviewed for 100% of subjects. This inspection included verifying the accuracy of data endpoints, adverse event reporting, IRB review and approval, adherence to protocol, monitoring reports, curriculum vitae, delegation of duties, 1572s, financial disclosure forms,

concomitant medications, and test article accountability. There were 35 subject records reviewed.

b. General observations/commentary: There were 124 subjects screened at the site, 105 subjects enrolled, and 104 subjects who completed the study. There were no issues with informed consents, adverse event reporting, protocol oversight, or test article accountability. No concerns regarding randomization were identified during a review of records at this site. The primary endpoint was verifiable. VAS was compared at all time points for a sample of subjects, which included one third of the total number of subjects, randomly selected from the beginning, middle, and end of the study period. There was only one instance in which a VAS was identified as being transcribed incorrectly. This was the 15 minute VAS for subject 076; the source document identifies this VAS as 63, but the case report form identifies the VAS as 62. A random subset of secondary efficacy endpoints was evaluated during the review of subject files. No discrepancies were noted.

At the conclusion of the inspection, no Form FDA 483, Inspectional Observations, was issued. Two items were presented as discussion items. First, one instance of a data transcription discrepancy was identified during the review of the primary efficacy endpoint (as noted above). Second, a discrepancy was noted upon review of Subject 092 records. The Inclusion Criteria checklist showed that the subject was signed-off as both "acceptable" and "unacceptable" to continue in study participation. The "deemed acceptable" signature was dated 24 JUL 12, the "deemed unacceptable" signature was dated 14 AUG 12. According to the same subject's Screening Visit, surgery was scheduled for July 6, 2012. This subject did not participate in the study. The principal investigator agreed that there appeared to be something wrong, but could not explain the discrepancy other than say it must have been a mistake for the signature on the "deemed acceptable" line as this subject was, in fact, not acceptable and was taken out of the study at the appropriate time.

c. Assessment of data integrity: The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

4. Premier Research Group
1500 Market Street
Suite 3500
Philadelphia, PA 19102 USA

a. What was inspected: The inspection included review of organization and personnel, selection and monitoring of clinical investigators, selection of monitor, monitoring procedures and activities, quality assurance, safety/adverse event reporting, data collection and handling, test article, and transfer of

responsibilities. Corrections to previous observations noted during a past inspection were also evaluated.

b. **General observations/commentary:** Review of the curriculum vitas for all the monitoring staff revealed that they met the job description criteria. Newly hired monitors and staff received adequate formal GCP training and specific monitoring training with pertinent training when procedures were issued/revised. There was no investigator training meeting. Therefore, study specific training was provided by the site monitor during the site initiation visit and via WebEx. Study drug was to be administered during the trials by an unblinded, third-party dose administration person who did not conduct any efficacy or safety assessments. The study drug was to be administered by blindfolding all subjects to ensure adequate blinding since the capsules were not identical in appearance. The unblinded dose administration persons were provided with additional training and a mock dosing was performed at each site. A complete list of individuals (Premier and site staff) that were trained and given access to enter the electronic data capture (EDC) system was reviewed and there were no issues. The Site Visit Reports for studies IND3-08-04b and IND3-10-06, sites 002 and 003, were reviewed and there were no objectionable conditions. All clinical investigators who signed the 1572s/agreements were observed to be included in the marketing application submission.

The cut-off for primary efficacy evaluation was on July 17, 2012 for study IND3-08-04b; and October 2, 2012 for study IND3-10-06. Data obtained throughout the trial were recorded by the sites into an eCRF (EDC system).

During the inspection, it was observed that according to the Close-Out Visit reports for study IND3-10-06, 365 subjects were completers. However, the application to the FDA reported 364 subjects to be completers. The staff at the inspected site explained that the monitors reported all subjects that completed treatment and the application counted all subjects that completed the follow up visit. Subject 001-046 did not complete the 48-hours follow up visit.

It was requested as part of the assignment that a statistical programing problem be evaluated. An Advice Letter sent to Iroko from the review team on August 14, 2012 recommended that subjects in the pivotal bunionectomy trials (IND3-08-04b and IND3-10-06) be instructed to capture a pain assessment prior to each dose of rescue medication, and that this score be imputed in place of the efficacy assessment following the receipt of rescue medication in the appropriate analyses. As clinical conduct of both trials had been completed by the time of Iroko's receipt of the Advice Letter, this strategy for data collection could not be implemented. In an attempt to address the recommendations, the Statistical Analysis Plan (SAP) for IND3-08-04b was amended post hoc to include an additional sensitivity data analysis using the mixed model analysis methodology (MMRM). The SAP for study IND3-10-06 was in the draft stage and this requirement was added prospectively prior to study unblinding:

"To assess the impact of using BOCF/LOCF imputation methodology in the assessment of the study's primary efficacy endpoint (VASPPID-48), sensitivity analyses will be performed. The sensitivity analyses will use BOCF imputations only for the assessments within 4 hours after taking rescue medications. Other assessments post rescue will retain the original pain score measurements."

Iroko was preparing the response to a Clinical Information Request received on August 2, 2013 from the review team, and discovered an error in the programming used for the sensitivity analyses performed on the primary and multiple secondary endpoints. One prospective efficacy analysis and multiple post-hoc efficacy analyses for both pivotal clinical trials (IND3-08-04b and IND3-10-06) as well as data tables presented in 2.7.3 Summary of Clinical Efficacy were affected by this inadvertent programming error.

Premier Research staff explained that the error was due to a misinterpretation of the requirement to replace the pain scores after 4 hours of rescue medications with the baseline-observation-carried-forward (BOCF [pain score pre-dose which is in most instances the strongest pain a subject experienced]). The Sponsor had intended Premier Research to replace the pain scores every time a rescue medication was taken. The firm only replaced the pain scores after 4 hours following the FIRST rescue medication.

The Sponsor was responsible for the final review and approval of data listings. The Sponsor also reviewed and approved the final statistical analysis. There were no objections. Following Iroko's discovery of this error, all affected analyses for trials IND3-08-04b and IND3-10-06 were re-run using the originally intended algorithm to apply BOCF to all efficacy data collected within 4 hours following each dose of rescue medication. In the original analyses, baseline value for subjects who took rescue medication is only being carried forward for 4 hours after taking the initial rescue medication dose. In the revised analyses, baseline value for subjects who took rescue medication is being carried forward for 4 hours after each dose of rescue medication. The corrected analyses had no impact on the clinical conclusions included in the original submission or the response to Clinical Information Amendment (0005) submitted on August 15, 2013.

During the previous inspection in 2012, Premier Research was cited for failure to select qualified investigators and failure to ensure proper monitoring of the studies inspected. During the current inspection, no objectionable conditions were noted regarding the monitor's qualifications or the monitoring activities.

At the conclusion of the inspection, no Form FDA 483, Inspectional Observations, was issued. Discussion items included the use of templates when writing Site Visit Reports, ensuring that correct and complete forms are maintained by the Clinical Research Associates (CRAs); and documenting discussions CRAs had with the clinical investigators regarding missing windows. (Staff explained that the windows were not specified in the protocols but were agreed upon between the sponsor and the firm).

c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this CRO appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of three domestic clinical sites as well as the contract research organization. All performed well with no significant regulatory violations noted. The classification for each is No Action Indicated (NAI). The study data appear reliable in support of NDA 204768.

Observations noted above for Drs. Patrick, Clark and Dickerson, and Premier Research are based on the preliminary review of the Establishment Inspection Reports. An inspection summary addendum will be generated if conclusions change upon OSI final classification.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

/s/

CYNTHIA F KLEPPINGER
01/21/2014

JANICE K POHLMAN
01/22/2014

KASSA AYALEW
01/22/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Memorandum

Date:	January 8, 2014
Reviewer:	Vicky Borders-Hemphill, Pharm.D Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, Pharm.D, BCPS Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Tivorbex (Indomethacin) Capsules, 20 mg and 40 mg
Application Type/Number:	NDA 204768
Applicant:	Iroko Pharmaceuticals, LLC
OSE RCM #:	2013-1486

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This memorandum evaluates the revised container labels, and insert and carton labeling for Tivorbex (Indomethacin) Capsules, 20 mg and 40 mg, submitted December 12, 2013 (see Appendices A and B). The Division of Medication Error and Prevention Analysis (DMEPA) initially reviewed the labels and labeling in OSE review 2013-1486, dated October 3, 2013.

2 MATERIALS REVIEWED

DMEPA evaluated the revised container labels and carton labeling submitted December 12, 2013. We compared the revised labels and labeling against our recommendations in OSE Review 2013-307, dated October 3, 2013, to assess whether the revised labels and labeling address our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMENDATIONS

Our review of the revised container labels and carton labeling determined the Applicant has implemented all of our recommendations and we find the revisions acceptable. Therefore, we have no further recommendations.

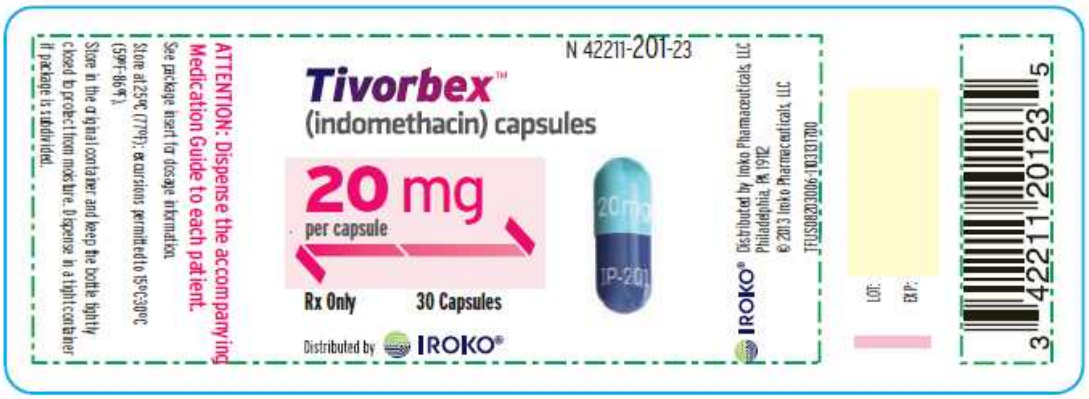
If you have further questions or need clarifications, please contact Lisa Skarupa, project manager, at 301-796-2219.

Reference ID: 3433004

APPENDICES

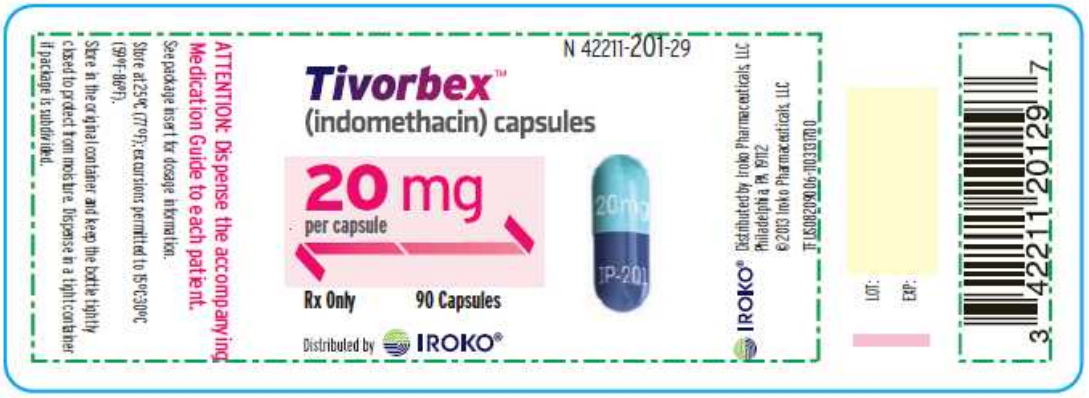
Appendix A. Container Labels

Bottle 30 count - 20 mg



Bottle 30 count - 40 mg

Bottle 90 count - 20 mg



Bottle 90 count - 40 mg

(b) (4)

[redacted]

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

---

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

/s/

BRENDA V BORDERS-HEMPHILL
01/08/2014

LUBNA A MERCHANT on behalf of IRENE Z CHAN
01/08/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Drug Use Review

Date:	October, 2013
Reviewer:	Travis Ready, PharmD, Drug Use Data Analyst Division of Epidemiology II (DEPI II)
Team Leader:	Hina Mehta, Pharm.D. Division of Epidemiology II (DEPI II)
Deputy Division Director:	Laura Governale, Pharm.D., MBA Division of Epidemiology II (DEPI II)
Drug Name(s):	(b) (4) (indomethacin)
Application Type/Number:	NDA: 204768
Applicant/Sponsor:	Iroko Pharmaceuticals
OSE RCM #:	2013-2218

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

EXECUTIVE SUMMARY

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) is currently evaluating the sponsor's claim that use of oral indomethacin capsules in pediatric patients is extremely low. In support of this effort, the Division of Epidemiology II was requested to evaluate the extent of oral indomethacin use in pediatric patients aged less than 1, 1, 2-5, 6-11, and 12-16, and 17+ years, for years 2008 through 2012, and year-to-date August 2013.

Summary of findings:

- During year 2012, approximately (b) (4) prescriptions were dispensed for oral indomethacin from U.S. outpatient retail pharmacies.
- During year 2012, approximately (b) (4) patients received a dispensed prescription for oral indomethacin from U.S. outpatient retail pharmacies.
- The overall use of oral indomethacin has remained relatively steady during the time examined.

(b) (4)

1 INTRODUCTION

1.1 BACKGROUND

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) is currently evaluating a new drug application (NDA 204768) for (b) (4) (nanoformulated indomethacin). As part of the approval process, the sponsor would be required to perform pediatric studies under the Pediatric Research Equity Act (PREA). Subsequently, the sponsor stated in their pediatric plan that their justification for not having a pediatric study is due to the extremely low use of oral indomethacin in children below the age of six. As a result, the Division of Epidemiology II (DEPI-II) was requested to determine the extent of oral indomethacin use in pediatric patients aged less than 1, 1, 2-5, 6-11, and 12-16 years. Using currently available proprietary drug utilization databases, this review provides the number of dispensed oral indomethacin prescriptions, the number of patients receiving a dispensed prescription for oral indomethacin, and the top diagnoses as reported by office-based physician surveys for the pediatric population aged less than 1, 1, 2-5, 6-11, and 12-16 and 17+ years, for years 2008 through 2012, and year-to-date August 2013.

1.2 PRODUCT LABELING

Indomethacin (Indocin) oral capsules were originally approved on June 10, 1965. Since then other formulations such as suppository, suspension, injection, and extended release capsules have been

approved. All formulations with the exception of the injection are indicated for moderate to severe rheumatoid arthritis including flares of chronic disease, moderate to severe ankylosing spondylitis, moderate to severe osteoarthritis, acute painful shoulder (bursitis and/or tendinitis), and acute gouty arthritis.[1] The injection is indicated to close a hemodynamically significant patent ductus arteriosus in premature infants weighing between 500 and 1750 g when after 48 hours of usual medical management is ineffective.[2]

Indomethacin is available as 25mg and 50 mg capsules, 50mg suppository, 25mg/5ml oral suspension, 75 mg extended release capsules, and 1mg EQ base/vial powder for injection. *For the purposes of this review only oral indomethacin formulations were included.*

2 METHODS AND MATERIALS

2.1 DETERMINING SETTINGS OF CARE

The IMS Health, IMS National Sales Perspective™ was used to determine the various retail and non-retail channels of distribution for all oral formulations of indomethacin. Sales data for year 2012 indicated that approximately (b) (4) of all oral indomethacin packages were sold to outpatient retail pharmacies, (b) (4) to non-retail settings, and (b) (4) to mail-order settings.[3] As a result, only outpatient retail pharmacy utilization patterns were examined. Neither mail-order/specialty pharmacy nor non-retail data were included in this analysis.

2.2 DATA SOURCES USED

Proprietary drug utilization databases were used to conduct this analysis (see Appendix 2 for full database description).

The IMS Health, National Prescription Audit (NPA) was used to obtain the nationally estimated number of prescriptions dispensed for oral indomethacin from U.S. outpatient retail pharmacies for years 2008 through 2012 and year-to-date August 2013. The IMS Health, Total Patient Tracker (TPT) was used to obtain the nationally estimated number of patients who received a dispensed prescription for oral indomethacin, stratified by patient age (< 1, 1, 2-5, 6-11, and 12-16, and 17+ years), from U.S. outpatient retail pharmacies for years 2008 through 2012, and year-to-date August 2013.

The top diagnoses associated with the use of oral indomethacin, stratified by patient age (< 1, 1, 2-5, 6-11, and 12-16, and 17+ years) were obtained (b) (4) (b) (4) for the cumulative time period from January 2008 through August 2013.

3 RESULTS

3.1 NATIONALLY ESTIMATED NUMBER OF PRESCRIPTIONS DISPENSED

1 http://dailymed nlm nih gov/dailymed/lookup cfm?setid=1ce9c3c5-0cf7-4760-988d-2559adcfb200#nlm34067-9

2 http://dailymed nlm nih gov/dailymed/lookup cfm?setid=0581fd65-63f9-4705-adbd-602fe7b55874#nlm34067-9

3 IMS Health, National Sales Perspective (NSP), Jan 2008 – Aug 2013, Extracted Oct 2013 File: NSPC 2012-2218 Indomethacin 10 9 13 xlsx

Figure 1 in Appendix 1 provides the nationally estimated number of prescriptions dispensed for oral indomethacin from U.S. outpatient retail pharmacies, for years 2008 through 2012 and year-to-date August 2013. During the entire time period examined, the total number of dispensed prescriptions for oral indomethacin remained relatively steady. During year 2008, there were approximately (b) (4) oral indomethacin prescriptions dispensed from U.S. outpatient retail pharmacies, dropping slightly to about (b) (4) prescriptions dispensed from U.S. outpatient retail pharmacies during year 2012.

3.2 NATIONALLY ESTIMATED NUMBER OF PATIENTS WHO RECEIVED A DISPENSED PRESCRIPTION

Table 1 provides the nationally estimated number of patients who received a dispensed prescription for oral indomethacin, stratified by patient age (< 1, 1, 2-5, 6-11, 12-16, and 17+ years), from U.S. outpatient retail pharmacies for years 2008 through 2012, and year-to-date August 2013.

Overall, the number of patients receiving a dispensed prescription for oral indomethacin remained relatively steady. During year 2008, approximately (b) (4) patients received a dispensed prescription for oral indomethacin, increasing slightly to about (b) (4) patients receiving a dispensed prescription for oral indomethacin during year 2012. There was a slight peak during year 2010 with about (b) (4) patients receiving a dispensed prescription for oral indomethacin.

(b) (4)

3.3 INDICATIONS FOR ORAL INDOMETHACIN

Table 2 in Appendix 1 shows the top diagnoses associated with the use of oral indomethacin, stratified by patient age, during the cumulative time period from January 2008 through August 2013. Diagnoses expressed in terms of *drug use mentions*[4] were coded according to the International Classification of Diseases (ICD-9-CM) and 95% confidence intervals were calculated for the estimates. (b) (4)

[4] The term "drug uses" refers to mentions of a drug in association with a diagnosis during an office-based patient visit This term may be duplicated by the number of diagnosis for which the drug is mentioned It is important to note that a "drug use" does not necessarily result in prescription being generated Rather, the term indicates that a given drug was mentioned during an office visit

(b) (4)

4 DISCUSSION

(b) (4)

Findings from this review should be interpreted in the context of the known limitations of the databases used. Based on the IMS Health, IMS National Sales Perspectives™, sales data for year 2012 showed that approximately (b) (4) oral indomethacin was distributed to outpatient retail pharmacies. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer to various channels of distribution.

Indications for use were obtained using a monthly survey of (b) (4) office-based physicians. Although these data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, physician survey data are best used to identify the typical uses for the products in clinical practice, and outpatient prescription data are best used to evaluate utilization trends over time. Results should not be overstated when nationally projected estimates of annual uses or mentions fall below (b) (4) as the sample size is very small with correspondingly large confidence intervals.

5 CONCLUSION

(b) (4)

APPENDIX 1: Figures and Tables

Figure 1.

Table 1.

Table 2.

APPENDIX 2: Drug Use Database Descriptions.

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

National Prescription Audit

The National Prescription Audit (NPA™) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions in the United States. The NPA audit measures both what is prescribed by the physician and what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies.

NPA™ receives over 2.7 billion prescription claims per year, captured from a sample of the universe of approximately 57,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 80% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data are available on-line for 72-rolling months with a lag of 1 month.

IMS, Vector One®: Total Patient Tracker (TPT)

The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. Furthermore, patient age subtotals may not sum exactly due to patients aging during the study period ("the cohort effect"), and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

*Subtotals may not sum exactly due to rounding. Because of patients aging during the study period ("the cohort effect"), patients may be counted more than once in the individual age categories. For this reason, summing across years is not advisable and will result in overestimates of patient counts.


(b) (4)

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

/s/

TRAVIS W READY
10/18/2013

HINA S MEHTA
10/18/2013
Drug use data cleared

LAURA A GOVERNALE
10/21/2013

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Application: 204768

Application Type: New NDA

Name of Drug: (b) (4) (indomethacin) capsules

Applicant: Iroko Pharmaceuticals, LLC

Submission Date: 4/30/13

Receipt Date: 4/30/13

1.0 Regulatory History and Applicant's Main Proposals

New NDA for another indomethacin product, a 505(b)(2) application in the NSAID class with the proposed indication of treatment for mild to moderate acute pain

2.0 Review of the Prescribing Information (PI)

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

3.0 Conclusions/Recommendations

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

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by July 28, 2013. The resubmitted PI will be used for further labeling review.

Reference ID: 3338353

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

INSTRUCTIONS FOR COMPLETING THE SRPI
There is one drop-down menu and one comment field for each item.

Drop-Down Menu: "NO" is the default option. For each SRPI item, click on the word "NO" and choose one of three following options:

- **NO: The PI does not meet the requirement for this item (deficiency).**
- **YES: The PI meets the requirement for this item (no deficiency).**
- **N/A (not applicable): This item does not apply to the specific PI under review.**

Comment Field: Comments are optional. To insert a comment for a particular item, click on the word "*Comment*" and insert your comment.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

NO 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**

Reference ID: 3338353

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

NO 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

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

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

Reference ID: 3338353

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

NO 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

YES 12. All text must be **bolded**.

Comment:

YES 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

YES 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year

format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

NO 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment: (b) (4) [redacted]

YES [redacted] is listed in the FPI, but not in HLs.

24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include <u>one</u> of the following three **bolded** verbatim statements (without quotation marks):

<u>If a product **does not** have FDA-approved patient labeling</u>:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

<u>If a product **has** FDA-approved patient labeling</u>:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Reference ID: 3338353

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

YES 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES

Reference ID: 3338353

38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

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

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

Reference ID: 3338353

Selected Requirements of Prescribing Information (SRPI)

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES 42. All text is **bolded**.

Comment:

YES 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

YES 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

Reference ID: 3338353

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
07/09/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
NDA # 204768	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Established/Proper Name: indomethacin Dosage Form: capsules Strengths: 20 mg and 40 mg		
Applicant: Iroko Pharmaceuticals, LLC Agent for Applicant (if applicable): CSC		
Date of Application: 4/30/13 Date of Receipt: 4/30/13 Date clock started after UN: N/A		
PDUFA Goal Date: 2/28/14	Action Goal Date (if different):	
Filing Date: 6/29/13	Date of Filing Meeting: 6/20/13	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication(s)/Proposed change(s): nonsteroidal anti-inflammatory drug (NSAID) indicated for treatment of mild to moderate acute pain in adults		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

Reference ID: 3333986

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*): N/A

List referenced IND Number(s): 101940

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:			X	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

Reference ID: 3333986

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***		X		
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:		X		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***		X		

Reference ID: 3333986

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

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

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

Reference ID: 3333986

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

Reference ID: 3333986

Note: *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	Electronic
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:			**X**	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X			
If a request for full waiver/partial waiver/deferral is		X		Have requested

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

Reference ID: 3333986

included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]			X	
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			This was not submitted as a separate submission and so the firm was directed via email to submit properly.
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	■ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ■ Medication Guide (MedGuide) ■ Carton labels ■ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***				
Is the PI submitted in PLR format?[4]	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	X		X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate	X			

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

Reference ID: 3333986

container labels) consulted to OPDP?				
MedGuide, consulted to OSE/DRISK? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		X		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 6/8/10 ***If yes, distribute minutes before filing meeting***	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 10/23/12 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

Reference ID: 3333986

ATTACHMENT

MEMO OF FILING MEETING

DATE: 6/20/13

BLA/NDA/Supp #: 204768

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: indomethacin

DOSAGE FORM/STRENGTH: capsules, 20 and 40 mg

APPLICANT: Iroko Pharmaceuticals

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): treatment of mild to moderate acute pain in adults

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kim Compton	Y
	CPMS/TL:	Matt Sullivan (acting)	N
Cross-Discipline Team Leader (CDTL)	Ellen Fields		Y
Clinical	Reviewer:	Anjelina Pokrovnichka	N
	TL:	Ellen Fields	Y

Reference ID: 3333986

Clinical Pharmacology	Reviewer:	Suresh Naraharisetti	Y
	TL:	Yun Xu	N
Biostatistics	Reviewer:	Yan Zhou	Y
	TL:	Janice Derr	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Alex Xu	Y
	TL:	Adam Wasserman	Y
Product Quality (CMC)	Reviewer:	Xioben Shen	Y
	TL:	Julia Pinto	Y
Quality Microbiology	Reviewer:	Erika Pfeiler	N
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Vicky Borders-Hemphill	N
	TL:		
OSE/DRISK (REMS)	Reviewer:	Reema Mehta	Y
	TL:		

Reference ID: 3333986

Bioresearch Monitoring (OSI)	Reviewer:	Cynthia Kleppinger	Y
	TL:		
Other reviewers	Biopharm (ONDQA) -Elsbeth Chikhale (Y), OPDP-Shenee Toombs (N), PLT-Nathan Caulk (N)		
Other attendees	Mark Liberator, OSE PM (covering for assigned PM)		Y

FILING MEETING DISCUSSION:

GENERAL	
• 505(b)(2) filing issues:	☐ Not Applicable
o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☒ NO
o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☒ YES ☐ NO
Describe the scientific bridge (e.g., BA/BE studies):	BA study to Mylan product
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☒ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**:	☐ YES Date if known: ☒ NO

Reference ID: 3333986

If no, for an NME NDA or original BLA , include the reason. For example: o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ To be determined Reason: this drug is not the first in its class
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Reference ID: 3333986

Comments:	☐ Review issues for 74-day letter

PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Bob Rappaport **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐ The application is unsuitable for filing. Explain why:	

Reference ID: 3333986

☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
	ACTIONS ITEMS
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Reference ID: 3333986

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

Reference ID: 3333986

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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
06/28/2013