CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204768Orig1s000

CHEMISTRY REVIEW(S)

NDA 204-768

Tivorbex™ Capsules
(Indomethacin)

Iroko Pharmaceuticals, LLC

Xiaobin Shen, Ph.D.
for
Division of Anesthesia, Analgesia and Addiction Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 204-768

2. REVIEW #: 1

3. REVIEW DATE: 16-Jan-2014

4. REVIEWER: Xiaobin Shen, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NA	NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	30-Apr-2013
Amendment 0001	04-Jun-2013
Amendment 0004	26-Jul-2013
Amendment 0008	11-Sep-2013
Amendment 0011	29-Oct-2013
Amendment 0018 (covered by biopharm review)	19-Dec-2013
Amendment 0019 (covered by biopharm review)	13-Jan-2014
Amendment 0020	15-Jan-2014

Other amendments dated older than the last listed do not have CMC related information for review.

7. NAME & ADDRESS OF APPLICANT:

Name: Iroko Pharmaceuticals, LLC

Address: One Kew Place, 150 Rouse Boulevard, Philadelphia, PA 19112

Chemistry Review Data Sheet

Representative (Agent):	Steve Jensen One Kew Place, 150 Rouse Boulevard, Philadelphia, PA 19112
Telephone:	267-546-3019
Fax:	267-546-3004
Email:	sjensen@iroko.com

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Tivorbex™
b) Non-Proprietary Name (USAN): Indomethacin
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NDA 505(b)(2)

10. PHARMACOL. CATEGORY: Non-steroidal anti-inflammatory drug (NSAID)

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 20 mg and 40 mg

13. ROUTE OF ADMINISTRATION: Oral

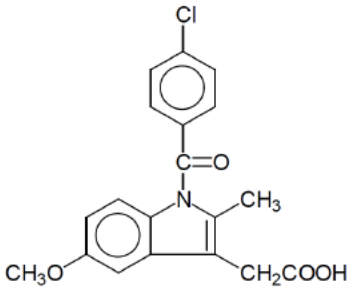
14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

Chemical name: 1-(4-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid
United States Adopted Name (USAN): Indomethacin
Compendial name: Indomethacin
Chemical structure:



Molecular formula: $C_{19}H_{16}ClNO_4$
Molecular weight: 357.80 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Indomethacin drug substance	3	Adequate	30-Aug-2013	There has been no change to the DMF that affects its quality since the last review
26340	II	Iroko Pharmaceuticals, LLC	Indomethacin drug substance submicron particles	1	Adequate	16-Jan-2014	There has been no change to the DMF that affects its quality since the last review
(b) (4)	IV	(b) (4)		4	NA	NA	NA
				4	NA	NA	NA

(b) (4)		(b) (4)				
	III		4	NA	NA	NA
			4	NA	NA	NA
	III		4	NA	NA	NA
	III		4	NA	NA	NA
	III		4	NA	NA	NA
	III		4	NA	NA	NA
	III		4	NA	NA	NA
	III		4	NA	NA	NA
	III		4	NA	NA	NA

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA	NA	NA

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	26-Sep-2013	Xiaobin Shen
Pharm/Tox	Acceptable	26-Sep-2013	Dr. Alex Xu

Chemistry Review Data Sheet

Biopharm	Acceptable	15-Jan-2014	Dr. Elsbeth Chikhale
Methods Validation	Not needed	26-Sep-2013	Xiaobin Shen
EA	Adequate	26-Sep-2013	Xiaobin Shen
Microbiology	Adequate	13-May-2013	Dr. Erika Pfeiler

The Chemistry Review for NDA 200-403

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval.

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

NA.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

Indomethacin drug substance is a white to yellow crystalline powder. Its support is completely referenced to DMF (b) (4) The NDA provided no physicochemical properties of the drug substance. Indomethacin is practically insoluble in water (according to public literature). The NDA did not provide pharmacological related information about the drug substance either, it is filed in reference to the FDA approved Indocin® capsule product.

The drug substance indomethacin is manufactured (b) (4) per DMF (b) (4) The DMF was last reviewed by Dr. Andrew Langowski in Aug. 2013 in support of ANDA 202-572 regarding a capsule product and deemed adequate. There has been no change to the DMF that impacts its quality since that review. The manufacturer site has satisfactory EES status.

Specifications for indomethacin drug substance include both USP and ICH requirements. Collectively they include appearance, identification, X-ray diffraction, assay, impurities, loss on drying, residue on ignition, heavy metals, and residual solvents. The drug substance is packaged (b) (4) The drug substance stability data was referenced to DMF (b) (4) which supports a retest period (b) (4)

The drug product is available as 20 mg and 40 mg strength capsules. The 20 mg strength capsule consists of a dark blue body with "IP-201" imprinted in white ink, and a light blue cap with "20 mg" imprinted in white ink. The 40 mg strength capsule consists of a dark blue body with "IP-202" imprinted in white ink, and a light blue cap

with "40 mg" imprinted in white ink. Both product strength has the same formulation composition. [redacted] The excipients include lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, and sodium stearyl fumarate. The capsule shells are sourced from [redacted] Both lactose monohydrate and the capsules meet the Agency's BSE/TSE requirements. The imprint ink composition includes FD&C Blue #2, titanium dioxide, gelatin, and white ink, all are of compendial grade. The capsules are packaged in HDPE bottles as 30 count and 90 count commercial products [redacted] The drug product is manufactured [redacted] and packaged [redacted] both sites have satisfactory EES status.

The drug product specifications include appearance, identification, assay, related substances, content uniformity, [redacted] trace metals, heavy metals, and dissolution. Microbial burden is included for stability testing but not release testing, based on the applicant's justifications Microbiologist Dr. Erika Pfeiler has deemed it acceptable.

The drug product primary stability studies were conducted on 3 batches for each strength and packaging configuration combinations. 18 months of stability data are provided for the long term (25°C/60% RH) storage conditions, 12 months of stability data are provided for the intermediate storage conditions (30°C/65% RH), and up to 36 months of stability study is planned for the long term condition. Six months of stability data are provided for the accelerated conditions (40°C/75% RH). Assay, impurities, [redacted] and microbial results remained relatively stable for the studied periods for all product strength/packaging configuration combinations and for all storage conditions. Dissolution [redacted] rates still meet the proposed and justified acceptance limits under long term storage condition. Overall, the provided stability data support the applicant proposed 24 month product expiry.

All IQA comments have been evaluated and resolved.

During the review, information requests were communicated to the applicant. Responses to the information requests (included in the list of reviewed Amendments) are evaluated at the related sections of this review.

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

The product is indicated for treatment of mild to moderate acute pain in adults. It is proposed to be administered at 20 mg three times daily or 40 mg two to three times daily, at the lowest effective dose for the shortest duration.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provided acceptable information on the chemistry, manufacturing, and controls of the indomethacin capsules. The product is recommended for approval based on the following:

- The drug substance and product specifications provided adequate controls;
- The drug product excipients are of USP/NF grade;
- The drug product container closure systems are acceptable for pharmaceutical use.
- Both drug substance and drug product are stable in the studied stability period and support the currently claimed 24 months of drug product expiry.

III. Administrative

A. Reviewer's Signature

Review is digitally signed off in DARRTS.

B. Endorsement Block

Chemist Name/Date: See digital sign off at end of document
Chemistry Branch Chief Name/Date: See digital sign off at end of document

C. CC Block

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III. EES Report

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 204768/000	**Sponsor:**	IROKO PHARMS LLC
Org. Code:	170		1 KEW PL 150 ROUSE BLVD
Priority:	3		PHILADELPHIA, PA 19112
Stamp Date:	30-APR-2013	**Brand Name:**	TIFORBEX
PDUFA Date:	28-FEB-2014	**Estab. Name:**	
Action Goal:		**Generic Name:**	INDOMETHACIN
District Goal:	30-DEC-2013	**Product Number; Dosage Form; Ingredient; Strengths**	002; CAPSULE; INDOMETHACIN; 40MG 001; CAPSULE; INDOMETHACIN; 20MG

FDA Contacts:	X. SHEN	Prod Qual Reviewer	3017961411
	L. RIVERA	Product Quality PM	3017964013
	K. COMPTON	Regulatory Project Mgr	3017961191
	J. PINTO	Team Leader	3017961733

Overall Recommendation:	ACCEPTABLE	on 20-SEP-2013	by R. WITTORF	()	2404023113
	PENDING	on 29-MAY-2013	by EES_PROD		
	PENDING	on 29-MAY-2013	by EES_PROD		
	PENDING	on 29-MAY-2013	by EES_PROD		
	PENDING	on 29-MAY-2013	by EES_PROD		

Establishment:	**CFN:**	(b) (4)	**FEI:**	(b) (4)	
				(b) (4)	
DMF No:			**AADA:**		
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER				
	FINISHED DOSAGE MANUFACTURER				
	FINISHED DOSAGE RELEASE TESTER				
Profile:	CAPSULES, PROMPT RELEASE		**OAI Status:**	NONE	
Last Milestone:	OC RECOMMENDATION				
Milestone Date:	20-SEP-2013				
Decision:	ACCEPTABLE				
Reason:	DISTRICT RECOMMENDATION				

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:**	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE RELEASE TESTER		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	29-MAY-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE RELEASE TESTER		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	29-MAY-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE LABELER		
	FINISHED DOSAGE PACKAGER		
Profile:	CAPSULES, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	29-MAY-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

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/s/

XIAOBIN SHEN
01/16/2014
The NDA is recommended for approval from CMC perspective.

PRASAD PERI
01/17/2014
I concur

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204768	**Biopharmaceutics Reviewer:** Elsbeth Chikhale, PhD	
Submission Date:	April 30, 2013		
Division:	Division of Anesthesia, Analgesia and Addiction Products	**Biopharmaceutics Team Leader:** Angelica Dorantes, PhD	
Applicant:	Iroko Pharmaceuticals, LLC	**Acting Supervisor:** Richard Lostritto, PhD	
Trade Name:	(b) (4) (indomethacin) Capsules	**Date Assigned:**	May 1, 2013
Generic Name:	Indomethacin	**Date of Review:**	January 15, 2014
Indication:	Treatment of mild to moderate acute pain in adults	**Type of Submission:** 505(b)(2) Original New Drug Application	
Dosage form/ strengths	Capsules/ 20 mg/capsule and 40 mg/capsule		
Route of Administration	Oral		

SUMMARY

Submission: This 505(b)(2) New Drug Application is proposing (b) (4) (indomethacin) Capsules (20 mg and 40 mg strengths) for the treatment of mild to moderate acute pain in adults. Indomethacin is a nonsteroidal anti-inflammatory drug (NSAID) with antipyretic, anti-inflammatory, and analgesic properties. Indomethacin was first approved in 1965 as Indocin® 25 mg and 50 mg capsules (NDA 016059 – Iceutica Operations). Iceutica has since then discontinued manufacturing and distribution for reasons not related to safety or efficacy. This NDA relies on literature and Indomethacin 50 mg capsules manufactured by Mylan (ANDA 70624) as the listed drug.

Review: The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of:
1) the proposed dissolution methodology
2) the dissolution acceptance criterion

RECOMMENDATION:

ONDQA-Biopharmaceutics has evaluated the information provided in NDA 204768 and concludes the following:

The dissolution method and acceptance criterion as summarized below are acceptable.

Dissolution method:

USP Apparatus I (basket)
Temperature: 37 °C
Rotation speed: 100 rpm
Medium: 750 mL of 10 mM citric acid buffer, pH 5.75

Dissolution acceptance criterion:

Q= (b) (4) at 15 minutes

The provided dissolution data support the proposed drug product expiry date of 24 months when stored at 25 °C/60% RH.

From the Biopharmaceutics perspective, NDA 204768 for (b) (4) (indomethacin) Capsules (20 mg and 40 mg strengths) is recommended for **APPROVAL**.

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

BIOPHARMACEUTICS EVALUATION – REVIEWER NOTES

SUBMISSION:

This 505(b)(2) New Drug Application is proposing (b) (4) (indomethacin) Capsules (20 mg and 40 mg strengths) for the treatment of mild to moderate acute pain in adults. Indomethacin is a nonsteroidal anti-inflammatory drug (NSAID) with antipyretic, anti-inflammatory, and analgesic properties. Indomethacin was first approved in 1965 as Indocin® 25 mg and 50 mg capsules (NDA 016059 – Iceutica Operations). Iceutica has since then discontinued manufacturing and distribution for reasons not related to safety or efficacy. Therefore, the Indomethacin 50 mg Capsules manufactured by Mylan and approved under ANDA 70624 were used as the reference product for the studies conducted under this NDA.

Although the proposed (b) (4) capsules contain 20% less active ingredient than the previously approved indomethacin products, effective analgesia and pain relief is expected with the potential for fewer drug-related adverse effects, because of the enhanced absorption rate of indomethacin from the proposed (b) (4) capsules. A special manufacturing technique is utilized to significantly reduce the particle size of the drug substance in the proposed drug product, which in turn, leads to enhanced dissolution (b) (4)

The clinical development program supporting the approval of this 505(b)(2) NDA submission for (b) (4) capsules consists of 5 clinical trials. The trials included a Phase 1 relative bioavailability trial and a Phase 2 efficacy trial that was conducted with the Proof of Concept (POC) formulation of (b) (4) capsules. Changes to the formulation and manufacturing process were made during the development of the commercial formulation of (b) (4) capsules. A second Phase 1 bioavailability trial and two Phase 3 efficacy trials were conducted with the commercial formulation. These studies are being evaluated by the Clinical and Clinical Pharmacology teams.

BIOPHARMACEUTICS INFORMATION:

The Biopharmaceutics review for this NDA is being focused on the evaluation and acceptability of;
1) the proposed dissolution methodology
2) the dissolution acceptance criterion

The composition of the content per capsule with the commercial formulations for the 20 mg and 40 mg strength capsules is shown in the table below:

Formulation of the Proposed [redacted] (indomethacin) Capsules

Component	Amount per Capsule (mg/capsule weight)	Amount per Capsule (mg/capsule weight)	Function
Indomethacin, USP	20.00	40.00	Active pharmaceutical ingredient
Lactose monohydrate	[redacted]		
Microcrystalline cellulose			
Croscarmellose sodium			
Sodium lauryl sulfate			
Sodium stearyl fumarate			
Total capsule fill weight			

DISSOLUTION METHOD:

The proposed dissolution method is as follows:

USP Apparatus I (basket)
Temperature: 37 °C
Rotation speed: 100 rpm
Medium: 750 mL [redacted] of [redacted] buffer [redacted]

The dissolution method development report (provided in section 3.2.P.2) describes the selection of the dissolution test conditions as follows:

Selection of dissolution medium:

The initial dissolution method evaluation focused on developing a dissolution method capable of discriminating the critical quality attribute of the drug product [redacted]

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(b) (4)

Reviewer's Initial Assessment of the proposed dissolution method:

The proposed dissolution method shows (b) (4)

The following information request (IR) was send to the Applicant on 10/3/13:

- Your proposed dissolution method is not (b) (4) appropriate. We

recommend that you change this metho (b) (4)

- Explain the discrepancy (b) (4) as depicted in Figure 5-1 of the dissolution method report.
- Using the recommended pH (b) (4) method, provide full dissolution profiles (5, 10, 15, 20, 30, 45, 60, and 75 minute time points; individual, mean, SD, profiles, tables and figures) for the phase 3 clinical and registration batches. Start collecting stability data using the revised dissolution method as soon as possible (next stability time point).

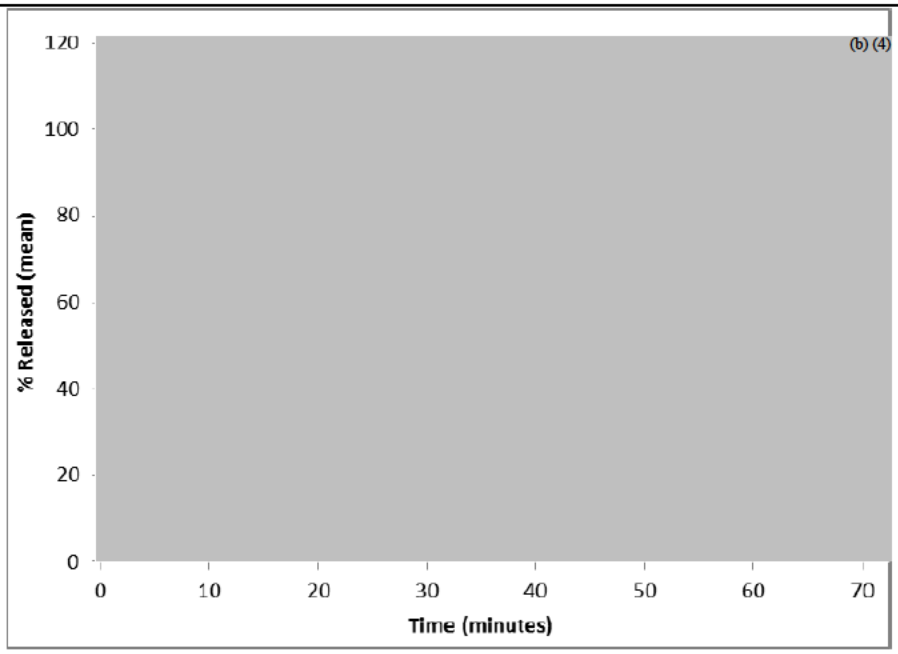
Responses dated 10/29/13 to IR dated 10/3/13:

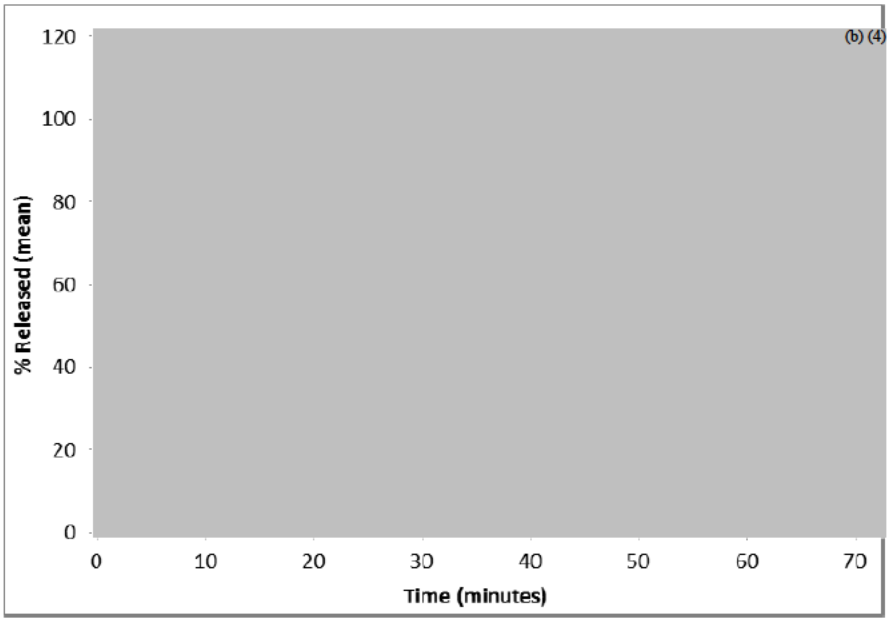
(b) (4)

- The Applicant did not revise the dissolution method, and therefore, has not analyzed stability samples with a revised dissolution method.

Based on the Applicant's response, a telephone conference was held on 12/4/13 between FDA and the Applicant to discuss the most appropriate dissolution method. (b) (4) It was agreed that the Applicant would provide dissolution profile data using the revised pH 5.75 dissolution method for the clinical and registration batches currently stored at room temperature.

Additional information dated 12/19/13 provided as follow up on t-con dated 12/4/13:
The complete dissolution data from the Phase 3 Clinical and Primary Stability Batches for the 20 mg and 40 mg drug product stored for approximately 21 months at 25°C/60% are provided. Dissolution testing (n=12 capsules per batch) was conducted in 750 mL of 10 mM citric acid buffer, pH 5.75 at 37.0°C ±0.5°C using USP Apparatus 1 (baskets) with a rotation speed of 100 RPM:





(b) (4)

On 1/13/14, as follow up to the teleconference dated 12/4/13, the Applicant provided additional validation information for the pH 5.75 dissolution method with regards to specificity, linearity, accuracy, repeatability, precision, sample stability, and robustness.

Reviewer's Assessment of the revised dissolution method and validation data: ACCEPTABLE

[redacted] (b) (4)

The revised pH 5.75 dissolution method is acceptable.

DISSOLUTION ACCEPTANCE CRITERION:

In order to set the dissolution acceptance criterion, the Applicant was asked during the teleconference held on 12/4/13, to submit dissolution profile data (*individual, mean, SD, profiles, tables and figures*) using the revised pH 5.75 dissolution method for the phase 3 clinical and registration batches. These dissolution data are shown in the above two figures received on 12/19/13. Based on these data the Applicant has proposed to keep the originally proposed dissolution acceptance criterion of Q= (b) (4) at 15 minutes.

Reviewer's Assessment of the proposed dissolution acceptance criterion: ACCEPTABLE

The provided dissolution data using the revised pH 5.75 dissolution method adequately support the proposed criterion of Q= (b) (4) at 15 minutes.

DISSOLUTION STABILITY DATA:

The drug product shows (b) (4) dissolution upon storage at intermediate and accelerated conditions. The provided long term dissolution stability data indicate that the drug product meets the Q= (b) (4) at 15 minutes acceptance criterion up to 18 months when stored at 25 °C/60% RH. Based on the decision tree in the ICH Q1E guidance, the provided dissolution data support the proposed drug product expiry date of 24 months when stored at 25 °C/60% RH.

RECOMMENDATION:

The dissolution method and acceptance criterion as summarized below are acceptable.

Dissolution method:
- USP Apparatus I (basket)
- Temperature: 37 °C
- Rotation speed: 100 rpm
- Medium: 750 mL of 10 mM citric acid buffer, pH 5.75

Dissolution acceptance criterion:
- Q= (b) (4) at 15 minutes

The provided dissolution data support the proposed drug product expiry date of 24 months when stored at 25 °C/60% RH.

From the Biopharmaceutics perspective, NDA204768 (b) (4) (indomethacin) Capsules (20 and 40 mg/capsule) is recommended for **APPROVAL**.

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/s/

ELSBETH G CHIKHALE
01/15/2014

ANGELICA DORANTES
01/15/2014

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	204-768
Submission Date	4/30/13
Product name, generic name of the active	(b) (4) (indomethacin) Capsules
Dosage form and strength	Capsules - 20 mg/capsule and 40 mg/capsule
Route of Administration	Oral
Applicant	Iroko Pharmaceuticals, LLC
Clinical Division	Division of Anesthesia, Analgesia, & Addiction Products
Type of Submission	Original NDA – 505(b)(2)
Biopharmaceutics Reviewer	Elsbeth Chikhale, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full Biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS
A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING

	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?	x		
2.	Is the dissolution test part of the DP specifications?	x		Proposed method: Apparatus 1 (basket), 750 mL of (b) (4) buffer: (b) (4) and 100 rpm Proposed acceptance criteria: Q= (b) (4) at 15 minutes
3.	Does the application contain data to support the proposed dissolution acceptance criteria?		x	Complete dissolution profile data on the clinical and registration batches are lacking. These data will be requested in the 74-day letter.
4.	Does the application contain the dissolution method development report?	x		Section 3.2.P.2
5.	Does the application contain data on the discriminating ability of the dissolution method?	x		Section 3.2.P.2
6.	Is there a validation package for the analytical method and dissolution methodology?	x		Section 3.2.P.5.3
7.	Does the application include a biowaiver request?		x	
8.	Does the application include an IVIVC model?		x	

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

9.	Is information such as BCS classification mentioned, and supportive data provided?		x	
10.	Is information on mixing the product with foods or liquids included?		x	
11.	Is there any in *vivo* BA or BE information in the submission?	x		Relative bioavailability studies for the proposed 20 and 40 mg capsules versus the reference product 50 mg capsules were conducted. These studies will be reviewed by OCP.
12.	Does the application include in *vitro* alcohol interaction studies?		x	Not applicable
B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
13.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
14.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable
15.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable
16.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		See information request below.

SUBMISSION:

This 505(b)(2) New Drug Application is proposing [redacted] (b) (4) (indomethacin) Capsules (20 mg and 40 mg strengths) for the treatment of mild to moderate acute pain in adults. Indomethacin is a nonsteroidal anti-inflammatory drug (NSAID) with antipyretic, anti-inflammatory, and analgesic properties. Indomethacin was first approved in 1965 as Indocin® 25 mg and 50 mg capsules (NDA 016059 – Iceutica Operations). Iceutica has since then discontinued manufacturing and distribution for reasons not related to safety or efficacy. This NDA relies on literature and Indomethacin 50 mg capsules manufactured by Mylan (ANDA 70624) as the reference product.

Although (b) (4) capsules contain 20% less active ingredient than the previously approved indomethacin products, effective analgesia and pain relief is expected with the potential for fewer drug-related adverse effects because of the enhanced absorption rate of indomethacin from (b) (4) capsules. A special manufacturing technique is utilized to significantly reduce the particle size of the drug substance in the proposed drug product, which in turn, leads to enhanced dissolution (b) (4) The clinical development program supporting the 505(b)(2) NDA submission for (b) (4) capsules consisted of 5 clinical trials. The trials included a Phase 1 relative bioavailability trial and a Phase 2 efficacy trial that was conducted with the Proof of Concept (POC) formulation of (b) (4) capsules. Changes to the formulation and manufacturing process were made during the development of the commercial formulation of (b) (4) capsules. A second Phase 1 bioavailability trial and 2 Phase 3 efficacy trials were conducted with the commercial formulation. The compositions of the POC and commercial formulations are shown in the table below:

Components	(b) (4) Capsules 40 mg				(b) (4) Capsules 20 mg			
	POC Formulation		Commercial Formulation		POC Formulation		Commercial Formulation	
	mg/capsule	% w/w	mg/capsule	% w/w	mg/capsule	% w/w	mg/capsule	% w/w
Indomethacin, USP	40.0	(b) (4)	40.0	(b) (4)	20.0	(b) (4)	20.0	(b) (4)
Lactose monohydrate, NF (b) (4)								(b) (4)
Sodium lauryl sulfate, NF (b) (4)								
Microcrystalline cellulose, NF								
Croscarmellose sodium, NF								
Sodium stearyl fumarate, NF								
Total								

Abbreviations: N/A = not applicable; NF = National Formulary; POC = Proof of Concept; USP = United States Pharmacopeia
[a] Used in the POC Formulation (b) (4)

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of
1) the proposed dissolution methodology, and
2) the proposed dissolution acceptance criterion

In order to set the dissolution acceptance criterion, the Applicant will be asked to provide the dissolution profile data using the proposed dissolution method for the clinical batches with the commercial formulation and registration batches.

INFORMATION REQUEST:

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

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

RECOMMENDATION:
ONDQA-Biopharmaceutics has reviewed NDA 204768 for filing purposes and we found this NDA filable from a Biopharmaceutics perspective. The Applicant has submitted a reviewable submission.

{See appended electronic signature page}
Elsbeth Chikhale, Ph.D. 6/21/13
Biopharmaceutics Reviewer Date
Office of New Drug Quality Assessment

{See appended electronic signature page}
Angelica Dorantes, Ph.D. 6/21/13
Biopharmaceutics Team Leader Date
Office of New Drug Quality Assessment

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

/s/

ELSBETH G CHIKHALE
06/21/2013

ANGELICA DORANTES
06/21/2013

Initial Quality Assessment
Office of New Drug Quality Assessment
Division of Pre-Marketing Division III, Branch I

OND Division:	Anesthesia, Analgesia and Addiction
NDA:	204768
Applicant:	Iroko Pharmaceuticals
Stamp date:	April 30, 2013
PDUFA Date:	February 28, 2014
Trademark:	NA
Established Name:	Indomethacin
Proposed Name:	(b) (4)
Dosage Form:	Capsules 20mg and 40mg
Route of Administration:	Oral
Indication:	Treatment of mild to moderate acute pain

Pharmaceutical Assessment Lead: Julia C. Pinto, Ph.D.

	YES	NO
ONDQA Fileability:	√	
Comments for 74-Day Letter:	√	

Summary, Critical Issues and Comments

A. Summary

The application is filed as a 505(b)(2), non-priority NDA with 10-month review clock. The API is indomethacin, an NSAID for the relief of mild to moderate acute pain. The Sponsor is using proprietary technology (SoluMatrix™) for the reduction in particle size, to enhance rates of dissolution (b) (4)

The original submission of April 30, 2013, did not include any information in the drug substance module 3.1.S, other than the manufacturing facilities, since the drug substance is referenced to DMF (b) (4) An

IR was emailed to the Sponsor and in their response of June 4, 2013, an updated submission included a completed drug substance module 3.1.S.

The Sponsor does not state whether the API is tested upon receipt from the (b) (4) (manufacturer). Therefore one comment is sent to the Sponsor in the 74-day letter. No critical issues are identified in this initial assessment. All manufacturing facilities are entered into EES and submitted to Compliance for inspection. Consults to the Microbiology and Biopharmaceutics Teams have been sent. This NDA is therefore considered fillable from the CMC perspective.

Comment 1:
Clarify whether there is quality control testing of the drug substance upon receipt from (b) (4) and prior to use in the manufacture of the drug product. Provide in-house acceptance criteria for quality control testing and validated analytical methods used for the testing of the drug substance prior to use in the manufacture of the drug product.

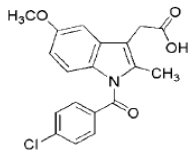
B. Review: Drug Substance

Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight

Nomenclature

Chemical name(s):	1-(*p*-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid
Other chemical name(s):	1H-Indole-3-acetic acid, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-
Compendial Name(s):	Indomethacin, United States Pharmacopeia (USP)
Other name(s):	Indometacin (INN) Indomethacin (USAN)
Chemical Abstracts Service (CAS) registry number:	53-86-1

Structure



Molecular Formula: $C_{19}H_{16}ClNO_4$

Molecular Weight: 357.8

Characterization, Manufacture, Control, and Impurities

The drug substance, indomethacin, is supplied (b) (4)
Characterization of Indomethacin, description of the manufacturing processes, controls and process impurities are referenced to the Drug Master File (DMF) (b) (4) last reviewed as adequate August 20, 2012 by Xueli Zhu (Review #18) . Letter of Authorization (LoA) is included in the NDA.

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Drug Substance Specifications

API specifications are shown below. The API is controlled in accordance with the USP monograph for Indomethacin.

Test	Method	Acceptance Criteria
Appearance	(b) (4)	A white to yellow crystalline powder
Identification by IR	USP <197>	(b) (4)
Identification by UV	USP <197>	
X-ray powder diffraction	USP <941>	
Assay by HPLC (%w/w)	(b) (4	
Individual known impurities by HPLC:	(b) (4)	
Single unspecified impurity		
Total impurities by HPLC		
Loss on drying	USP <731>	
Residue on ignition (%w/w)	USP<281>	
Heavy metals	USP <231> Method II	
Residual solvents:	(b) (4	

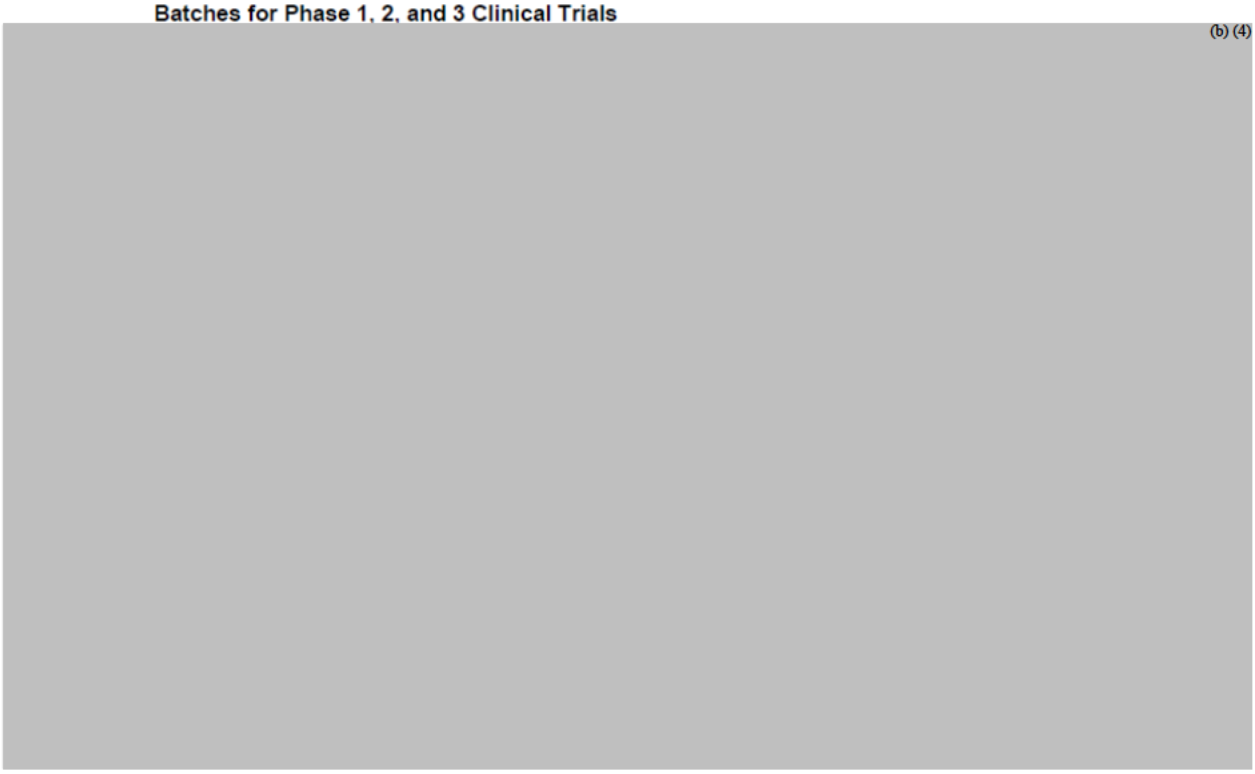
Abbreviations: %w/w = % weight/weight; HPLC = High Performance Liquid Chromatography; IR = Infrared Spectroscopy; NMT = Not More Than; ppm = parts per million; UV = Ultraviolet Spectroscopy; (b) (4)

(b) (4)

Batch analysis:

Batch analysis Data is provided for four batches used in Phase 1, 2 and 3 clinical studies and primary stability studies. Comparative data is shown below. COA's are also provided.

Table 3.2.S.4.4.2-1 Batch Analysis Results for Indomethacin Lots Used to Manufacture Clinical Supply Batches for Phase 1, 2, and 3 Clinical Trials



Analytical Methods and Validations:
Referenced to DMF (b) (4)

Reference standard:
No Certificates of Analysis for the working reference standards have been included; these were referenced to the DMF.

Container Closure System:
Referenced to DMF (b) (4)

Drug substance Stability:
The Twelve month time point of stability data one batches of API used to make two drug product batches is provided. Further supporting stability data is referenced to DMF (b) (4) A retest period (b) (4) is proposed.

Drug product

(b) (4) Capsules are provided in 2 strengths, 20 mg and 40 mg. Both strengths (b) (4) encapsulated in hard gelatin capsule shells. The drug product formulations

are shown below. No novel excipients are used. A BSE/TSE statement for the (b) (4) capsules is provided.

Table 3.2.P.1.2-1 Composition of (b) (4) Capsules 20 mg

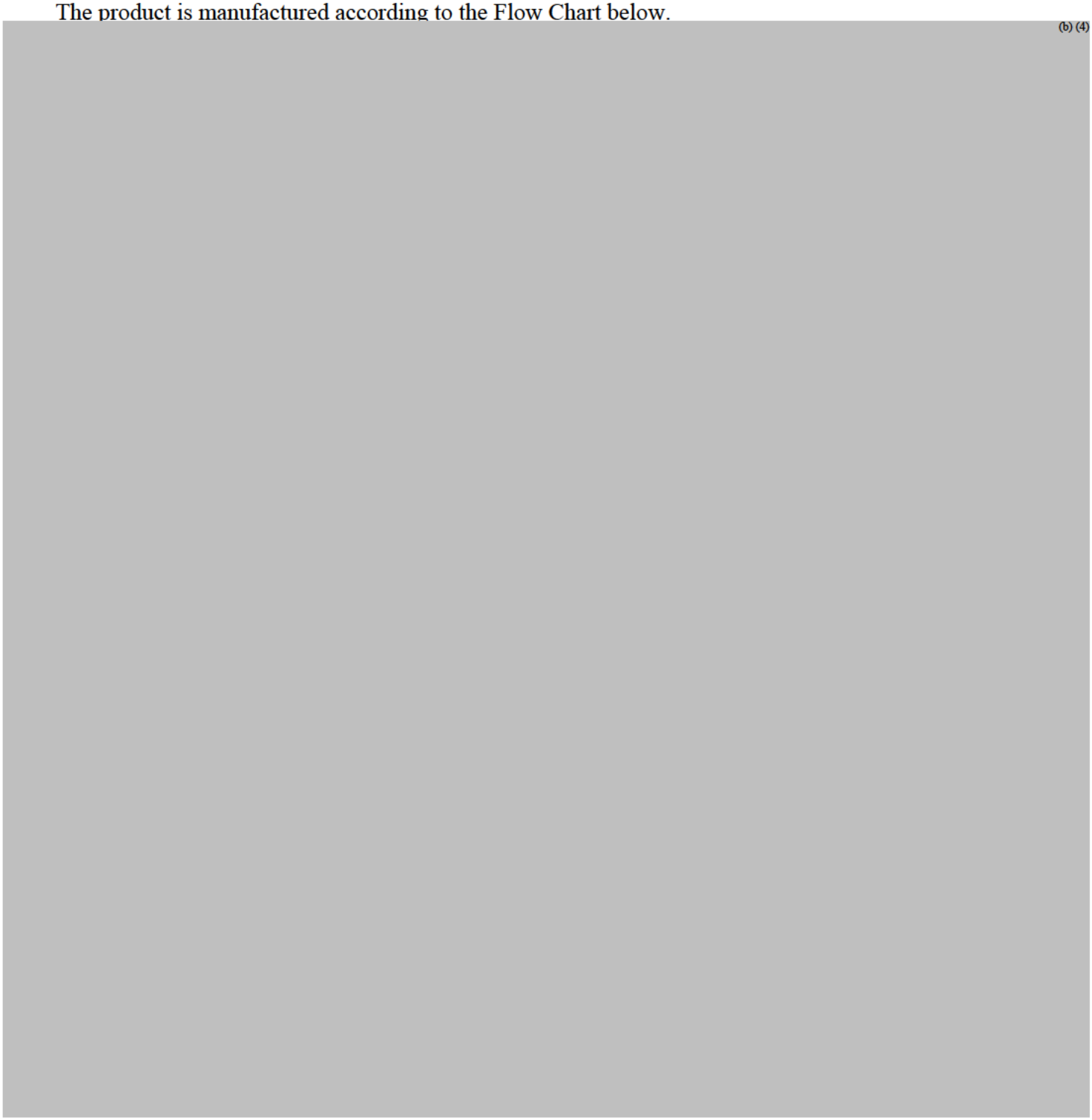
Component	Amount per capsule (mg/capsule weight)	Function	Quality Standard
Indomethacin, USP	20.00	Active pharmaceutical ingredient	(b) (4)
Lactose monohydrate	(b) (4)		
Microcrystalline cellulose			
Croscarmellose sodium			
Sodium lauryl sulfate			
Sodium stearyl fumarate			
Total capsule fill weight			
(b) (4) capsule consisting of a dark blue body with "IP-201" imprinted in white ink, and a light blue cap with "20 mg" imprinted in white ink	1 capsule	Capsule shell	

Table 3.2.P.1.2-2 Composition of (b) (4) Capsules 40 mg

Component	Amount per capsule (mg/capsule weight)	Function	Quality Standard
Indomethacin, USP	40.00	Active pharmaceutical ingredient	(b) (4)
Lactose monohydrate	(b) (4)		
Microcrystalline cellulose			
Croscarmellose sodium			
Sodium lauryl sulfate			
Sodium stearyl fumarate			
Total capsule fill weight			
(b) (4) capsule consisting of a dark blue body with "IP-202" imprinted in white ink, and a blue cap with "40 mg" imprinted in white ink	1 capsule	Capsule shell	

Drug Product Manufacture:

The product is manufactured according to the Flow Chart below.



Drug Product Specifications:

Table 3.2.P.5.1-1 Release Specifications for (b) (4) Capsules 20 mg

Test	Method	Acceptance Criteria
Appearance	Visual	(b) (4) capsule with a dark blue body with "IP-201" imprinted in white ink and light blue cap with "20 mg" imprinted in white ink containing a white powder
Identification	HPLC retention time	(b) (4)
Assay (% label claim)	HPLC assay and related substances	
Indomethacin related substances		
Individual unknown impurities		
Total impurities		
Content uniformity	HPLC	
(b) (4)		
Trace metals	ICP/MS USP <232>	
Heavy metals	USP <231>, Method II	
Dissolution	Dissolution	Q= (b) (4) at 15 minutes

(b) (4)

Abbreviations: ICP/MS = Inductively Coupled Plasma Mass Spectrometry; NMT = not more than

(b) (4)

Table 3.2.P.5.1-2 Release Specifications for (b) (4) Capsules 40 mg

Test	Method	Acceptance Criteria
Appearance	Visual	(b) (4) capsule with a dark blue body with "IP-202" imprinted in white ink and a blue cap with "40 mg" imprinted in white ink containing white powder
Identification	HPLC retention time	(b) (4)
Assay (% label claim)	HPLC assay and related substances	
Indomethacin related substances		
Individual unknown impurities		
Total impurities		
Content uniformity	HPLC	
(b) (4)		
Trace metals	ICP/MS USP <232>	
Heavy metals	USP <231>, Method II	
Dissolution	Dissolution	Q= (b) (4) at 15 minutes

(b) (4)

Abbreviations: ICP/MS = Inductively Coupled Plasma Mass Spectrometry; NMT = not more than

(b) (4)

Batch Analysis

Batch analysis data on 3 batches of each strength of primary stability drug product batches (b) (4) in addition to 3 batches of each strength of demonstration drug product batches are provided in this submission.

Container Closure:

(b) (4) Capsules 20 mg and 40 mg will be provided in 100 cc round HDPE bottles (b) (4) Both strengths will be provided in 90-count bottles and 30-count bottles. (b) (4)

[redacted] (b) (4)

Stability:

Following Stability data is provided in this submission. In addition, regression analysis is provided to support an additional 12 month time point, for a proposed expiry of 24 months. Data from a stress testing and a photostability study is also provided.

Table 3.2.P.8.1.1.1-1 Primary Stability Study Summary - [redacted] (b) (4) Capsules 20 mg and 40 mg

Study Type	Container	Number of Batches	Storage Conditions Evaluated	Time Completed
Primary stability[a]	[redacted] (b) (4)	3 for 20 mg 3 for 40 mg	25°C/60% RH (long term) 30°C/65%RH (intermediate) 40°C/75% RH (accelerated)	12 months 12 months 6 months
Primary stability[a]		3 for 20 mg 3 for 40 mg	25°C/60% RH (long term) 30°C/65%RH (intermediate) 40°C/75% RH (accelerated)	12 months 12 months 6 months
Primary stability[a]		3 for 20 mg 3 for 40 mg	25°C/60% RH (long term) 30°C/65%RH (intermediate) 40°C/75% RH (accelerated)	12 months 12 months 6 months

[a] Used in Phase 3 (IND3-08-04b and IND3-10-06) and Phase 1 (IND1-12-07) trials

D. **Comments for 74-day Letter**:

None

E. **Recommendation for fileability**: The NDA is considered fileable based on data provided in the April 30 and June 4, 2013 submission, for the drug product packaged in HDPE bottles [redacted] (b) (4) with 12-month long term/6-month accelerated stability data. The NDA is suitable for evaluation and assessment based on FDA and ICH guidelines for submitting CMC information for New Drug Applications.

Recommendation for Team Review: The NDA is not recommended for a team review.

Consults:
1. Microbiology Team
2. Biopharmaceutics, ONDQA

NDA Number: 204768 **Supplement Number and Type:** **Established/Proper Name:** (b) (4) **Indomethacin**

Applicant: Iroko Pharma. **Letter Date: 04/30/2013** **Stamp Date: 04/30/2013**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		IND 101940

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			NA

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		[redacted] (b) (4) DMF [redacted] (b) (4)
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?		X	

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		Referenced to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Referenced to DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Referenced to DMF (b) (4)
15.	Does the section contain controls for the DS?	X		Specifications included in the NDA
16.	Has stability data and analysis been provided for the drug substance?	X		Referenced to DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		Pharmaceutical Development of the drug product is referenced to DMF 26340.
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	X		Based on pre-NDA agreements and sufficient data
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		X	

Julia C. Pinto, Ph.D. — 6/17/2013
CMC Lead, ONDQA — Date

Prasad Peri, Ph.D. — 6/17/2013
Branch II Chief, ONDQA — Date

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

/s/

JULIA C PINTO
06/20/2013

PRASAD PERI
06/21/2013
I concur