

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204592Orig1s000

CHEMISTRY REVIEW(S)

ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Application: NDA 204592/000
App Date: 20-DEC-2012
App No.: 20-OCT-2013

Action Goal:
District Goal: 21-AUG-2013

Applicant: IROKO PHARMS LLC
 1 KEW PL 150 ROUSE BLVD
 PHILADELPHIA, PA 19112

Brand Name: ZORVOLEX (DICLOFENAC ACID)
Estab. Name:
Generic Name:

Priority: 3
Code: 170

Product Number; Dosage Form; Ingredient; Strengths
 001; CAPSULE; DICLOFENAC; 18MG
 002; CAPSULE; DICLOFENAC; 35MG

Application Comment:

Contacts:	Y. WANG	Prod Qual Reviewer		3017961479
	S. DONALD	Micro Reviewer	(HFD-805)	3017960586
	L. RIVERA	Product Quality PM		3017964013
	S. PATWARDHAN	Regulatory Project Mgr	(HF-01)	3017964085
	J. PINTO	Team Leader		3017961733

Overall Recommendation:	ACCEPTABLE	on	(b) (4)	by C. CAPACCI-DANIEL	()	3017963532
	PENDING	on	31-JAN-2013	by EES_PROD		

**ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
F No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
 FINISHED DOSAGE MANUFACTURER

Establishment Comment: TEST RAW MATERIALS, MANUFACTURE DRUG PRODUCT, TEST (b) (4) MATERIALS, RELEASE TESTING OF (b) (4) DRUG PRODUCT, STORE AND PERFORM. STABILITY TESTING. (on (b) (4) by L. RIVERA () 3017964013)
File: CAPSULES, PROMPT RELEASE OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
3MITTED TO OC	31-JAN-2013				RIVERAL
3MITTED TO DO CHG INITIAL	31-JAN-2013	10-Day Letter			SHARPT
RECOMMENDATION AN ABBREVIATED CGMP/PAI FOR THE SAME PROFILE CLASS (CHG) WAS CONDUCTED (b) (4) NO FDA 483 WAS ISSUED. BASED ON FILE REVIEW, KAN-DO RECOMMENDS APPROVABLE.	(b) (4)			ACCEPTABLE	SBERRYMA
				(b) (4) BASED ON FILE REVIEW	
RECOMMENDATION	(b) (4)			ACCEPTABLE	SHARPT
				DISTRICT RECOMMENDATION	

ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

F No: **AADA:**

Capabilities: FINISHED DOSAGE PACKAGER

Establishment Name: PACKAGING AND LABELING OF DRUG PRODUCT, CONTROL OF PACKAGING CONTAINER CLOSURE COMPONENT (on (b) (4) by L. RIVERA () 3017964013)
File: CAPSULES, PROMPT RELEASE **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
MITTED TO OC	31-JAN-2013				RIVERAL
RECOMMENDATION	(b) (4)			ACCEPTABLE BASED ON PROFILE	SHARPT

ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)
F No: **ADA:**
Capabilities: DRUG SUBSTANCE RELEASE TESTER
Establishment Name: DRUG SUBSTANCE LABORATORY TESTING (on (b) (4) by L. RIVERA () 3017964013)
File: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
MITTED TO OC	31-JAN-2013				RIVERAL
RECOMMENDATION	(b) (4)			ACCEPTABLE BASED ON PROFILE	SHARPT

ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Establishment: **CFN:** **FEI:** (b) (4)
 (b) (4)
 (b) (4)

F No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
 DRUG SUBSTANCE STABILITY TESTER

Establishment Name: DRUG SUBSTANCE MANUFACTURER & STABILITY TESTING (or (b) (4) by L. RIVERA () 3017964013)
File: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
COMMITTED TO OC	31-JAN-2013				RIVERAL
COMMITTED TO DO LAST INSPECTION FOR CSN (b) (4)	31-JAN-2013	GMP Inspection	GREATER THAN 3 YRS		SHARPT
SIGNED INSPECTION TO IB	09-FEB-2013	GMP Inspection			PHILPYE
RECOMMENDATION	(b) (4)			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
RECOMMENDATION	(b) (4)			ACCEPTABLE DISTRICT RECOMMENDATION	CAPACCIDANIC

NDA 204592

Zorvolex (Diclofenac) Capsules

Iroko Pharmaceuticals, LLC

Ying Wang, PhD

Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment III
Branch VIII**

**CMC REVIEW OF NDA 204592
For the Division of Anesthesia, Analgesia and Addition Products**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 204592
2. REVIEW #: 1
3. REVIEW DATE: Sept. 16, 2013
4. REVIEWER: Ying Wang, PhD
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	12/20/2012
Correspondence (C)	
Amendment (BC)	5/1/2013
Amendment (BC)	8/15/2013

7. NAME & ADDRESS OF APPLICANT:

Name: Iroko Pharmaceuticals, LLC
Address: 150 Rouse Blvd., Philadelphia, PA 19112
Representative: Michelle Wilson, 100 Springhouse Dr. Suite 205,
Collegeville, PA 19426
Telephone: 513-829-1108

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Zorvolex Capsules
- b) Non-Proprietary Name: Diclofenac
- c) Code Name/# (ONDQA only):
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 5
 - Submission Priority: Standard

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

10. PHARMACOL. CATEGORY: NSAID

11. DOSAGE FORM: Capsule

CMC Review Data Sheet

12. STRENGTH/POTENCY: 18 mg, 35 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

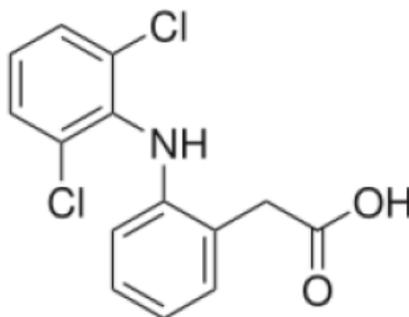
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

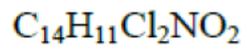
1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name(s)(IUPAC)	2-[2-(2,6-dichlorophenylamino)phenyl]acetic acid
Other chemical name(s)	[o-(2,6-dichloroanilino) phenyl] acetic acid
Other non-proprietary name(s)	Diclofenac acid
USAN:INN ^a	Diclofenac
Chemical Abstracts Service (CAS) registry number	15307-86-5



Molecular Formula

CMC Review Data Sheet



Molecular Weight: 296.15

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)	(b) (4)	1	Adequate	6/23/2010	By Stuart Zimmerman
	III			2			Type III DMF not reviewed per ONDQA policy
	III			2			Type III DMF not reviewed per ONDQA policy
	III			2			Type III DMF not reviewed per ONDQA policy
	III						Type III DMF not reviewed per ONDQA policy
	III						Type III DMF not reviewed per ONDQA policy
	III						Type III DMF not reviewed per ONDQA policy
	III						Type III DMF not reviewed per ONDQA policy
	III						Type III DMF not reviewed per ONDQA policy
	III						Type III DMF not reviewed per ONDQA policy
	II					1	Adequate
26224		Iroko Pharmaceutical	Pharmaceutical Development	1	Adequate	9/16/2013	By Ying Wang

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

CMC Review Data Sheet

- 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: N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	6/13/2013	Office of Compliance
Pharm/Tox	Approval	9/16/2013	Alex Xu
Biopharm	Approval	9/16/2013	Banu Zolnik
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA	See review	9/12/2013	Vicky Borders-Hemphill
EA	Categorical exclusion (see NDA review)		
Microbiology	Approval	4/4/2013	Steven P. Donald

Executive Summary Section

The CMC Review for NDA 204592

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval from Chemistry, Manufacturing, and Control (CMC) perspective. 24 months shelf life is proposed and granted when stored at 25°C (77°F) with excursions permitted to 15°C-30°C (59°F-86°F).

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

N/A

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

Drug substance diclofenac (also referred to as diclofenac acid) is white to off-white (b) (4) powder. It is freely soluble in dimethyl formamide and dimethyl sulfoxide and is practically insoluble in water. Drug substance information is referenced in DMF (b) (4) for which (b) (4) is the holder. Specifications as amended are adequate and meet ICH Q3A guideline.

(2) Drug Product

Zorvolex capsules are provided in two strengths, 18 mg and 35 mg. Both strengths contain (b) (4) white to off-white powder encapsulated in hard gelatin capsule shells. The 18 mg capsules have a blue body imprinted with IP-203 and light green cap imprinted with 18 mg in white ink. The 35 mg capsules have a blue body imprinted with IP-204 and green cap imprinted with 35 in white ink.

Pharmaceutical development information is referenced to the DMF 26224 for which the applicant Iroko Pharm is the holder. The Zorvolex™ Capsules commercial manufacturing process involves (b) (4)

Executive Summary Section

(b) (4)

The drug products are packaged in high density polyethylene (HDPE) bottles. The submitted drug product stability data include 12 months at long term storage condition of 25°C/60%RH and 6 month accelerated storage condition of 40°C/75%RH for 3 batches of each strength. The stability data supports the proposed 24 month shelf life for the drug product when stored at the proposed 25°C (77°F), excursions permitted between 15°C and 30°C (between 59°F and 86°F).

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

The drug product is indicated for treatment of mild to moderate acute pain in adults. The recommended dose is 18 mg or 35 mg three times daily. Used the lowest effective dose for the shortest duration consistent with individual patient treatment goals.

C. Basis for Approvability or Not-Approval Recommendation

This is a 505 (b)(2) application with Cataflam (diclofenac potassium) as the reference drug. The drug substance specifications as amended are adequate and meet ICH Q3A guideline. The drug product Zorvolex Capsules are made (b) (4). Both 10 mg and 35 mg capsules (b) (4) dose strength is achieved by fill weight. The drug products are stable and there is no apparent trend during stability. The drug product specifications as amended are adequate and meet ICH Q3B guideline.

An overall "Acceptable" recommendation was issued by the Office of Compliance on June 13, 2013.

Executive Summary Section

III. Administrative**A. Reviewer's Signature:**

(See appended electronic signature page)

Ying Wang, PhD

B. Endorsement Block:

(See appended electronic signature page)

Prasad Peri, PhD, Branch Chief, Branch VIII, ONDQA

C. CC Block: entered electronically in DFS

60 Page(s) 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/

YING WANG
09/16/2013

PRASAD PERI
09/17/2013
I concur

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	NDA 204592
Submission Date	12/20/2012
Product name, generic name of the active	Zorvolex (diclofenac acid)
Dosage form and strength	Capsules, 18 mg and 35 mg
Applicant	Iroko
Clinical Division	Division of Anesthesia, Analgesia and Addiction Products
Type of Submission	505 (b) (2) Standard Review
Biopharmaceutics Reviewer	Banu S. Zolnik, PhD
Biopharmaceutics Secondary Reviewer	Sandra Suarez-Sharp, PhD
Biopharmaceutics Team Leader	Angelica Dorantes, PhD

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		USP I (basket), 100 rpm, 900 mL of 10 mM citric acid buffer (pH 5.5) with 0.05 SLS
2.	Is the dissolution test part of the DP specifications?	X		Q= $\frac{6}{4}$ % at 20 minutes
3.	Does the application contain the dissolution method development report?	X		Report contains data on the solubility of diclofenac in different media pH, surfactant levels in the media, and basket rotational speed. Discriminating ability of the dissolution method was tested with several formulations intentionally manufactured to exhibit different dissolution profiles.
4.	Is there a validation package for the analytical method and dissolution methodology?	X		
5.	Does the application contain in vitro alcohol induced dose dumping studies?		X	Alcohol induced dose dumping studies are not required for immediate release formulations.
6.	Does the application include a biowaiver request?		X	The applicant conducted PK studies with proof of concept formulation and commercial formulations with both strengths of 18 mg and 35 mg.
7.	Is there information provided to support the biowaiver request?			N/A
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 <i>in vivo</i> BA or BE information in the submission?	X		The applicant conducted the following two BE studies: Phase 1 DIC 1-08-01: Single dose five way cross over studies with proof of concept formulations of 18 mg (fast), 35 mg (fast and fed), and Cataflam 50 mg (fast and fed). Phase 1 DIC 1-12-07: Single dose five way cross over studies with commercial formulations of 18 mg (fast), 35 mg (fast and fed), and Cataflam 50 mg (fast and fed). These studies will be reviewed by OCP.
12.	Are there any manufacturing changes implemented to the clinical trial and bio batch formulations?	X		Components of the Proof of Concept formulation and Commercial Formulation are different from each other. However, the dissolution specifications were set based on the commercial formulation.
13.	Is there any data submitted to support the manufacturing changes implemented to the clinical trial and biobatch formulations?			Bioavailability studies were conducted on both formulations. See Comment 11 above. Additionally, comparative dissolution data submitted from POC formulation and Commercial formulation for 35 mg strength.
14.	Is there any data submitted to support the proposed dissolution specification?			Dissolution acceptance criterion was set based on the batches used in the clinical study, and biobatches. Refer to Dissolution Summary Tables below for more information on the batches used in the clinical studies as well as in the dissolution studies.

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
15.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		
16.	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.			N/A

**PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW**

17.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			N/A
18.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	

BIOPHARMACEUTICS INITIAL ASSESSMENT

SUMMARY

The applicant Irako Pharmaceuticals submitted a 505(b)(2) NDA application to obtain approval of Zorvolex Capsules 18 mg and 35 mg for the treatment of acute pain of mild to moderate ^{(b) (4)} in adults. Zorvolex capsules are the reformulation of diclofenac with reduced particle size. The reference listed drug for this 505 (b) (2) application is Cataflam® 50 mg (diclofenac potassium immediate release tablets, NDA 20142).

(b) (4)

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

Proposed Dissolution method for Zorvolex capsules				
USP Apparatus	Rotation Speed	Medium Volume	Temp	Medium
USP Type I (basket)	100 rpm	900 mL	37°C ±0.5°C	10 mM citric acid buffer (pH 5 ^{(b) (4)}) with 0.05 %SLS

Proposed Acceptance Criterion for Zorvolex Capsules (% of the labeled amount dissolved)
Q= ^{(b) (4)} % at 20 minute

The tables below show the composition differences in the formulations between the Proof of Concept Formulation and Commercial Formulation for 18 mg and 35 mg strengths.

Table 2.3.P.2-1 Overview of the Components of Zorvolex Capsules 18 mg Used in Clinical Studies

Study Phase	Initial Phase 1 ^b and Phase 2 ^c		Phase 1 ^d		Phase 3 ^e	
	% w/w	mg	% w/w	mg	% w/w	mg
Component	(b) (4)	18.0	(b) (4)	18.0	(b) (4)	18.0
Diclofenac	(b) (4)		(b) (4)		(b) (4)	
Lactose monohydrate, NF	(b) (4)		(b) (4)		(b) (4)	
Microcrystalline cellulose, NF	(b) (4)		(b) (4)		(b) (4)	
Croscarmellose sodium, NF	(b) (4)		(b) (4)		(b) (4)	
Sodium lauryl sulfate, NF	(b) (4)		(b) (4)		(b) (4)	
Sodium stearyl fumarate, NF	(b) (4)		(b) (4)		(b) (4)	
Purified water, USP ^a	(b) (4)		(b) (4)		(b) (4)	
Total (mg/capsule)	(b) (4)		(b) (4)		(b) (4)	

Abbreviations: NF=National Formulary; USP = United States Pharmacopeia; %w/w = %weight/weight

^a Used in POC Formulation for Initial Phase 1 and Phase 2 in (b) (4)

(b) (4)

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

**Table 2.3.P.2-2 Overview of the Components of Zorvolex Capsules 35 mg
Used in Clinical Studies**

Study Phase	Initial Phase 1 ^b and Phase 2 ^c		Phase 1 ^d		Phase 3 ^e	
	% w/w	mg	% w/w	mg	% w/w	mg
Diclofenac	(b) (4)	35.0	(b) (4)	35.0	(b) (4)	35.0
Lactose monohydrate, NF	(b) (4)					
Microcrystalline cellulose, NF						
Croscarmellose sodium, NF						
Sodium lauryl sulfate, NF						
Sodium stearyl fumarate, NF						
Purified water, USP ^a						
Total (mg/capsule)						

Abbreviations: NF=National Formulary, USP = United States Pharmacopeia; %w/w = %weight/weight

^a Used in POC Formulation for Initial Phase 1 and Phase 2

(b) (4)

(b) (4)

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

RECOMMENDATION:

From the ONDQA-Biopharmaceutics perspective, NDA 204592 for Zorvolex Capsules (diclofenac) is fileable.

{See appended electronic signature page}

Banu S. Zolnik, PhD
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

02/22/13
Date

{See appended electronic signature page}

Sandra Suarez Sharp, Ph.D.
Secondary Signature
Office of New Drug Quality Assessment

02/22/13
Date

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

/s/

BANU S ZOLNIK
02/27/2013

SANDRA SUAREZ
02/27/2013

Initial Quality Assessment
Division of Pre-Marketing Assessment III, Branch VII
Office of New Drug Quality Assessment
Division of Anesthesia, Analgesia and Addiction Products

OND Division: Anesthesia, Analgesia and Addiction
NDA: 204592
Chemical Classification 3S
Applicant: Iroko Pharmaceuticals, LLC
Stamp date: December 20, 2012
PDUFA Date: October 20, 2013
Trademark: NA
Established Name: Zorvolex™ Capsules
Dosage Form: 18mg and 35 mg Capsules
Route of Administration: Oral
Indication: Management of mild to moderate acute pain

Initial Quality Assessment: Julia Pinto, Ph.D.

	YES	NO
ONDQA Fileability:	<u>√</u>	<u> </u>
Comments for 74-Day Letter:	<u> </u>	<u>√</u>

Summary, Critical Issues and Comments

A. Summary

The application is filed as a 505(b)(2), non-priority NDA with 10-month review clock for Zorvolex™ Capsules 18 mg and 35 mg for the treatment of mild to moderate acute pain. Zorvolex Capsules are a reformulation of diclofenac designed to reduce the particle size (diclofenac (b)(4)). The drug substance is diclofenac acid is supplied by (b)(4) under DMF (b)(4). The description of the drug substance, the manufacturing process, controls, analytical methods, and specifications of the API are referenced to this DMF (b)(4). An LOA is provided.

The drug product, Zorvolex™ capsules, is prepared in 18mg and 35 mg strengths. Both strengths are from (b)(4) white powder encapsulated in hard gelatin capsule shells. The excipients used in the composition are all compendial (NF). The container closure system comprises of two commercial presentations of 30-count and 90-count HDPE bottles and (b)(4) blister packages as physician samples. Twelve months of real time data for 6 primary batches is provided as support for a 24- month expiry.

B. Drug Substance

Molecular Structure, Chemical Name, Molecular Formula and Molecular Weight

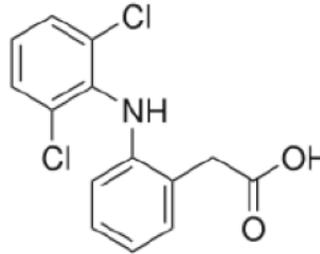
Chemical names:

2-(2-(2,6-dichlorophenylamino)phenyl)acetic acid

Molecular Formula: C₁₄H₁₁Cl₂NO₂

CAS: 15307-86-5

MW: 296.15



Drug Substance commercial batches of API will be manufactured and stability tested by (b)(4). The release testing of the batches to be used in the preparation of the drug product will be done by (b)(4). The manufacture, quality control and stability are referenced to DMF (b)(4) and an LOA is provided.

Potential Impurities and degradation products:

Several process impurities are identified and referenced to DMF (b)(4). Only related substance A is present at about (b)(4)% while the other impurities are detected at below the limit of quantitation of (b)(4)%.

Drug Substance Specifications:

Drug substance specifications are shown below.

Table 2.3.S.4-1 Diclofenac Acid Drug Substance Sponsor Specifications

Test	Method	Acceptance Criteria
Appearance	Visual (method QM0028)	A white to slight yellowish (b) (4) powder
Identification by HPLC	HPLC retention time (method QM4261)	The HPLC retention time of the main peak is within 0.5 minutes of the main peak for the reference standard injections
Identification by FTIR	USP <197>	The sample spectrum and the reference standard spectrum are consistent in all essential detail
Assay by HPLC (%w/w)	QM4261	(b) (4)
Individual known impurities	QM4261	NMT (b) (4)%
Unknown impurities	QM4261	NMT %
Total impurities	QM4261	NMT %
Loss on drying	USP <731>	NMT %
Residue on ignition (%w/w)	USP <281>	NMT %
(b) (4)		
Heavy metals	USP <231> Method II	NMT (b) (4)

Abbreviations: NMT=Not More Than; %w/w = %weight/weight

(b) (4)

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Container Closure:

Zorvolex Capsules 18 mg and 35 mg will be stored in 100 cc round HDPE bottles (b) (4). Both strengths will be available in 90-count bottles and 30-count bottles.

Physician samples of Zorvolex Capsules 18 mg and 35 mg will be packaged as blisters packaged in clear (b) (4) film with push through paperback foil. Both strengths will be provided as (b) (4) blister packs. Respective DMF's are referenced.

Stability:

Data for three batches of each strength of drug product (total of 6 batches) stored in 30-count, 90-count and 3-count blister packages, under long term, intermediate and accelerated conditions is provide. Further a regression analysis of an additional 12 months of data is also provided. An expiry of 24 months is requested.

C. Critical issues for review and recommendation

During assessment of the CMC information provided in this NDA, the primary reviewer should consider addressing issues identified above and other related ones, summarized here, for their impact on drug product quality and performance throughout the shelf-life:

1. Limits of impurities and related substances in the drug substance as per ICH Q3A(R), in consultation with the Toxicology Division and limits of residual solvents for compliance with ICH Q3C.
2. The suitability of the compendial specifications of excipients for drug product manufacturability, quality and performance should be assessed.
3. Details of the manufacturing process of the drug product, e.g.: in-process controls, hold times of the compounded solution and manufacturing conditions
4. Drug product specifications, e.g., impurity/degradant limits as per ICH Q3B(R), impurity limits as a structural alert, and unidentified impurity limits, in consultation with the Toxicology Division.
5. The suitability of the analytical methods for related substances and degradation products.

D. Recommendation for fileability: The NDA is fileable based on 14 clinical batches and 6 primary stability batches with 12 month long term/intermediate and /6-month accelerated stability data for drug product packaged in the three proposed presentations. 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.

Julia Pinto, Ph.D. _____

February 12, 2013 _____

Pharmaceutical Assessment Lead(acting)

Date

Prasad Peri, Ph.D. _____

February 12, 2013 _____

Branch Chief, ONDQA

Date

NDA Number: 204592

Supplement Number and Type: 3s

Established/Proper Name:

Zorvolex™ Capsules

Applicant:

Iroko Pharmaceuticals, LLC

Letter Date: December 20, 2011

Stamp Date: December 20, 2011

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		

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.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • 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		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • 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.	<p>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:</p> <ul style="list-style-type: none"> • 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		
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* 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		
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		
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	capsules
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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	

{See appended electronic signature page}

Name of

PAL: Julia Pinto, Ph.D

Primary CMC Reviewer: Ying Wang, Ph.D.

Division of Pre-Marketing Assessment I ; Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Name of

Branch Chief : Prasad Peri, Ph.D.

Division of Pre-Marketing Assessment I; Office of New Drug Quality Assessment

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
02/25/2013

PRASAD PERI
02/25/2013