CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204417Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approve

NDA 204417
Review # 4

Drug Name/Dosage Form	Elepsia (levetiracetam) extended-release tablets
Strength	1000 mg, 1500 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Sun Pharma Global FZE
US agent, if applicable	Jin Shang, Ph.D., Sun Pharmaceuticals Industries, Inc.

Quality Review Team

DISCIPLINE	REVIEWER	SECONDARY REVIEWER
Drug Substance	Dan Berger	Charles Jewell
Drug Product	Dan Berger	Wendy Wilson-Lee
Process	Tianhong (Tim) Zhou	Nallaperumal Chidambaram
Facility	Tianhong (Tim) Zhou	
Biopharmaceutics	Qi Zhang	Ta-Chen Wu
Regulatory Business Process Manager	Dahlia A. Woody	--
Application Technical Lead	Martha Heimann	--
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Analysis (EA)	N/A	

SUBMISSIONS REVIEWED (SD #)	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD-0041, Resubmission after CR	7/2/2018	All
SD-0043, response to IR	11/6/2018	Biopharmaceutics
SD-0045, response to IR	11/14/2014	Product

NDA 204417 Resubmission

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
21414	II	Sun Pharmaceutical	Levetiracetam	Adequate	11/8/2018	Reviewed by Dan Berger
(b) (4)	III		(b) (4)	N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	

[1] Adequate information in application or no changes to information since previous reviews.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22285	Keppra XR (levetiracetam) extended-release tablets 500 mg and 750 mg. This application is referenced under 505(b)(2) to support approval of NDA 204417.
ANDA	203059	Sun Pharma application for generic 500 mg and 750 mg levetiracetam extended-release tablets

2. CONSULTS

N/A

NDA 204417 Resubmission

Executive Summary

I. Recommendations and Conclusion on Approvability

The Office of Product Quality (OPQ) review team recommends that the Agency **Approve** NDA 208684 for Elepsia® (levetiracetam) extended-release tablets. From a quality perspective, the application, as amended, provides adequate information to ensure that the applicant can consistently manufacture a product that is suitable for use by the intended patients.

II. Summary of Quality Assessments

A. Product Overview

Levetiracetam was first marketed within the US by UCB Pharma (UCB), as Keppra® tablets. Subsequently, the Agency approved NDAs submitted by UCB for Keppra oral solution, extended-release tablets, and injection. Additional dosage forms have been approved under 505(b)(2) applications submitted by other firms.

Sun Pharma Global developed an extended-release formulation of levetiracetam tablets based on its patented "Wrap-Matrix" technology and submitted ANDA 203059 for 500 mg and 750 mg strengths as generic equivalents of the corresponding Keppra strengths. ANDA 203059 was approved 9/9/2013. NDA 204417, which provides for 1000 mg and 1500 mg strengths was submitted under 505(b)(2) on 5/12/2012. The initial submission was deemed acceptable from a quality perspective; however, a Complete Response Letter (CRL) was issued due to deficiencies identified by other review disciplines. CRLs were issued for two subsequent resubmissions due to cGMP issues at the drug product manufacturing site.

The current resubmission provides the applicant's response to the facility deficiency cited in the CRLs. Additionally, the applicant proposes minor changes to the formulation of the 1000 mg strength and manufacturing process for both strengths, and addition of another packaging configuration.

Proposed Indication(s) including Intended Patient Population	Adjunctive therapy in the treatment of partial onset seizures in patients 12 years of age and older with epilepsy.
Duration of Treatment	Chronic
Maximum Daily Dose	3000 mg
Alternative Methods of Administration	No other alternative methods of administration are proposed.

B. Quality Assessment Overview

Drug Substance

The bulk active pharmaceutical ingredient (API), levetiracetam, is a well characterized, neutral, small molecule that is highly water-soluble (538 mg/mL). The bulk drug substance is manufactured by Sun Pharmaceutical Industries (SPI) in Gujarat, India. Information regarding the characterization, manufacture, and control of the API is incorporated by cross-reference to SPI's drug master file (DMF) 21414. The DMF was reviewed and deemed adequate during the review of the original NDA. Subsequent changes to the DMF were reviewed to support the resubmission and the DMF remains adequate to support approval of the NDA. Information submitted by the applicant directly to the NDA is consistent with the information in DMF 21214.

Drug Product

Elepsia (levetiracetam extended-release tablets) contain 1000 mg or 1500 mg and excipients that are commonly used in extended-release oral dosage forms. The tablet design comprises a bilayer tablet core with (b) (4) (b) (4) (b) (4) a laser-drilled hole on the side (b) (4) (b) (4)

In the resubmission, applicant proposes to modify the quantitative composition of the 1000 mg strength (b) (4), (b) (4) (b) (4). The change is the result of internal review of dissolution data from the registration batches submitted to the original NDA after extended storage (up to 36 months) under long-term stability storage conditions. It is noted that the 36-month data remained within specification and were submitted in a stability update [S-0022, 12/1/2014] during an earlier review cycle. However, the applicant indicates that the results from the 4-hour time point trended toward the higher side of the specified range. (b) (4) (b) (4) The review team concurs with the applicant that the changes are Level 1 changes per the SUPAC-MR guidance. Based on comparative dissolution profiles provided in response to an information request, the changes are not expected to impact on product performance. Results of comparative dissolution testing, i.e., essentially overlapping dissolution profiles with f_2 similarity values > 50, show that the proposed CMC changes did not significantly alter the drug release rates of the post-change drug

product batches, compared to the pre-change (bio-batch), ensuring similar in-vivo performance between pre-and post-change drug products.

Elepsia extended-release tablets are manufactured (b) (4). (b) (4) (b) (4). Changes proposed in the resubmission include reduction of the commercial batch scale, use of alternate equipment with similar design and operating principles (b) (4) (b) (4)

The product specification was updated, per Agency request, to provide consistent acceptance criteria at release and during shelf life. The tighter acceptance criteria for product release submitted by the applicant are considered internal control limits adopted by the applicant to ensure consistent compliance with the regulatory specification. The only other changes are correction of a typographical error and minor changes to one analytical procedure.

In the original NDA, the applicant packaging Elepsia tablets in 30-, 100- and 500-count (b) (4) HDPE bottles with (b) (4) child-resistant (b) (4) closures. (b) (4) (b) (4). Based on the long-term and accelerated stability data provided, the requested 24-month expiration dating period for product stored under controlled room temperature conditions is granted.

Facilities

All facilities that will be involved in commercial manufacture and testing of Levetiracetam and Elepsia® (levetiracetam) extended-release tablets are currently acceptable.

Environmental Assessment

The applicant submitted a claim for categorical exclusion under 21 CFR § 25.31 (a). Approval of the application is not expected to increase use of the active moiety and there are no extraordinary circumstances. The claim remains acceptable and is granted.

C. Special Product Quality Labeling Recommendations

There are no special labeling recommendations.

D. Final Risk Assessment

When the original NDA was reviewed and recommended for approval from a quality perspective, formal risk assessment was not part of the review process. Given the limited changes in the resubmission, risk assessment is not deemed necessary.

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LABELING

{For NDA Only}

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Adequate
Dosage form, route of administration	Adequate
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Adequate

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	NA

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Adequate
Strengths: in metric system	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Adequate

4. ***Section 11 Description***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Adequate
Dosage form and route of administration	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	Adequate
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Adequate with edits made
Statement of being sterile (if applicable)	NA
Pharmacological/ therapeutic class	Adequate
Chemical name, structural formula, molecular weight	Adequate
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	Adequate

5. ***Section 16 How Supplied/Storage and Handling***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Adequate
Available units (e.g., bottles of 100 tablets)	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Adequate
Special handling (e.g., protect from light)	Adequate
Storage conditions	Adequate
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Adequate

Reviewer's Assessment of Package Insert: ***Adequate***
Section 11 has been edited to list of inactive ingredients in alphabetical order. With these edits, the prescribing information meets all regulatory requirements from a CMC perspective.

II. Labels:

(b) (4)

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Item	Information provided in the container label (b) (4) and bottles)	Information provided in the carton label(s) (b) (4) and bottle cartons)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Adequate	Adequate
Dosage strength	Adequate	Adequate
Net contents	Adequate	Adequate
"Rx only" displayed prominently on the main panel	Adequate (b) (4)	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Adequate	Adequate
Lot number and expiration date (21 CFR 201.17)	Adequate	Adequate
Storage conditions	Adequate	Adequate
Bar code (21CFR 201.25)	Adequate	Adequate
Name of manufacturer/distributor	Adequate	Adequate
And others, if space is available		

Reviewer's Assessment of Labels: ***Adequate***
The bottle, (b) (4) and carton labels comply with all regulatory requirements from a CMC perspective.

List of Deficiencies:

None.

Overall Assessment and Recommendation:

One Prescribing Information deficiency was addressed. The Prescribing Information and labels, as revised, comply with all regulatory requirements from a CMC perspective.

Primary Labeling Reviewer Name and Date:

Dan Berger November 29, 2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Wendy Wilson November 29, 2018

Dan Berger

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Date: 11/30/2018 09:28:04AM
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Wendy Wilson- Lee

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Martha
Heimann

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QUALITY ASSESSMENT
Biopharmaceutics Review

NDA: 204417-ORIG-1-RESUB-42
Submission Classification/Type: 505(b)(2); Type 5-New Formulation
Drug Product Name: Levetiracetam Extended-Release Tablets 1000 mg and 1500 mg
Applicant Name: Sun Pharmaceutical Industries, Ltd.
Dosage Forms and Strengths: Extended Release (ER) Tablets; 1000 mg and 1500 mg
Route of Administration: Oral (maximum recommended dose: 3000 mg once daily).
Indication: Adjunctive therapy in the treatment of partial onset seizures in patients 12 years of age and older with epilepsy
Re-submission Date: 7/2/2018
Primary Reviewer: Qi Zhang, Ph.D.
Secondary Reviewer: Ta-Chen Wu, Ph.D.

Background:
The current submission, a 505(b)(2) NDA 204417-ORIG-1-RESUB-42, provides the Applicant's response to the Complete Response Letter dated 3/22/2017 for the deficiencies associated with the continued facility OAI status. In addition, this resubmission includes proposed changes with regards to the drug substance identification method, quantitative composition of the 1000 mg strength drug product to be in line with SUPAC Level 1 Change, an added container closure system (b) (4), and other minor additions/changes to the specifications and testing. The Listed Drug (LD) is Keppra XR® (levetiracetam) extended-release tablets, 750 mg [NDA 022285, UCB Inc., approved on 9/12/2008].

Review Summary:
The Biopharmaceutics review evaluates the adequacy of the provided in-vitro dissolution information/data in supporting the proposed CMC changes. Results of the comparative dissolution testing, i.e., essentially overlapping dissolution profiles with f_2 similarity values > 50, show that the proposed CMC changes did not significantly alter the drug release rates of the post-change drug product batches, compared to the pre-change (bio-batch), ensuring similar in-vivo performance between pre- and post-change drug products.

Recommendation:
From the Biopharmaceutics perspective, NDA 204417-ORIG-1-RESUB-42 for Levetiracetam Extended-Release Tablets 1000 mg and 1500 mg is **ADEQUATE** for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

LIST of SUBMISSIONS BEING REVIEWED

eCTD # (SND #)	Received date	Document
0000 (0)	5/29/2012	Original submission
0041 (42)	7/2/2018	Resubmission
0043 (44)	11/6/2018	Quality/Response to information request

PROPOSED CHANGES IN QUANTITATIVE COMPOSITION OF DRUG PRODUCT

The Applicant proposes to [redacted] and to [redacted] for the 1000 mg strength. Per the Applicant, these changes are proposed due to the dissolution data trending towards the upper dissolution limit at 4 hour for multiple batches at release and stability testing.

Table 1: Proposed Changes in The [redacted] Excipient

[redacted] Components for Levetiracetam Extended Release Tablets 1000 mg	Composition as submitted in the original NDA	Proposed Composition
	Amount (mg/Tablet)	Amount (mg/Tablet)
[redacted]	[redacted]	[redacted]
Hypromellose [redacted] USP		
Amino Methacrylate Copolymer, NF		
[redacted]		
Ethyl cellulose [redacted] NF		
[redacted]		

Reviewer's Assessment:

The change for the [redacted] excipient is [redacted] out of the total [redacted] components, and the change for [redacted] excipients is less than [redacted] out of the total tablet weight [redacted]. These changes were discussed with the CMC Reviewers, and are considered as SUPAC-MR Level 1 Change in Composition, for which comparative dissolution data generated using the application dissolution method, are required.

*To support the proposed multiple CMC changes, this Reviewer recommended that the Applicant provide the complete multipoint dissolution profile data for the post-change drug product batches (refer to Information Request sent on 10/22/2018 (see **Appendix**) and requested dissolution data submitted on 11/06/2018).*

Note that the drug substance is highly soluble irrespective of pH and the drug product exhibits pH-independent dissolution. The proposed dissolution method and acceptance criteria for this drug product were previously approved and determined to be adequate (refer to Biopharmaceutics Reviews by Dr. John Duan, dated 3/7/2013 in DARRTS, and by Dr. Elsbeth Chikhale, dated 11/19/2014 in PANORAMA).

DISSOLUTION INFORMATION

Dissolution Method and Acceptance Criteria:
The Applicant conducted the dissolution testing using the dissolution method approved for this drug product. The approved dissolution method and acceptance criteria are summarized in the table below.

USP Apparatus	Speed	Medium	Volume/Temp	Acceptance Criteria
III (reciprocating cylinder)	15 dips/min	pH 4.5 Sodium Acetate Buffer	900 mL/37°C	1 hour: (b) (4) % 4 hours: (b) (4) % for 1000 mg % for 1500 mg 12 hours: NLT (b) (4) %

Dissolution Profile Data:
The currently submitted dissolution data for the post-change drug product batches for each of the 1000 mg and 1500 mg strengths, and dissolution data for the bio-batch (#JKJ1197, 1500 mg) provided in the original NDA (\\cdsesub1\evsprod\nda204417\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5313-in-vitro-in-vivo-corr-stud-rep\multi-media-disso.pdf) are summarized in **Figure 1**. The dissolution profile similarity f_2 results based on the mean dissolution data are presented in **Table 2**. Data analysis was performed by this Reviewer using the automation tool developed by the Division of Biopharmaceutics.

(b) (4)

Table 2: Dissolution Profile Similarity f_2 Results

Comparisons	f_2 Values
JKJ1197_1500 mg_Biobatch Vs JKR6453_1500 mg	93.64
JKJ1197_1500 mg_Biobatch Vs JKR6454_1500 mg	89.60
JKJ1197_1500 mg_Biobatch Vs JKR6870_1000 mg	85.88
JKJ1197_1500 mg_Biobatch Vs JKR6871_1000 mg	76.41
JKJ1197_1500 mg_Biobatch Vs JKR7235_1000 mg	97.35
JKJ1197_1500 mg_Biobatch Vs JKR7236_1500 mg	81.41
JKJ1197_1500 mg_Biobatch Vs JKR6453_1500 mg	93.64

Reviewer's Assessment:

All exhibit batches for each of the 1000 mg and 1500 mg strengths met the dissolution acceptance criteria at Stage 1. Results of the comparative dissolution testing with f_2 similarity values > 50 suggest similar drug release rates between the bio-batch and post-change drug product batches, supporting the proposed CMC changes.

APPENDIX

BIOPHARMACEUTICS INFORMATION REQUESTS (10/22/2018)

To facilitate FDA's review on your proposed multiple changes and the setting of the dissolution acceptance criteria, provide complete dissolution profile data (n = 12, individual, mean, RSD, and profiles at each sampling time points e.g. 1,2,4,6,8,10 and 12 hours) for the exhibit batches of the post-change drug product for both strengths, using the proposed dissolution method. Submit complete dissolution profile data in ".xlsx" format.

Qi Zhang

Digitally signed by Qi Zhang
Date: 11/26/2018 10:34:32AM
GUID: 547e178000007695c91eb10380b07939

Ta-Chen Wu

Digitally signed by Ta-Chen Wu
Date: 11/26/2018 10:58:10AM
GUID: 508da6df000269e151ff37cd8f4e13a1

TO: CMC MEMO-TO-FILE

FROM: P. Shiromani, Ph.D

SUBJECT: NDA 204417: Levetiracetam Etended Release Tablets, 1000 & 1500 mg
DATE: 12-Mar-2013

ONDQA Biopharm submitted their review to DARRTS on 07-Mar-2013, with the following comment to the applicant. Their recommendation was accepted by the applicant in their response letter of 02-Mar-2013, reflected in their revised drug product specification. The revised specifications are included in this memo.

There are no other CMC pending issues. Accordingly, this NDA is recommended for approval from a CMC perspective. The CMC Review was submitted to DARRTS on 01-Mar-2013.

FDA's Comment

The provided dissolution data from the clinical and stability batches support the following acceptance criteria for your product.

Acceptance criteria:

1 hour: (b) (4)%

4 hour: % for 1000 mg strength

% for 1500 mg strength

12 hour: NLT (b) (4)%

Accordingly, the applicant has provided the following revised specification tables for both strengths with the recommended dissolution acceptance criteria incorporated there-in:

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Evaluation

Adequate.

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/s/

PRAFULL K SHIROMANI
03/13/2013

RAMESH K SOOD
03/13/2013

ONDQA BIOPHARMACEUTICS REVIEW - UPDATED VERSION

Original NDA:	**204-417**
Submission Date:	5/28/2012, 10/11/2012, 3/4/2013
Drug Name:	Levetiracetam Extended-Release Tablets
Formulation:	Extended-Release Tablets
Strength:	1000 and 1500 mg
Applicant:	Sun Pharma, Inc
Reviewer:	John Duan, Ph.D.
Submission Type:	505(b)(2) NDA

PREFACE TO THE UPDATED REVIEW

This is an updated version of the original review of NDA 204-417 Levetiracetam Extended-Release Tablets signed in DARRTS on 2/28/2013. The updates include the revised dissolution acceptance criteria and the final Biopharmaceutics recommendation. This version supersedes the version in DARRTS signed on 2/28/2013. The differences between these two versions are in the following sections of the review.

1. The addition of this PREFACE TO THE UPDATED REVIEW section
2. COMMENTS section
3. RECOMMENDATION section
4. The subsection "5. Setting of Acceptance Criteria for the Dissolution Test" in Appendix I.

SYNOPSIS

Submission: NDA 204-417 Levetiracetam Extended-Release Tablets submitted on 5/24/2012 is proposed for partial onset seizures in patients (b) (4). The Applicant has developed higher strength tablets (1000 mg and 1500 mg) intended to be bioequivalent to the reference product (500 and 750 mg) when administered in the same total dose. The bioequivalence study was conducted using the 1500 mg strength and the Applicant requested a biowaiver for the lower strength 1000 mg.

Review: The Biopharmaceutics review is focused on the biowaiver request, the dissolution methodology and acceptance criteria, the in vitro alcohol dose dumping study and the extended release claim.

ONDQA-Biopharmaceutics has reviewed the NDA 204-417 Levetiracetam Extended-Release Tablets and has the following comments:

COMMENTS:

1. The provided data support the biowaiver request for the lower strength 1000 mg. Therefore, the biowaiver for this strength is granted, provided the bioequivalence study for the higher 1500 mg strength is approved by Office of Clinical Pharmacology.

2. The following proposed dissolution method and acceptance criteria are adequate and acceptable.

Apparatus:	USP III (reciprocating cylinder)
Medium:	pH 4.5 buffer
Volume:	230 mL
Agitation speed:	15 dips/min
Acceptance Criteria:	1 hour: (b) (4)%
	4 hours: (b) (4)% for 1500 mg
	% for 1000 mg
	12 hours: NLT (b) (4)%

3. The results from the in vitro study evaluating the alcohol-induced dose dumpling of Levetiracetam Extended-Release Tablets, 1500 mg showed a dose dumping effect at the higher concentration of alcohol ((b) (4)%) at pH 4.5.

   On 2/25/2013, the following comment was conveyed to the Clinical and Clinical Pharmacology Reviewers.

   Biopharmaceutics Comment to the Clinical & Clinical Pharmacology Reviewers
   Based on the results from the in-vitro alcohol dose-dumping study showing an interaction in the presence of (b) (4) % EtOH in the dissolution medium, the Clinical and Clinical Pharmacology Reviewers should decide if:
   - the in vitro dose-dumping effect is clinically relevant and an in vivo study will be needed to assess the potential for a dose dumping due to the concomitant administration of alcohol with levetiracetam; or
   - an in vivo study is not needed and the findings can be addressed in the labeling of the product.

RECOMMENDATION

From the Biopharmaceutics perspective, an Approval is recommended for NDA 204-417 Levetiracetam Extended-Release Tablets.

John Duan, Ph.D.
Reviewer
ONDQA Biopharmaceutics

Angelica Dorantes, Ph.D.
Team Leader
ONDQA Biopharmaceutics

cc: NDA 204-417/*DARRTS, RLostritto*

Appendix I. BIOPHARMACEUTICS EVALUATION

1. Introduction

Levetiracetam is an antiepileptic agent, which is approved for the adjunctive treatment of various seizure types. The extended-release tablet KEPPRA XR is approved only for partial onset seizures in patients at age of 16 years and above. Treatment with levetiracetam in an extended-release form is initiated with a dose of 1000 mg once daily, and adjusted in increments of 1000 mg to a maximum recommended daily dose of 3000 mg. Two strengths are available, 500 mg and 750 mg. In order to reduce the number of tablets to be taken daily, the Applicant developed higher strength tablets (1000 mg and 1500 mg) intended to be bioequivalent to the reference product when administered in the same total dose.

The schematic representation of system construction and mechanism of drug release for Levetiracetam Extended Release Tablets is shown in following figures:

Figure A: Wrap Matrix™: Dosage form Design

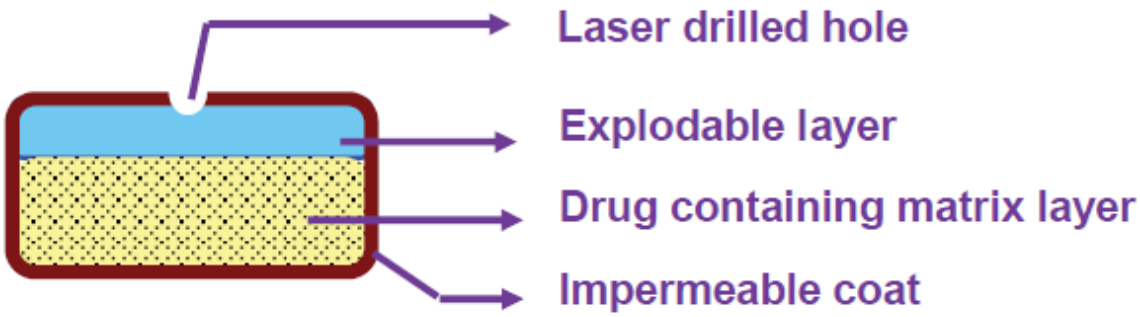
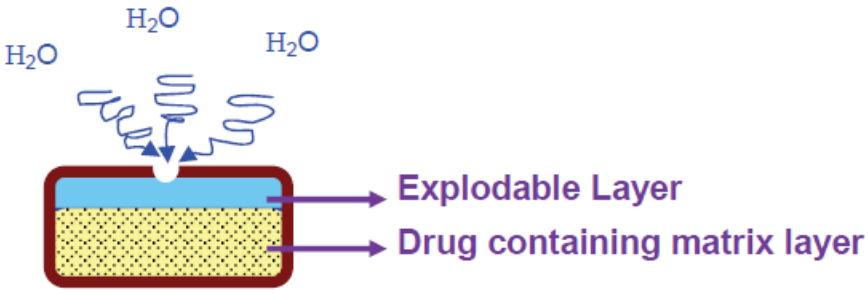
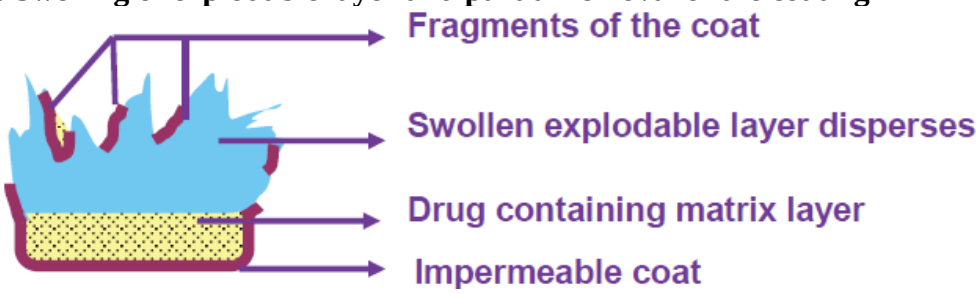


Figure B: Mechanism of release

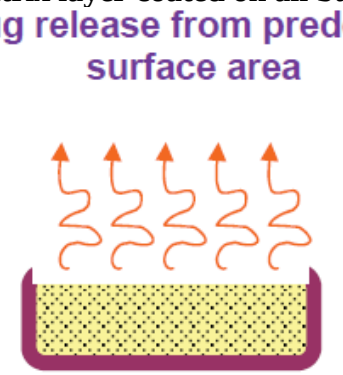
Step 1: Imbibition of dissolution fluid by the Explodable layer



Step 2: Swelling of explodable layer and partial removal of the coating



Step 3: Drug containing matrix layer coated on all but open on one side



As seen from the schematic representation, drug release is primarily a function of exposed surface area as other sides are covered by impermeable coat.

The exposed surface area through which dissolution of the drug occurs is generated by rupture of the coat which is in the proximity of an openable layer (Step 2).

Reviewer's Comment: *The release mechanism for Levetiracetam Extended Release Tablets shows that the dissolution may be condition independent.*

2. The Compositions of the Proposed Drug Product

Table 1 presents the composition of the formulations for the newly proposed 1000 mg and 1500 mg strengths of the drug product.

TABLE 1

Composition of Drug Product

Components	Amount (mg)/Tablet		Amount % w/w
Strength	1000 mg	1500 mg	1000 mg and 1500 mg
	(b) (4)		
Levetiracetam, USP	1000.00	1500.00	(b) (4)
Povidone (b) (4) USP			(b) (4)
Hypromellose (b) (4) USP (b) (4) (b) (4)			
Amino Methacrylate Copolymer, NF (b) (4)			
Colloidal silicon dioxide, NF			
Magnesium stearate, NF (b) (4)			
Talc, USP (b) (4)			

Components	Amount (mg)/Tablet		Amount % w/w
Strength	1000 mg	1500 mg	1000 mg and 1500 mg
			(b) (4)
Silicified Microcrystalline Cellulose, NF (b) (4)			
Crospovidone, NF (b) (4)			
Sodium lauryl sulfate, NF			
FD and C Blue No. 1 Aluminum Lake (b) (4)			
(b) (4)			
Ethyl cellulose (b) (4)			(b) (4)
Dibutyl Sebacate, NF			
Triethyl Citrate, NF			
Polysorbate 20, NF (b) (4)			
(b) (4)			

Reviewer's Comment: *As presented in the above Table 1, the two new proposed 1000mg and 1500 mg strengths are compositionally proportional.*

3. Biowaiver request for the lower strength

A bioequivalence study was conducted for the higher 1500 mg strength and the Applicant requested a biowaiver for the lower 1000 mg strength based on the following:

- The lower strength (1000 mg) and the higher strength (1500 mg) are similar in their active and inactive ingredients as shown in Table 1 listed in Section.

- Dissolution studies in various dissolution media (i.e. proposed medium; pH 4.5 Buffer, pH 1.2 Buffer, pH 6.0 Buffer and pH 6.8 Buffer) were carried out for profile comparisons between the Levetiracetam Extended Release Tablets 1000 mg and 1500 mg. The similarity factors (f2) were calculated.

The dissolution parameters used were as follows.

Apparatus: USP Apparatus III (b) (4)
Agitation: 15 dip per minute.

Medium:	4 media as specified in the following figure and table.
Temperature:	37°C ± 0.5 °C.
Volume:	230 mL.
Time:	1, 2, 3, 4, 6, 8, 10 and 12 hours.
Filter:	Nylon 0.45 µ membrane filter.

The following Table 2 and Figure 1 show the results of dissolution profile comparison in pH 4.5 buffer.

TABLE 2

(b) (4)

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The similarity factors (f_2) are above 50 for all the dissolution media tested (pH 1.2 Buffer, pH 6.0 Buffer and pH 6.8 Buffer) including the QC dissolution medium at pH 4.5.

Reviewer's Comments: *The biowaiver request is supported by adequate information. Levetiracetam Extended Release Tablets 1000 mg is compositionally similar to Levetiracetam Extended Release Tablets 1500 mg. The release profiles of Levetiracetam Extended Release Tablets 1000 mg are similar (f2 factor more than 50) to Biobatch - Levetiracetam Extended Release Tablets 1500 mg in pH 1.2, pH 4.5, pH 6.0 and pH 6.8 dissolution media. Therefore, the biowaiver request is granted, provided the bioequivalence study is acceptable by the Office of Clinical Pharmacology.*

4. Proposed Dissolution Methodology

The dissolution method development report supporting the proposed methodology was provided, in which different apparatus, media and agitation speeds were investigated. The following conditions were selected.

Apparatus:	USP III (reciprocating cylinder)
Medium:	pH 4.5 buffer
Volume:	230 mL
Agitation speed:	15 dips/min

The rationale for the selected testing conditions is summarized below:

(b) (4)

5. Setting of Acceptance Criteria for the Dissolution Test

Through the investigations in the above section, the following testing conditions were used for the collection of data used to set the acceptance criteria.

Apparatus:	USP III (reciprocating cylinder)
Medium:	pH 4.5 buffer
Volume:	230 mL
Agitation speed:	15 dips/min

In the original submission, the Applicant proposed the following time points and acceptance criteria for dissolution.

1 hour:	(b) (4) %
4 hour:	%
12 hour:	NLT (b) (4) %

During the filing communication dated August 10, 2012, the following comments were sent to the Applicant.

> *Your proposed acceptance criteria for the dissolution test should be fully justified with data. Therefore, provide the complete dissolution profile data and any other information/data (i.e., IVIVC, BE, etc.) supporting your selection. Note that the dissolution acceptance criteria for your product should be based on the following:*
>
> - *The dissolution profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your product (i.e., specification sampling time points and specification ranges).*
>
> - *The in vitro dissolution profiles should encompass the timeframe over which at least (b) (4) % of the drug is dissolved or where the plateau of drug dissolved is reached if incomplete dissolution is occurring.*
>
> - *The acceptance criteria should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).*
>
> - *At least three specification time-points covering the initial, middle, and terminal phases of the complete dissolution profile data should be set. The specification ranges should be based on the overall dissolution data generated at these times.*
>
> - *The selection of the dissolution specification ranges is based on mean target value ± 10% and NLT (b) (4) % for the last specification time-*

point. Wider specification ranges may be acceptable if they are supported by an approved In Vitro-In Vivo Correlation (lVIVC) model or an approved bioequivalence (BE) study demonstrating that the proposed lower and higher specification ranges are bioequivalent.

On October 11, 2012, the Applicant provided the following revision for the 1 and 4 hours time points.

TABLE 14

Previous Specification		Proposed	
1 Hour:	(b) (4)	1 Hour:	(b) (4)
4 Hour:		4 Hour:	

(b) (4)

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Reviewer's Comments: The information provided shows a potential of dose dumping in the presence of high (b) (4)% alcohol concentrations. The Clinical and the Clinical Pharmacology Reviewers have been informed of the dose dumping effect and they should provide a recommendation regarding the need or not for an in vivo drug interaction study with alcohol for Levetiracetam ER Tablets.

6. Extended release claim

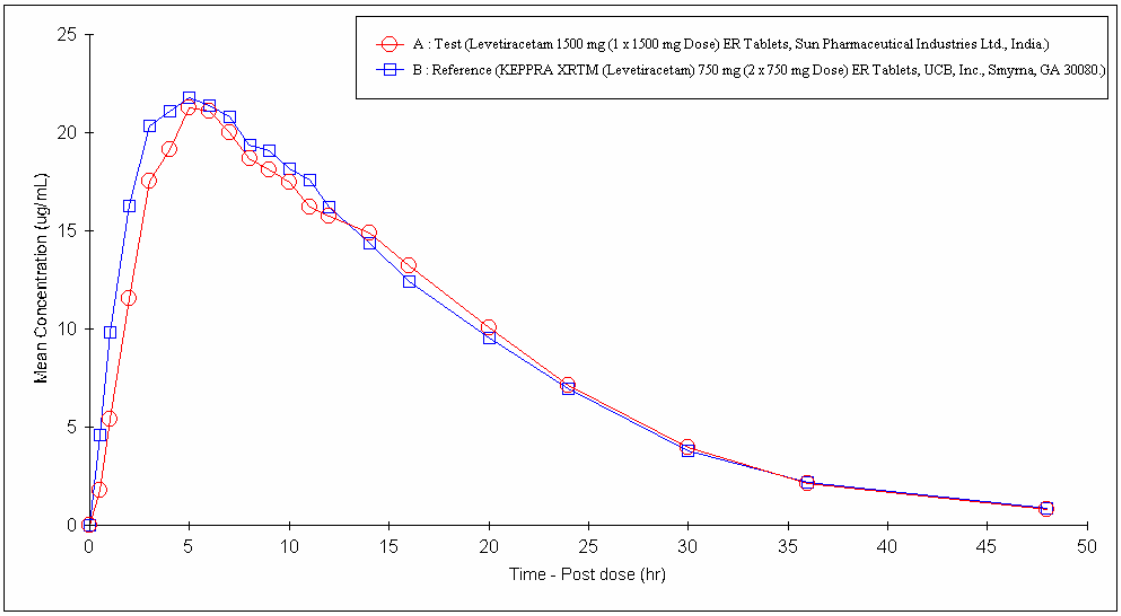
This is a 505(b)(2) submission and KEPPRA XR (levetiracetam) Extended-Release Tablets was used as the reference listed drug product, which is an approved product with an extended release claim. The following Table 15 and Figure 18 show the comparison of the mean plasma concentrations between the test and the reference products for 1500 mg strength.

TABLE 15 Mean (%CV) Pharmacokinetic Parameters and Analysis of Levetiracetam under Fasting Conditions (Study PKD_10_130; N=18)

Parameter (unit)	Arithmetic Means		Ratio of Least-Square Means[1]	90% Geometric CI
	Levetiracetam ER 1500-mg Tablets	Keppra XR® 2×750-mg Tablets		
C_{max} (µg/mL)	23.2 (27.9)	23.8 (21.4)	95.84	81.80 to 112.27
AUC_{0-t} (µg·h/mL)	402.4 (24.1)	416.1 (30.7)	97.74	83.40 to 114.54
$AUC_{0-\infty}$ (µg·h/mL)	411.1 (24.2)	426.1 (31.5)	97.67	83.27 to 114.56
T_{max} (h)[2]	5.0 [3.0 – 16.0]	4.0 [3.0 – 11.0]	--	
$T_{1/2}$ (h)	7.7 (11.2)	7.9 (12.8)	--	
K_{el} (h^{-1})	0.091 (11.4)	0.089 (13.1)	--	

[1] Test (Levetiracetam ER Tablets) to Reference (Keppra XR®)
[2] Median [range]

Figure 18: Mean Concentration Profile of Levetiracetam under Fasting Conditions (Study PKD_10_130; N=18)



As shown in the figure, the test product under fasting condition and fed condition is, on average, similar to the reference product, which is approved for the extended release claim. Therefore, the proposed product is expected to show extended release characteristics.

Reviewer's Comment: *The extended release characteristics of the proposed product are confirmed.*

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/s/

JOHN Z DUAN
03/07/2013

ANGELICA DORANTES
03/07/2013

NDA 204-417

Levetiracetam Etended Release Tablets, 1000 mg & 1500 mg

Sun Pharma Global FZE (Sun)

Prafull Shiromani Ph.D.

Division of Pre-Marketing Assessment 1
Division of Neurology Products
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 204-417

2. REVIEW #: 1

3. REVIEW DATE: 28-Feb-2013

4. REVIEWER: Prafull Shiromani PhD

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA	29-May-2012
Applicant's Response to Agency CMC IR Letter	29-nov-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Mr. Vishwanath Kenkare, Sun Pharma Global FZE (Sun)
Address:	Office # 43, Block Y, SAIF Zone, P.O. Box # 122304, Sharjah, U.A.E.
Representative:	Karin A. Kook, PhD, Salamandra, LLC, One Bethesda Center 4800, Hampden Lane, Suite 900, Bethesda, Maryland 20814-2998

Telephone: 301-652-6110

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: To be determined
b) Non-Proprietary Name (USAN): levetiracetam
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Anti-epileptic drug

11. DOSAGE FORM: Extended release tablet

12. STRENGTH/POTENCY: 1000 mg & 1500 mg

13. ROUTE OF ADMINISTRATION: Oral

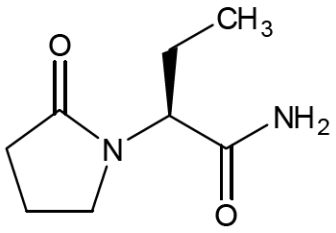
14. Rx/OTC DISPENSED: _x__Rx ___OTC

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:

(αS)- (-) - (S)-α-Ethyl-2-oxo-1-pyrrolidineacetamide

Chemical Structure	
Molecular Formula	$C_8H_{14}N_2O_2$
Molecular Weight	170.21

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS LOA Date
21414	II	Sun Pharmaceutical Industries Ltd	Levetiracetam	1	Adequate	29-Nov-2011	23-May-2012
(b) (4)	III		(b) (4)	4			16-Jun-2009
	III			4			04-May-2009
	III			4			16-Jun-2009
	III			4			15-Jun-2009
	III			4			17-Jun-2009
	III			4			04-May-2009
	III			4			30-Apr-2009;

Chemistry Review Data Sheet

(b) (4)		(b) (4)				
						16-Sep-2009 (Two LOAs provided for different components)
	III		4			06-May-2009
	III		4			18-Sep-2009
	III		4			18-Sep-2009
	III		4			09-Jun-2009
	III		4			18-Sep-2009
	III		4			10-Jun-2009
	III		4			27-May-2009
	III		4			09-Jun-2009
	IV		4			20-May-2009 08-Jun-2009 05-Oct-2009

[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: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	25-Jan-2013	T. Sharp
Pharm/Tox			
Biopharm	Pending		
LNC			
Methods Validation	Samples of the DS, DP and reference compounds are available		Validation is not required since the analytical methods are conventional
OPDRA			
EA	Their claim for categorical exclusion is acceptable.		P. Shiromani
Microbiology	N/A		

The Chemistry Review for NDA 204417

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has provided adequate responses to the FDA CMC IR Letter. OC's overall acceptable recommendation has been issued based on site inspection. Though the original ONDQA Biopharm review has been completed, their final recommendation for approvability of this NDA is dependent upon the agreement by the applicant of the recommended regulatory dissolution acceptance criteria. At the time a final approvability recommendation is made by the biopharm reviewer, this reviewer will write a Memo-to-File, noting ONDQA Biopharm's NDA approvability and including consequent revised drug product specification. Thereafter, as there are no other CMC pending issues, the final ONDQA recommendation for this NDA will be made from a CMC perspective.

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

N/A

II. Summary of Chemistry Assessments

Levetiracetam is an anti-epileptic drug that was first approved in 1999 as an immediate-release tablet (Keppra®, UCB Pharma). The mechanism of action is not known. Levetiracetam is currently available in a number of dosage forms, including extended-release tablets, under various NDAs and ANDAs. The current NDA from Sun Pharma Global (Sun) provides for marketing of levetiracetam extended-release tablets in two strengths, 1000 mg and 1500 mg. The recommended dose is between 1000 mg and 3000 mg, taken once daily.

The drug substance and drug product are both manufactured by this applicant; the former at Panoli, India and the latter at Halol, Gujarat, India.

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

Drug Substance

The drug substance, Levetiracetam USP [(αS)-(-) - (S)-α-Ethyl-2-oxo-1-pyrrolidineacetamide], is a well characterized neutral small molecule. It is a white to off-white crystalline powder, S-isomer, highly soluble in water (538 mg/mL) and slightly hygroscopic. It is a BCS Class 1, with no polymorphs. The very low impurity content in three production batches attests to a synthesis which consistently produces a high quality product.

The bulk drug substance is manufactured and supplied by Sun Pharmaceutical Industries Ltd., Gujarat, India. A letter of reference, dated 23-May-2012, from Sun Pharmaceutical Industries Limited authorizing Food and Drug Administration to refer drug master file # 21414 for Levetiracetam pursuant to the requirements of 21 CFR § 314.50(d)(1)(i) is attached.

The DMF was reviewed on 17-Jul-2012 to be adequate by OGD (Dr. Ryan Nguyen) on 29-Nov-2011 for ANDA 203059. and by this reviewer (P. Shiromani) on 17-Jul-2012 and considered to be adequate to support this NDA 204-417.

The NDA itself includes general information, characterization data, and drug substance specifications. In addition to compliance with the current USP monograph, the drug product manufacturer's specification includes tests for solubility, clarity, color index, optical rotation, residual solvents, bulk density and particle size.

The drug substance is assigned a (b) (4) re-testing period.

The applicant's response, dated 29-Nov-2012, to the FDA CMC IR Letter comment on validation of their analytical procedures for particle size by Laser Diffraction is satisfactory and the same included in this review.

Drug Product

The proposed dosage form is an extended-release tablet based on the applicant's proprietary "*Wrap Matrix*" technology. The applicant has previously applied this technology under ANDA 91-272 (venlafaxine extended-release tablets, approved

2010) and ANDA 203059 (lower doses) reviewed to be acceptable on 03-Aug-2012.

Kappa XR (levetiracetam extended release tablets) is the reference listed drug (NDA 22-285, approved 12-Sep-2008) for this NDA.

The proposed dosage form is an extended release tablet containing 1000 mg and 1500 mg of levetiracetam. The 1000 mg tablet is an oval, biconvex coated bilayer tablet with blue layer having laser drilled hole and white to off white layer, imprinted with "574" with black ink on one side and plain on the other side. The 1500 mg is an oval, biconvex coated bilayer tablet with blue layer having laser drill and white to off white layer, imprinted with "575" with black ink on one side and plain on the other side. The two strengths are distinguished from each other by size and imprinting.

The NDA registration stability package is consistent with ICH guidance. Two batches of each strength were manufactured at pilot scale and one batch was manufactured at a smaller scale. Six months accelerated data and a minimum of 12 months long-term data is provided for all strengths and bottle sizes. 18 months long term stability data is provided for the 1500 mg biobatch (Batch No. JKJ1197). Additional 18-24 months stability data at the long-term storage condition on several stability batches were included in their over-all response (to the CMC IR Letter) submission of 11/29/12. These data were determined to be satisfactory on review. The applicant proposes a 24 month tentative expiry period. Based on the satisfactory stability data and on ICH Q1E, their proposal is acceptable. They intend to initiate a stability study on the first three commercial batches.

The applicant's responses, dated 29-Nov-2012, to the FDA CMC IR Letter are satisfactory; especially, their agreement to include a test for microbial purity in the drug product specification and to include both the stability storage conditions (long-term and accelerated) in their post-approval stability protocol.

Compliance issued an overall recommendation for approval on 25-Jan-2013; their summary report is attached to this review.

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

INDICATIONS AND USAGE

Levetiracetam is an antiepileptic drug indicated for adjunctive therapy in the treatment of partial onsetseizures in patients ≥(b) (4) years of age with epilepsy.

DOSAGE AND ADMINISTRATION
Treatment should be initiated with a dose of 1000 mg once daily. The daily dosage may be adjusted in increments of 1000 mg every 2 weeks to a maximum recommended daily dose of 3000 mg **(2)**.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided adequate responses to the FDA CMC IR Letter. OC's overall acceptable recommendation has been issued based on site inspection. Though the original ONDQA Biopharm review has been completed, their final recommendation for approvability of this NDA is dependent upon the agreement by the applicant of the recommended regulatory dissolution acceptance criteria. At the time a final approvability recommendation is made by the biopharm reviewer, this reviewer will write a Memo-to-File, noting ONDQA Biopharm's NDA approvability and including consequent revised drug product specification. Thereafter, as there are no other CMC pending issues, the final ONDQA recommendation for this NDA will be made from a CMC perspective.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Prafull Shiromani PhD
ChemistryTeamLeaderName/Date: Ramesh Sood PhD
ProjectManagerName/Date: Lana Y Chen

C. CC Block

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(b) (4)

III. List Of Deficiencies To Be Communicated

None

Conclusion

The applicant has provided adequate responses to the FDA CMC IR Letter. OC's overall acceptable recommendation has been issued based on site inspection. Though the original ONDQA Biopharm review has been completed, their final recommendation for approvability of this NDA is dependent upon the agreement

by the applicant of the recommended regulatory dissolution acceptance criteria. At the time a final approvability recommendation is made by the biopharm reviewer, this reviewer will write a Memo-to-File, noting ONDQA Biopharm's NDA approvability and including consequent revised drug product specification. Thereafter, as there are no other CMC pending issues, the final ONDQA recommendation for this NDA will be made from a CMC perspective.

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/s/

PRAFULL K SHIROMANI
03/01/2013

RAMESH K SOOD
03/01/2013

ONDQA BIOPHARMACEUTICS REVIEW

Original NDA:	**204-417**
Submission Date:	5/28/2012, 10/11/2012
Drug Name:	Levetiracetam Extended-Release Tablets
Formulation:	Extended-Release Tablets
Strength:	1000 and 1500 mg
Applicant:	Sun Pharma, Inc
Reviewer:	John Duan, Ph.D.
Submission Type:	505(b)(2) NDA

SYNOPSIS

Submission: NDA 204-417 Levetiracetam Extended-Release Tablets submitted on 5/24/2012 is proposed for partial onset seizures in patients (b) (4) years and above. The Applicant has developed higher strength tablets (1000 mg and 1500 mg) intended to be bioequivalent to the reference product (500 and 750 mg) when administered in the same total dose. The bioequivalence study was conducted using the 1500 mg strength and the Applicant requested a biowaiver for the lower strength 1000 mg.

Review: The Biopharmaceutics review is focused on the biowaiver request, the dissolution methodology and acceptance criteria, the in vitro alcohol dose dumping study and the extended release claim.

ONDQA-Biopharmaceutics has reviewed the NDA 204-417 Levetiracetam Extended-Release Tablets and has the following comments:

COMMENTS:

1. The provided data support the biowaiver request for the lower strength 1000 mg. Therefore, the biowaiver for this strength is granted, provided the bioequivalence study for the higher 1500 mg strength is approved by Office of Clinical Pharmacology.

2. The following proposed dissolution method is adequate and acceptable.

Apparatus:	USP III (reciprocating cylinder)
Medium:	pH 4.5 buffer
Volume:	230 mL
Agitation speed:	15 dips/min

   However, the acceptance criteria at 4 h should be revised.

   Acceptance Criteria:

1 hour: (b) (4)%
4 hour: % for 1500 mg
% for 1000 mg
12 hour: NLT (b) (4)%

The results from the in vitro study evaluating the alcohol-induced dose dumpling of Levetiracetam Extended-Release Tablets, 1500 mg showed a dose dumping effect at the higher concentration of alcohol ((b) (4)%) at pH 4.5.

On 2/25/2013, the following comment was conveyed to the Clinical and Clinical Pharmacology Reviewers.

Biopharmaceutics Comment to the Clinical & Clinical Pharmacology Reviewers

- Based on the results from the in-vitro alcohol dose-dumping study showing an interaction in the presence of (b) (4)% EtOH in the dissolution medium, the Clinical and Clinical Pharmacology Reviewers should decide if:
    - the in vitro dose-dumping effect is clinically relevant and an in vivo study will be needed to assess the potential for a dose dumping due to the concomitant administration of alcohol with levetiracetam; or
    - an in vivo study is not needed and the findings can be addressed in the labeling of the product.

RECOMMENDATION

At this stage of the review process, our Biopharmaceutics recommendation for NDA 204-417 for Levetiracetam Extended-Release Tablets is pending, because the implementation of the final regulatory dissolution acceptance criteria for this product still is a pending issue that needs to be resolved with the Applicant.

Note that an information request was sent to the Applicant on 2/28/2013. Once the Applicant provides their response to our inquiry, our final recommendation regarding the approvability of this NDA will be made. An amendment to this original review will be written to document our final recommendation.

_____ _____

John Duan, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____

Angelica Dorantes, Ph.D. Date
Team Leader
ONDQA Biopharmaceutics

cc: NDA 204-417/*DARRTS, RLostritto*

Appendix I. BIOPHARMACEUTICS EVALUATION

1. Introduction

Levetiracetam is an antiepileptic agent, which is approved for the adjunctive treatment of various seizure types. The extended-release tablet KEPPRA XR is approved only for partial onset seizures in patients at age of 16 years and above. Treatment with levetiracetam in an extended-release form is initiated with a dose of 1000 mg once daily, and adjusted in increments of 1000 mg to a maximum recommended daily dose of 3000 mg. Two strengths are available, 500 mg and 750 mg. In order to reduce the number of tablets to be taken daily, the Applicant developed higher strength tablets (1000 mg and 1500 mg) intended to be bioequivalent to the reference product when administered in the same total dose.

The schematic representation of system construction and mechanism of drug release for Levetiracetam Extended Release Tablets is shown in following figures:

Figure A: Wrap Matrix™: Dosage form Design

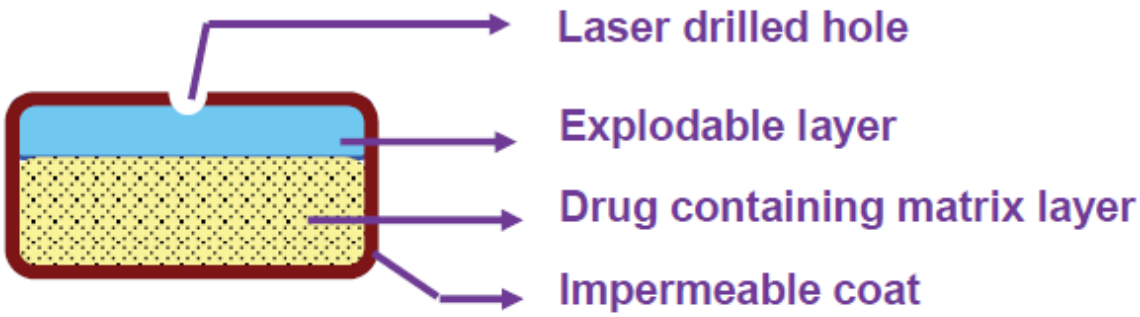
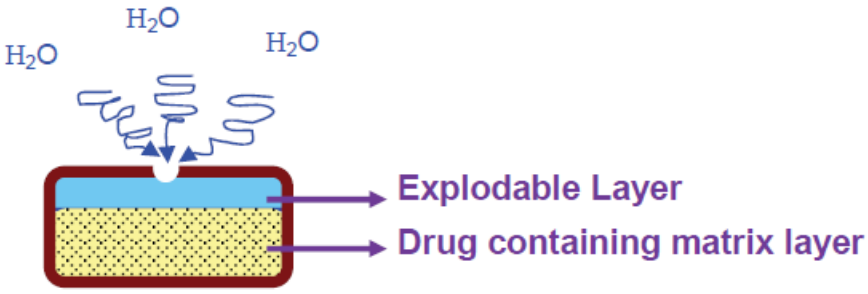
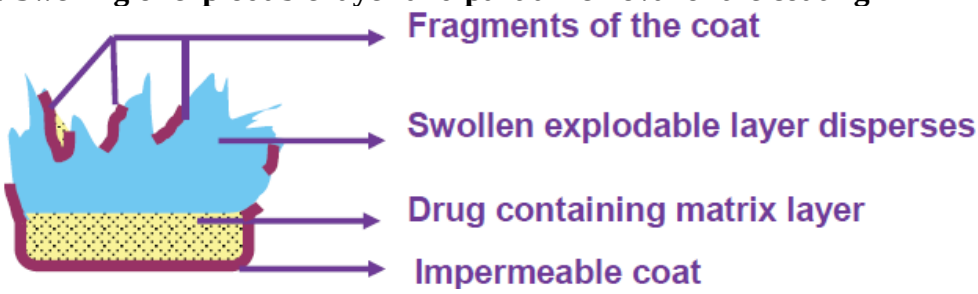


Figure B: Mechanism of release

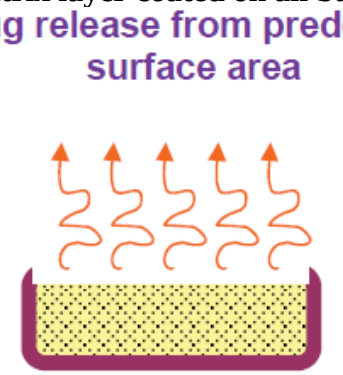
Step 1: Imbibition of dissolution fluid by the Explodable layer



Step 2: Swelling of explodable layer and partial removal of the coating



Step 3: Drug containing matrix layer coated on all but open on one side



As seen from the schematic representation, drug release is primarily a function of exposed surface area as other sides are covered by impermeable coat.

The exposed surface area through which dissolution of the drug occurs is generated by rupture of the coat which is in the proximity of an openable layer (Step 2).

Reviewer's Comment: *The release mechanism for Levetiracetam Extended Release Tablets shows that the dissolution may be condition independent.*

2. The Compositions of the Proposed Drug Product

Table 1 presents the composition of the formulations for the newly proposed 1000 mg and 1500 mg strengths of the drug product.

TABLE 1

Composition of Drug Product

Components	Amount (mg)/Tablet		Amount % w/w
Strength	1000 mg	1500 mg	1000 mg and 1500 mg
	(b) (4)		
Levetiracetam, USP	1000.00	1500.00	(b) (4)
Povidone (b) (4) USP			(b) (4)
Hypromellose (b) (4) USP (b) (4) (b) (4)			
Amino Methacrylate Copolymer, NF (b) (4)			
Colloidal silicon dioxide, NF			
Magnesium stearate, NF (b) (4)			
Talc, USP (b) (4)			

Components	Amount (mg)/Tablet		Amount % w/w
Strength	1000 mg	1500 mg	1000 mg and 1500 mg
	(b) (4)		
Silicified Microcrystalline Cellulose, NF (b) (4)			
Crospovidone, NF (b) (4)			
Sodium lauryl sulfate, NF			
FD and C Blue No. 1 Aluminum Lake (b) (4)			
			(b) (4)
Ethyl cellulose (b) (4) (b) (4)			(b) (4)
Dibutyl Sebacate, NF			
Triethyl Citrate, NF			
Polysorbate 20, NF (b) (4) (b) (4)			

(b) (4)

Reviewer's Comment: *As presented in the above Table 1, the two new proposed 1000mg and 1500 mg strengths are compositionally proportional.*

3. Biowaiver request for the lower strength

A bioequivalence study was conducted for the higher 1500 mg strength and the Applicant requested a biowaiver for the lower 1000 mg strength based on the following:

- The lower strength (1000 mg) and the higher strength (1500 mg) are similar in their active and inactive ingredients as shown in Table 1 listed in Section.

- Dissolution studies in various dissolution media (i.e. proposed medium; pH 4.5 Buffer, pH 1.2 Buffer, pH 6.0 Buffer and pH 6.8 Buffer) were carried out for profile comparisons between the Levetiracetam Extended Release Tablets 1000 mg and 1500 mg. The similarity factors (f2) were calculated.

The dissolution parameters used were as follows.

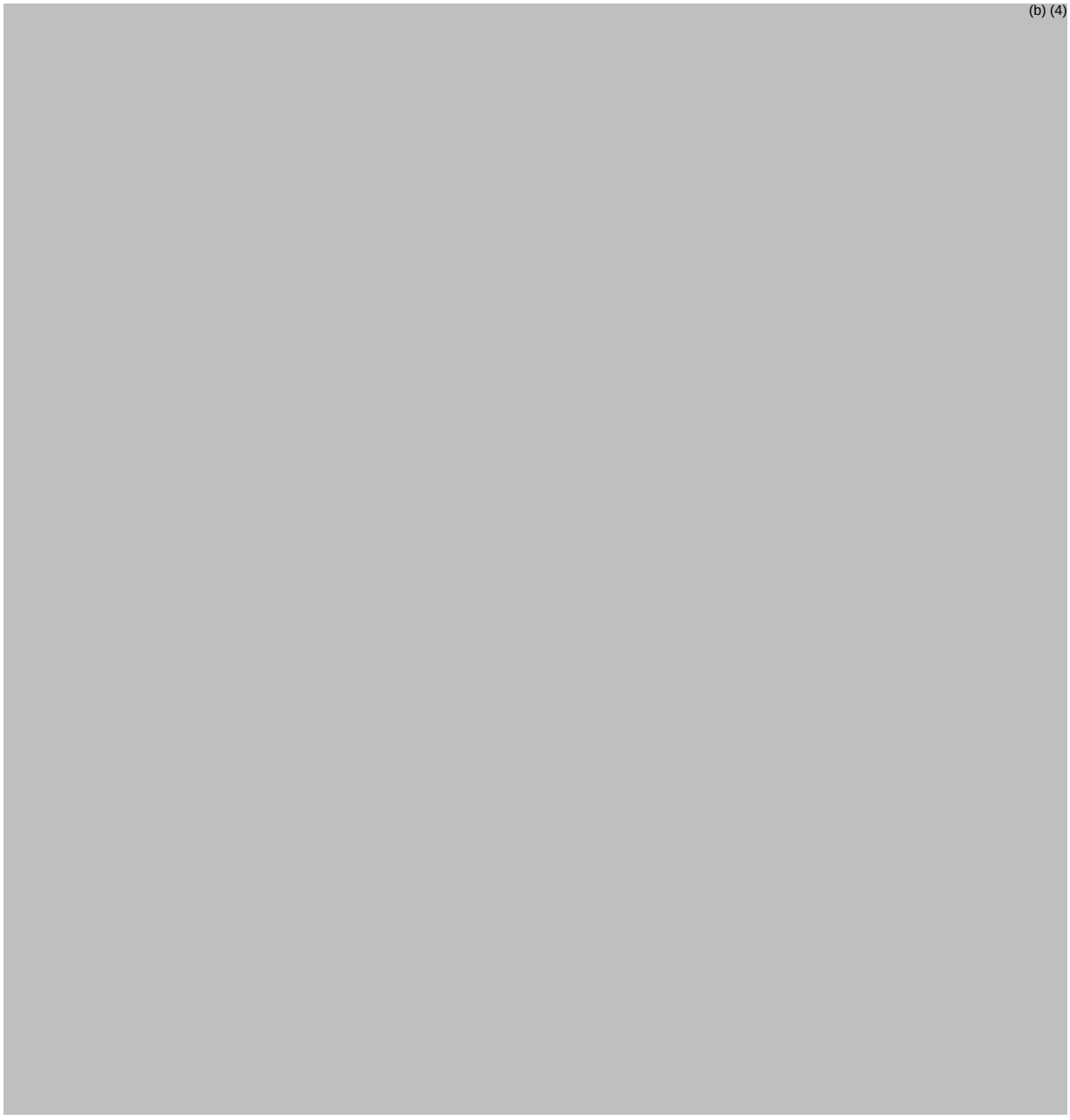
Apparatus: USP Apparatus III (b) (4)
Agitation: 15 dip per minute.

Medium:	4 media as specified in the following figure and table.
Temperature:	37°C ± 0.5 °C.
Volume:	230 mL.
Time:	1, 2, 3, 4, 6, 8, 10 and 12 hours.
Filter:	Nylon 0.45 µ membrane filter.

The following Table 2 and Figure 1 show the results of dissolution profile comparison in pH 4.5 buffer.

TABLE 2

(b) (4)



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(b) (4)

Reviewer's Comments: *The biowaiver request is supported by adequate information. Levetiracetam Extended Release Tablets 1000 mg is compositionally similar to Levetiracetam Extended Release Tablets 1500 mg. The release profiles of Levetiracetam Extended Release Tablets 1000 mg are similar (f2 factor more than 50) to Biobatch - Levetiracetam Extended Release Tablets 1500 mg in pH 1.2, pH 4.5, pH 6.0 and pH 6.8 dissolution media. Therefore, the biowaiver request is granted, provided the bioequivalence study is acceptable by the Office of Clinical Pharmacology.*

4. Proposed Dissolution Methodology

The dissolution method development report supporting the proposed methodology was provided, in which different apparatus, media and agitation speeds were investigated. The following conditions were selected.

Apparatus:	USP III (reciprocating cylinder)
Medium:	pH 4.5 buffer
Volume:	230 mL
Agitation speed:	15 dips/min

The rationale for the selected testing conditions is summarized below:

1) The selection of dissolution medium

It should be noted that the FDA's OGD website describes the following dissolution conditions for Levetiracetam Extended Release Tablets:

Apparatus:	USP Apparatus 1 (Basket)
Medium:	900 mL of 0.05 M Phosphate Buffer, pH 6.0 at 37.0 ºC ± 0.5ºC.
Speed:	100 rpm.
Time:	1, 2, 4, 6, 8 and 12 Hours.

During the dissolution method development, the Applicant used OGD's recommended methodology and the results of the dissolution profile of Levetiracetam Extended Release Tablets 1000 mg and 1500 mg as per above dissolution conditions are tabulated below in Tables 6 and 7, respectively**.**

(b) (4)

5. Setting of Acceptance Criteria for the Dissolution Test

Through the investigations in the above section, the following testing conditions were used for the collection of data used to set the acceptance criteria.

Apparatus:	USP III (reciprocating cylinder)
Medium:	pH 4.5 buffer
Volume:	230 mL
Agitation speed:	15 dips/min

In the original submission, the Applicant proposed the following time points and acceptance criteria for dissolution.

1 hour:	(b) (4) %
4 hour:	%
12 hour:	NLT (b) (4) %

During the filing communication dated August 10, 2012, the following comments were sent to the Applicant.

> *Your proposed acceptance criteria for the dissolution test should be fully justified with data. Therefore, provide the complete dissolution profile data and any other information/data (i.e., IVIVC, BE, etc.) supporting your selection. Note that the dissolution acceptance criteria for your product should be based on the following:*
>
> - *The dissolution profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your product (i.e., specification sampling time points and specification ranges).*
>
> - *The in vitro dissolution profiles should encompass the timeframe over which at least (b) (4) % of the drug is dissolved or where the plateau of drug dissolved is reached if incomplete dissolution is occurring.*
>
> - *The acceptance criteria should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).*
>
> - *At least three specification time-points covering the initial, middle, and terminal phases of the complete dissolution profile data should be set. The specification ranges should be based on the overall dissolution data generated at these times.*
>
> - *The selection of the dissolution specification ranges is based on mean target value ± 10% and NLT (b) (4) % for the last specification time-*

point. Wider specification ranges may be acceptable if they are supported by an approved In Vitro-In Vivo Correlation (lVIVC) model or an approved bioequivalence (BE) study demonstrating that the proposed lower and higher specification ranges are bioequivalent.

On October 11, 2012, the Applicant provided the following revision for the 1 and 4 hours time points.

TABLE 14

Previous Specification		Proposed	
1 Hour:	(b) (4)	1 Hour:	(b) (4)
4 Hour:		4 Hour:	

(b) (4)

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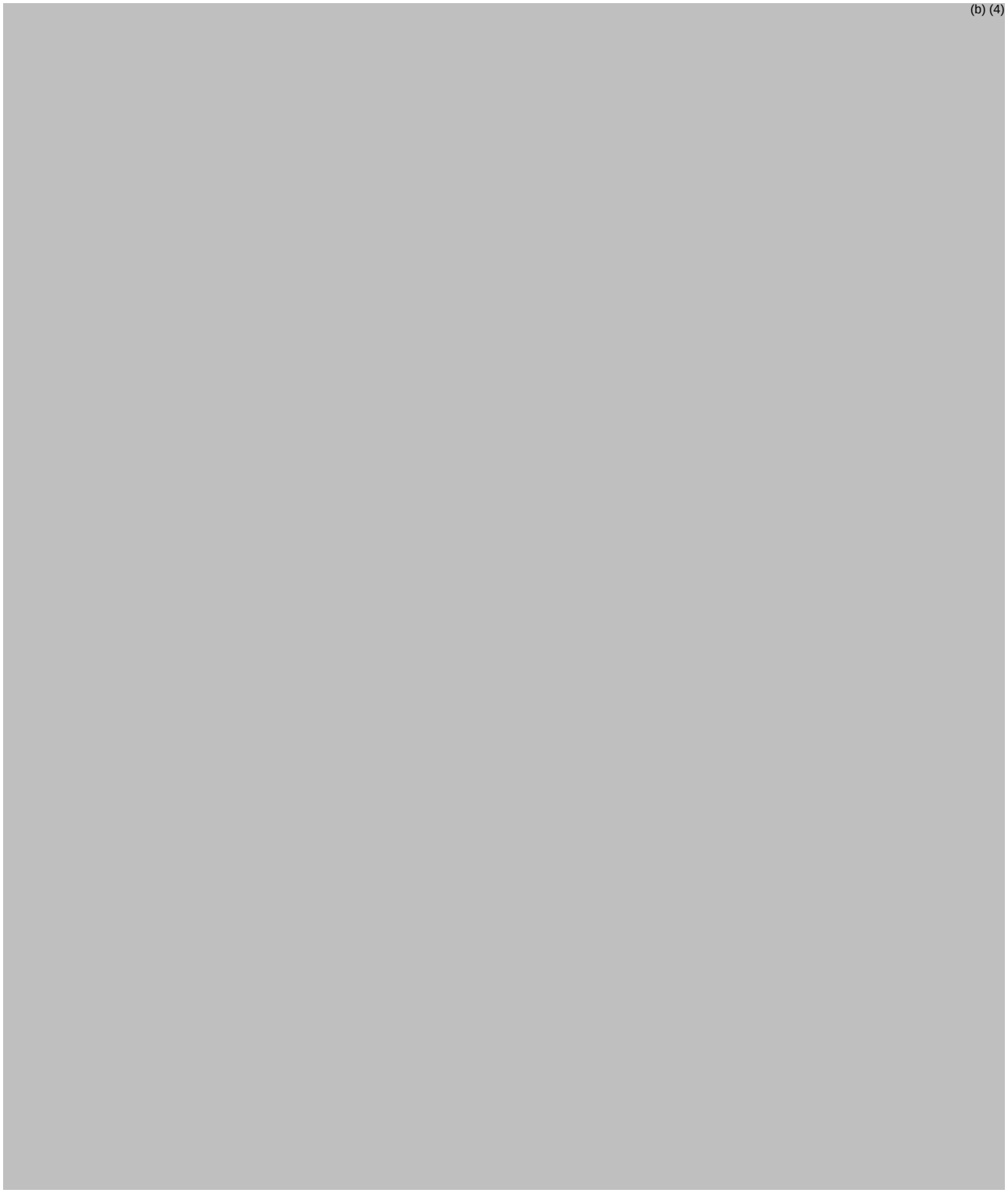


Reviewer's Comments: The information provided shows a potential of dose dumping in the presence of high (b) (4)% alcohol concentrations. The Clinical and the Clinical Pharmacology Reviewers have been informed of the dose dumping effect and they should provide a recommendation regarding the need or not for an in vivo drug interaction study with alcohol for Levetiracetam ER Tablets.

6. Extended release claim

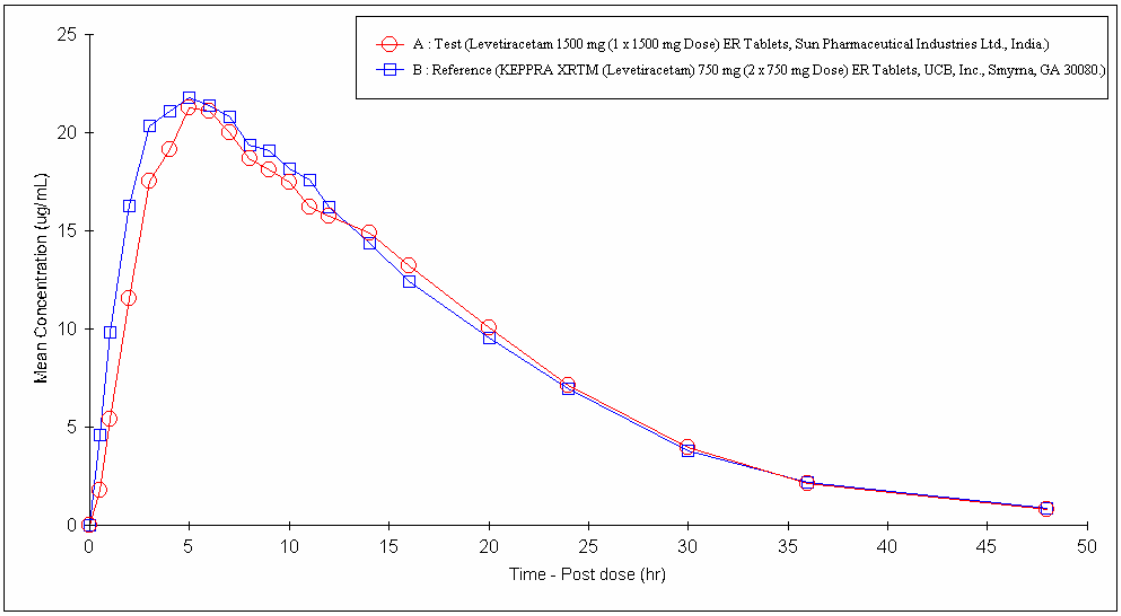
This is a 505(b)(2) submission and KEPPRA XR (levetiracetam) Extended-Release Tablets was used as the reference listed drug product, which is an approved product with an extended release claim. The following Table 15 and Figure 18 show the comparison of the mean plasma concentrations between the test and the reference products for 1500 mg strength.

TABLE 15 Mean (%CV) Pharmacokinetic Parameters and Analysis of Levetiracetam under Fasting Conditions (Study PKD_10_130; N=18)

Parameter (unit)	Arithmetic Means		Ratio of Least-Square Means[1]	90% Geometric CI
	Levetiracetam ER 1500-mg Tablets	Keppra XR® 2×750-mg Tablets		
C_{max} (µg/mL)	23.2 (27.9)	23.8 (21.4)	95.84	81.80 to 112.27
AUC_{0-t} (µg·h/mL)	402.4 (24.1)	416.1 (30.7)	97.74	83.40 to 114.54
$AUC_{0-\infty}$ (µg·h/mL)	411.1 (24.2)	426.1 (31.5)	97.67	83.27 to 114.56
T_{max} (h)[2]	5.0 [3.0 – 16.0]	4.0 [3.0 – 11.0]	--	
$T_{1/2}$ (h)	7.7 (11.2)	7.9 (12.8)	--	
K_{el} (h^{-1})	0.091 (11.4)	0.089 (13.1)	--	

[1] Test (Levetiracetam ER Tablets) to Reference (Keppra XR®)
[2] Median [range]

Figure 18: Mean Concentration Profile of Levetiracetam under Fasting Conditions (Study PKD_10_130; N=18)



As shown in the figure, the test product under fasting condition and fed condition is, on average, similar to the reference product, which is approved for the extended release claim. Therefore, the proposed product is expected to show extended release characteristics.

Reviewer's Comment: *The extended release characteristics of the proposed product are confirmed.*

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/s/

JOHN Z DUAN
02/28/2013

ANGELICA DORANTES
02/28/2013