CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207958Orig1s000

CHEMISTRY REVIEW(S)

Recommendation:
Approval

NDA 207958
Review # 1

Drug Name/Dosage Form	Levetiracetam Tablet
Strength	250 mg, 500mg, 750 mg, 1000mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Aprecia Pharmaceutical Company
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original NDA	October 1, 2014
Quality Amendment	November 12, 2014
Quality Amendment	December 1, 2014
Quality Amendment	December 30, 2014
Quality Amendment	January 8, 2015
Amendment	February 27, 2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Application Technical Lead	Mansoor Khan	OTR/Division of Product Quality Research
Drug Substance	Martha Heimann	ONDP/Division of New Drug Products I/Branch I
Drug Product	Thomas Wong	ONDP/Division of New Drug Products I I/Branch I
Process	Akm Khairuzzaman	OPF/Division I/Branch I
Microbiology	Jessica Cole	OPF/Division IV/Branch III
Facility	Vibhakar Shah	OPPQ/Division of Internal Policies and Programs/Branch II
Biopharmaceutics	Maziar Kakhi	ONDP/Division of Biopharmaceutics/Branch I
OTR Representative	Ziyaur Rahman	OTR/Division of Product Quality Research
Labeling	Andrei Ponta	ONDP/Division of New Drug Products I/Branch I
Project/Business Process	Teshara G. Bouie	OPRO/Division II/Branch IV

Manager		

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II	(b) (4)	Levetiracetam as manufactured by (b) (4)	Adequate	5/28/2015	
	Type III			4		
	Type III			4		
	Type III			4		
	Other					

[1] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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

Not Applicable

2. CONSULTS:

Not Applicable

Executive Summary

I. Recommendation: From a Quality (CMC) perspective, approval is recommended.

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues
2. Action letter language, related to critical issues such as expiration date
3. Benefit/Risk Considerations

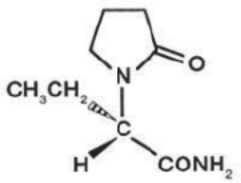
Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The sponsors are advised to continue to find ways to control the tablet hardness and ensure that none of the tablet's hardness falls below (b) (4). This is likely to ensure tablet integrity and dose accuracy for patients. The post approval stability protocol will include, at minimum, first three production batches of each of the strengths and at least one batch of each strength produced during particular calendar year thereafter at a storage condition of 25°C (b) (4) with release time points of every three months in the first year, every six months in the second year, and every year thereafter. As per the packaging master batch record, randomly selected blisters from beginning, middle, and end will be chosen from each of the stability batches. Post approval commitments include stability studies of appropriate number of batches if any changes are made to the product, submission of the stability data in the product annual report, withdrawal of the batches where stability data is found to be outside of acceptable limits, and discussion of occurrence of a single deviation with FDA when the deviation does not affect the safety and efficacy of the product. (b) (4)

II. Summary of Quality Assessments

A. Drug Substance/Levetiracetam Quality Summary

Levetiracetam [chemical name: (-)-(*S*)-α-ethyl-2-oxo-1-pyrrolidineacetamide] is a well characterized, small molecule that is the subject of four NDAs for tablets, extended-release tablets, oral solution, and injection under the trade name Keppra®. There are approved generic versions for each dosage form. The structure of levetiracetam is:



Levetiracetam is highly soluble in aqueous media. It is chemically stable in the solid phase. Thus, the physical properties of levetiracetam that may affect manufacture or physical integrity of the 3-D printed tablet product are more critical to product quality and performance. In addition to compliance with the USP monograph for levetiracetam, the drug substance specification includes controls for polymorphic form, particle size and bulk density. The bulk drug substance is manufactured at (b) (4). Manufacturing and control information is incorporated by cross-reference to (b) (4) DMF No. (b) (4). Per information provided in the NDA, levetiracetam is (b) (4)

Levetiracetam drug substance is packaged in standard bulk packaging. The bulk drug is (b) (4)

B. Drug Product Quality Summary

The product is novel as it quickly disintegrates in the mouth and is prepared by a 3D printing process. Unlike orally disintegrating tablets which are usually meant for low dose drugs, the present technology can be used for very high dosed drugs. While the active drug levetiracetam is available in a variety of dosage forms as tablets, ER tablets, solution, and injection, its high strength of individual dosage units of 250, 500, 750, and 1000 mg may pose problems of swallowing for some patients. Therefore, the the applicant, Apprecia licensed a new patented technology 3D printing process (b) (4) to obtain very porous quickly dispersible tablets for ease of swallowing. In the 3D process, (b) (4)

(b) (4) the tablets disperse in the mouth immediately, and that is why the sponsor has set a disintegration time of 10 seconds or less by a USP disintegration test method. (b) (4) tablets are fairly well

controlled with respect to quality. (b) (4) [redacted] he reviewers of drug substance, drug product, process, biopharmaceutics, and microbiology, had questions about hardness, shipping/friability, porosity, disintegration times, but were satisfied with the response they got from the applicant.

Throughout the reviews and inspection process, the sponsors have used the term (b) (4) [redacted] and the quality reviewers have used the term "tablets" for these 3D printed dosage forms. (b) (4) [redacted]

Other dosage forms (b) (4) [redacted] have been discussed before OPQ with assistance from division of labeling before the review goup decided on tablets. At this time there is no consensus agreement on naming the dosage form. It is important that the Agency and the sponsor agree on a term that is mutually agreeable. In their June 15 memo to FDA, the sponsors proposed three options for other names in the order of their preference for agency's consideration. (b) (4) [redacted] (b) (4) [redacted]

Strength:

1. 250 mg, 500 mg, 750 mg, and 1000 mg
2. Description/Commercial Image: Spiritam® (b) (4) [redacted] are (b) (4) [redacted] easy to swallow dosage forms prepared by a 3D printing (inkjet printing principles) technology to create very porous structures for quick disintegration in the mouth. A sip of (b) (4) [redacted] facilitates the swallowing

of dispersed mass in the mouth. These dosage forms are white, round, porous, and spearmint flavored for taste masking.

(b) (4)

3. Summary of Product Design
Product is designed as round porous tablets. (b) (4)

4. Process Selection (Unit Operations Summary): The manufacturing process operations include (b) (4)

(b) (4)

C. **Summary of Drug Product Intended**

Proprietary Name of the Drug Product	Spritam®
Non Proprietary Name of the Drug Product	levetiracetam (b) (4) tablets (in discussion)
Non Proprietary Name of the Drug Substance	levetiracetam
Proposed Indication(s) including Intended Patient Population	**Proposed Clinical Indications:** The indications proposed for our SPRITAM® (levetiracetam (b) (4)) product are the same as the currently approved indications for the RLD, KEPPRA tablets for oral use, NDA 021035 that received the initial U.S. approval in 1999. Partial Onset Seizures: Levetiracetam is indicated as adjunctive therapy in the treatment of partial onset seizures in adults and children (b) (4) of age and older with epilepsy. Myoclonic Seizures In Patients With Juvenile Myoclonic Epilepsy: Levetiracetam is indicated as adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents 12 years of age and older with juvenile myoclonic epilepsy.

	Primary Generalized Tonic-Clonic Seizures: Levetiracetam is indicated as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children 6 years of age and older with idiopathic generalized epilepsy.
Duration of Treatment	*Partial Onset Seizures* (b) (4) • (b) (4) and Older: 500 mg twice daily, increase as needed and tolerated in increments of 500 mg twice daily every 2 weeks to a maximum recommended dose of 1500 mg twice daily *Myoclonic Seizures in Adults and Pediatric Patients 12 Years and Older* • 500 mg twice daily, increase by 500 mg twice daily every 2 weeks to recommended dose of 1500 mg twice daily *Primary Generalized Tonic-Clonic Seizures* (b) (4) • (b) (4) and Older: 500 mg twice daily, increase by 500 mg twice daily every 2 weeks to recommended dose of 1500 mg twice daily
Maximum Daily Dose	3 g (1500 mg twice daily)
Alternative Methods of Administration	Product is to be taken with a sip of (b) (4) for quick disintegration in mouth.

D. Biopharmaceutics Considerations

1. BCS Classification:
   - Drug Substance: Applicant did not request BCS designation
   - Drug Product: Applicant did not request BCS designation

2. Biowaivers/Biostudies
    - Biowaiver Requests: Yes. Biowaiver request for proposed lower strengths (250 mg, 500 mg and 750 mg) has been granted.
    - PK studies: Yes. A 3-way crossover BA/BE study (LVA-P3-439/CL-LEV-001-R001) was conducted to compare PK profiles of levetiracetam between single dose of Spritam and Keppra IR at 1000 mg under fasted conditions; in addition, food effect of 1000 mg of Spritam was evaluated in the study. Reviewed and approved by Clinical Pharmacology (06/05/2015)
    - IVIVC: Not applicable.

E. **Novel Approaches:** A completely novel emerging technology of 3D printing method was used to manufacture very porous tablets.

F. Any Special Product Quality Labeling Recommendations

Depending upon the eventual acceptance of nomenclature of tablets (b) (4) or something else, appropriate labelling should ensure that these porous tablets are no directly substituted with (b) (4) levetiracetam tablets. (b) (4)

G. Life Cycle Knowledge Information (see Attachment A)

Drug Substance:
Prior to NDA submission, the applicant was informed by the drug substance supplier, (b) (4), that the (b) (4) site will discontinue manufacture of levetiracetam in the future. The Agency provided advice regarding the data required to support use of levetiracetam manufactured at the (b) (4) facility in (b) (4) during the pre-NDA meeting. Given the novelty of the 3-D printing process, the firm was advised to provide physical and chemical comparisons of the (b) (4) and (b) (4) sourced drug substances, and the resulting product. Additionally, the firm was advised to provide 3 months long term and accelerated stability data for three batches per strength of product manufactured from (b) (4) sourced bulk drug substance. When the NDA was submitted, the firm did not propose the (b) (4) site for commercial manufacture or provide any supporting data for the site.
The applicant submitted a comparability protocol to qualify the (b) (4) site, (b) (4)

Drug Product:
The manufacturing process, 3D printing is a new technology to produce solid oral tablets. These, tablets are (b) (4)

(b) (4)

[redacted]

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Mansoor Khan, Ph.D., OTR/Division of Product Quality Research

Mansoor A. Khan -S

Digitally signed by Mansoor A. Khan -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300230634, cn=Mansoor A. Khan -S
Date: 2015.07.02 16:27:45 -04'00'

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ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

23. **Are the in-vitro dissolution test and acceptance criteria adequate for assuring consistent bioavailability of the drug product?**

In this 505(b)(2) submission for NDA 207958 (Spritam), the *in-vitro* dissolution test is not part of the finished drug product release specifications. Instead, disintegration is proposed *in lieu* of dissolution for release and stability testing. Consequently, the Biopharmaceutics review presented below will primarily address if the proposed disintegration test and acceptance criterion are adequate for assuring consistent bioavailability of the drug product. Furthermore, this review will assess the proposed waiver for the submission of bioavailability (BA) of the proposed levetiracetam tablets (250 mg, 500 mg and 750 mg) based on BA/BE data for the higher strength. The biowaiver request is based on the Applicant's submitted comparative *in vitro* dissolution studies.

Background

Levetiracetam tablets (Keppra immediate release tablets, 250 mg, 500 mg and 750 mg) have been reviewed and approved (November 30, 1999) under NDA 21035[3]. The package insert for Keppra states that its solubility in water is 1.04 g/ml. Levetiracetam was classified as a BCS class 1 product by the BCS committee in May 2004 (based on supportive data from NDA 21035) according to the database managed by the Office of Generic Drugs. The Applicant in the current NDA 207958 under review has not yet made a formal request (with supporting data) for a BCS 1 designation for the drug substance and/or drug product.

[3] The 1000 mg strength was approved on January 6, 2006 under submission NDA 21035/S-048.

In NDA 207958 the Applicant proposes to use 3D printing technology to manufacture the drug product dosage form. The resulting 'tablet' matrix is more porous than conventionally manufactured tablets (b) (4). The proposed 3D printed tablet is formulated (b) (4) dosage form that disintegrates (in under (b) (4) seconds) in the mouth when taken with a "sip" (b) (4) of (b) (4). Due to the extremely high solubility of Levetiracetam, the active component can be expected to dissolve as soon as the dosage form disintegrates.

Based on the official minutes (dated April 26, 2013) of a Type B pre-IND meeting (PIND 117613)[4] on March 28, 2013, the Applicant stated that despite their attempts to manufacture drug product outside of the normal manufacturing process, dissolution of the product remained extremely rapid and the method was not able to discriminate formulations made within and outside of the acceptable manufacturing ranges. The FDA proposed that the Applicant submit all the dissolution method validation data in the NDA to support the lack of discriminating ability of the method. The Applicant stated that the changes in hardness of the product resulted in changes in disintegration time but had no impact on dissolution. The FDA suggested that the sponsor may consider the use of a disintegration test in lieu of dissolution if the conditions stated in the decision tree (Setting Acceptance Criteria for Drug Product Dissolution) as per ICHQ6A are met. The FDA also reminded the Applicant that even though disintegration may be adequate and dissolution may not be needed as a quality control specification, all the dissolution data must be submitted in the NDA for review. Additionally, the FDA stated that if the Applicant is planning on submitting a biowaiver request for the lower strengths of the drug product, dissolution data must be submitted.

In the NDA submission the Applicant's stated reasons for the use of the disintegration test in place of the dissolution test for all finished product release and stability testing are as follows:

- The dosage form is intended to disintegrate rapidly in the mouth.
- The drug has high aqueous solubility (1.04 g/ml) which is unaffected by pH.
- The dissolution of the drug from the dosage form is very rapid ((b) (4)% in less than (b) (4)min) at a pH of 1.2, 4.5, and 6.8; and all registration batches have been shown to have both rapid disintegration and rapid dissolution.
- Disintegration is the rate limiting step for dissolution of the product.
- The drug is nearly (b) (4)% bioavailable after oral administration.

<u>Reviewer's Comments</u>: The Applicant's rationale to propose the disintegration test in place of the dissolution test for finished product release and stability testing is adequate.

<u>Assessment of the Proposed Disintegration Test</u>

[4] \\cdsesub1\evsprod\nda207958\0000\m1\us\16-meet\correspond-meeting-let-fda-20130426.pdf

The Applicant's submission from October 1, 2014 only refers to the USP general chapter <701> for its description of this analytical testing procedure[5]. Results reported in section 3.2.P.5.4 (Batch Analyses)[6] show disintegration times to b (b) (4) seconds (b) (4) for all registration batches tested at release. It should be noted that these registration batches cover all proposed strengths of the drug product (in triplicate). As part of the Filing Communication (December 4, 2014) the Applicant was requested:

1. To provide a complete report detailing instrumentation and determination (and accuracy) of the disintegration end time point.

   In its response letter (January 8, 2015) the Applicant indicated that a (b) (4) unit was employed. A more detailed method validation report (# QC-AM-054-R01) was submitted in the February 27, 2015 amendment[7]. The test is conducted according to the following conditions listed in Table 1:

Table 1: Proposed disintegration method for Levetiracetam tablets, 250 mg, 500 mg, 750 mg and 1000 mg.

Apparatus	(b) (4)
Stroke frequency	
Stroke length	
Medium	
Volume	
Media Temperature	

(b) (4)

(b) (4)

Reviewer's Comments: The (b) (4) tester conforms with the dimensional tolerances specified in the USP general chapter <701>. The Applicant's confirmation that the disintegration test will performed in accordance with USP <701> with respect to run time and out-of-specification determinations are considered adequate. The proposed medium for the disintegration test is adequate.

2. Provide supporting data demonstrating the sensitivity of the disintegration test to critical product quality attributes (including hardness).

In its response letter (January 8, 2015) the Applicant provided very limited data to address this request. (b) (4)

Reviewer's Comments: The Applicant's comment implies that hardness cannot be controlled. Consequently, the disintegration test's discriminating ability with respect to hardness could not be verified adequately.

Assessment of the Proposed Dissolution Test

The dissolution method for Levetiracetam tablets is referenced in a USP monograph and the FDA dissolution drug database. The proposed dissolution method for NDA 207958 Levetiracetam tablets, 250 mg, 500 mg, 750 mg and 1000 mg is presented in Table 2. It differs from the approved method for the listed drug (Keppra), the USP monograph and FDA database, in the choice of dissolution medium – the latter three all specify (b) (4). NDA 207958 proposes pH (b) (4) as the dissolution

medium because of discussions between the Applicant and the FDA under PIND 117613. In an FDA response to the Applicant in correspondence dating from July 19, 2013[9] regarding the preferred choice of dissolution medium (b) (4) the FDA responded, "*It is our recommendation that you define the pH of the dissolution medium.*" Consequently, the Applicant adopted pH (b) (4) for all subsequent dissolution studies primarily because they assert that pH (b) (4) buffer solution provides for a pH-controlled dissolution medium.

Table 2: Proposed Dissolution method for Levetiracetam tablets, 250 mg, 500 mg, 750 mg and 1000 mg (Source: 3.2.P.5.2 Analytical Procedures and Report QC-AM-043-R02).

Apparatus	USP apparatus II (paddle)
Agitation speed	(b) (4)
Sampling Time	
Medium	
Volume	
Media Temperature	
HPLC UV Detection	

The Applicant performed a comparative dissolution study to investigate the effect of (b) (4) versus (b) (4). The results are presented in the dissolution method validation report (Report# MV-21-ROO-RPT, reviewed in detail in the section below). Table 3 below shows drug release at the (b) (4) minute time point for a pre-registration batch (lot # PTR-0044) corresponding to the 1000 mg strength.

(b) (4)

Reviewer's Comments: Given the very high aqueous solubility of Levetiracetam (irrespective of pH), the very short disintegration time of the 3D printed dosage form, it is concluded that the choice of (b) (4) in place of (b) (4) is immaterial. This is further confirmed by the results of Table 3. Furthermore, dissolution is only being used to address the biowaiver request for the proposed lower strengths (250 mg, 500 mg and 750 mg), whereby dissolution needs to be considered in several media spanning the physiological pH range, not just one particular pH.

[9] \\cdsesub1\evsprod\nda207958\0000\m1\us\16-meet\correspond-meeting-let-fda-20130719.pdf

Assessment of Dissolution Method Validation Report

The Applicant submitted a method validation report (MV -021-ROO-RPT[10]) to qualify the specificity, linearity, accuracy, system suitability, instrument precision, repeatability, robustness, solution stability and filter compatibility of the analytical procedure used to quantify the level of drug release in samples taken during the dissolution of Levetiracetam tablets. The dissolution test was performed according to the conditions presented in Table 2. A pre-registration 1000 mg strength tablet (lot # PTR-0044) was used for the studies. The PTR-batches are referenced in Table 7 of the Pharmaceutical Development report (p.16) and involve batch formulae similar or identical to the registration batches.

System Suitability

The System suitability was evaluated in each sequence during the entire validation and summarized in Table 4.

Table 4: Summary of system suitability results.

Sequence (Reference)	% RSD	Mean USP Tailing	Plate Count (N)	% Recovery	
				Check Standard	Bracketing Standard
(b) (4)					
Results	Pass	Pass	N/A	Pass	Pass

The RSD of the Levetiracetam working standard solution injections, average USP tailing factor and mean USP plate count are based on five samples.

Specificity

(b) (4)

(b) (4)

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(b) (4)

[redacted]

Reviewer's Assessment:

Proposed Disintegration Test:

The Applicant stated under PIND 117613 that disintegration was sensitive to tablet hardness. In its response to an information request, the Applicant reported that (b) (4) [redacted] **However, the primary concern from a Biopharmaceutics perspective is to ensure disintegration occurs in no more than** (b) (4) **seconds so that the relatively large dosage form may be adequately dispersed in the mouth when administered to the patient with a sip of** (b) (4)**. The proposed disintegration test does address this concern and is therefore considered acceptable.**

Proposed Dissolution Test:

The proposed dissolution test is found to be adequate with respect to choice of dissolution apparatus and medium and is therefore acceptable for the proposed commercial formulation and for the determination of the biowaiver request for the 250 mg, 500 mg, and 750 mg strengths.

The specificity, linearity, accuracy, precision, and solution stability of the proposed analytical procedure have been adequately demonstrated and are therefore acceptable.

Proposed Biowaiver Request for 250 mg, 500 mg, 750 mg Strengths
The biowaiver is granted for the lower strengths.

Bridging of the to-be-marketed product to Clinical Trial Formulations:
There are no bridging concerns in this submission because the formulation used in all the clinical studies is the proposed commercial formulation manufactured on the on the proposed commercial equipment.

Polymorphism:
The CMC review of the listed drug (Keppra, NDA 21035) from May 21, 1999 concluded that "the sponsor will not need to monitor (b) (4) **since the drug substance does not exhibit polymorphism". The Drug Substance review observes that since the approval of Keppra in 1999 polymorphs have been identified. In email communication Dr. Martha Heimann indicated that there is a control for polymorphic form in the drug substance and that the probability of polymorphic formation during and post-manufacture is very unlikely. Consequently, there are no concerns regarding polymorphism.**

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature:

The Division of Biopharmaceutics has reviewed the *in vitro* release information/data and the biowaiver request provided in NDA 207958 and considers that this information supports the approval of the Application. From a Biopharmaceutics perspective, NDA 207958 for Levetiracetam Tablets, 250 mg, 500 mg, 750 mg and 1000 mg, is recommended for APPROVAL.

Maziar Kakhi, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
ONDP/OPQ

Supervisor Comments and Concurrence:
I concur with Dr. Kakhi's assessment and recommendation of approval for NDA 207958.

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
ONDP/OPQ

ASSESSMENT OF MICROBIOLOGY

25. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Yes.

Reviewer's Assessment:

The (b) (4) controls and stability testing schedule are adequate to assure the microbial quality of the drug product. See the microbiology assessment under question 19 for more information.

2.3.P.7 Container/Closure System

26. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

This is not applicable to a non-sterile tablet.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

27. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response:

There are no ingredients used in the manufacture of levetiracetam (b) (4) that are of human or animal origin.

Reviewer's Assessment: Adequate

The applicant provided certifications from each excipient manufacturer that their ingredients are free from components of human or animal origin.

28. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response:

Not applicable.

Reviewer's Assessment:

Not applicable.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:
The drug product is adequately controlled from a microbiological perspective and is recommended for approval.

Jessica Cole, PhD

Secondary Review Comments and Concurrence:
I concur.

Bryan Riley, PhD

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

29. Is the applicant's claim for categorical exclusion acceptable?

    The applicant claimed for categorical exclusion according to 21 CFR 25.31 (a). However, the applicant needs to add the following statement to their environmental assessment:

    > In addition, to the best knowledge of Aprecia Pharmaceuticals Company, no extraordinary circumstances exist [21 CFR 25.15 (d)].

    In Amendment #0016 dated 5/28/2015, the applicant revised the Environmental Assessment with the addition of the following statement: Also, in accordance with 21 CFR 25.15(d), and to the applicant's knowledge, no extraordinary circumstances exist.

30. Is the applicant's Environmental Assessment adequate for approval of the application?

    Not Applicable.

Reviewer's Assessment: Acceptable

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:

NDA 207958 is recommended for approval.

Thomas Wong, Ph.D., ONDP/Division of New Drug Products I/Branch I

Secondary Review Comments and Concurrence:
I concur.

Wendy I. Wilson-Lee, Ph.D.
Acting Branch Chief
Division New Drug Products I
OPQ/ONDP

I. Review of Common Technical Document-Quality (CTD-Q) Module 1

Labeling & Package Insert

The annotated package insert labeling for the text of the proposed package insert is included in Section 1.14.3.1. As this 505(b)(2) NDA relies on the RLD Keppra® Tablets (NDA 021035) the majority of the annotation for labeling elements, content and format is referenced to the RLD current FDA approved labeling. Any SPRITAM® (levetiracetam) (b) (4) specific information is annotated in Section 1.14.3.1 to the appropriate sections of the NDA supporting the proposed labeling statements. Therefore only the annotated carton and blister labeling will appear in this section.

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Spritam Established Name: Levetiracetam	DMEPA accepted the propriety name on Dec 12, 2014
Dosage form, route of administration	Dosage: "(b) (4)" Route: Oral	Replace (b) (4) with "Tablet"
Controlled drug substance symbol (if applicable)	The product is not a controlled substance.	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Levetiracetam triturate, 250-, 500-, 750-, and 1000-mg.	The strengths are in agreement with the product description.

Conclusion: Acceptable. Final package insert language will be finalized with other review disciplines during labeling meetings.

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

3. DOSAGE FORMS AND STRENGTHS

SPRITAM 250 mg (b) (4) are round, white to off-white, marked with " " on one side.

SPRITAM 500 mg are round, white to off-white, marked with " " on one side.

SPRITAM 750 mg are round, white to off-white, marked with " " on one side.

SPRITAM 1000 mg are round, white to off-white, marked with " " on one side.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Tablets	Acceptable (in NDA, (b) (4) tablet. Applicant will be notified to use the correct dosage form name).
Strengths: in metric system	250, 500, 750, and 1000 mg	Acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	See above reproduced label text.	Acceptable

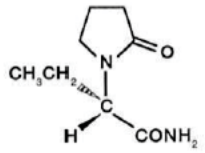
Conclusion: Acceptable. Final package insert language will be finalized with other review disciplines during labeling meetings

#11: Description (21CFR 201.57(c)(12))

SPRITAM is an antiepileptic drug available as 250 mg, 500 mg, 750 mg, and 1000 mg round, white to off-white, dye-free, spearmint-flavored [redacted] (b) (4) for oral administration.

The chemical name of levetiracetam, a single enantiomer, is (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide, its molecular formula is $C_8H_{14}N_2O_2$ and its molecular weight is 170.21. Levetiracetam is chemically unrelated to existing [redacted] (b) (4) (AEDs).

It has the following structural formula:



Levetiracetam is a white to off-white crystalline powder with a faint odor and a bitter taste. It is very soluble in water (104.0 g/100 mL). It is freely soluble in chloroform (65.3 g/100 mL) and in methanol (53.6 g/100 mL), soluble in ethanol (16.5 g/100 mL), sparingly soluble in acetonitrile (5.7 g/100 mL) and practically insoluble in n-hexane. (Solubility limits are expressed as g/100 mL solvent).

SPRITAM [redacted] (b) (4) levetiracetam. Inactive ingredients: colloidal silicon dioxide, glycerin, mannitol, microcrystalline cellulose, polysorbate 20, povidone, sucralose, butylated hydroxyanisole, and natural and artificial spearmint flavor.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Spritam (levetiracetam)	DMEPA accepted the propriety name on Dec 12, 2014
Dosage form and route of administration	Tablets for oral administration*	Acceptable
Active moiety expression of strength with equivalence statement for salt (if applicable)	250 mg, 500 mg, 750 mg and 1000 mg*	Acceptable
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	See above reproduced label text	Acceptable
Statement of being sterile (if applicable)	N/A oral product	
Pharmacological/ therapeutic class	Antiepileptic	Acceptable
Chemical name, structural formula, molecular weight	See above reproduced label text	Acceptable
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa, solubility, or pH)	Stated water solubility*	Acceptable
		* See above reproduced label text.

Conclusion: Acceptable. Final package insert language will be finalized with other review disciplines during labeling meetings.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Each SPRITAM [redacted] is supplied in child-resistant blisters as follows:

250 mg [redacted] round, white to off-white [redacted] marked with "[redacted]" on one side. [redacted] 60 [redacted] containing 6 blisters per card x 10 cards. (NDC 43485-101-60)

500 mg [redacted] round, white to off-white, [redacted] marked with "V" on one side. [redacted] 60 [redacted] containing 6 blisters per card x 10 cards. (NDC 43485-102-60)

750 mg [redacted] round, white to off-white [redacted] marked with "E" on one side. [redacted] 60 [redacted] containing 6 blisters per card x 10 cards. (NDC 43485-103-60)

1000 mg [redacted] round, white to off-white. [redacted] marked with "L" on one side. [redacted] 60 [redacted] containing 6 blisters per card x 10 cards. (NDC 43485-104-60)

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	250 mg, 500 mg, 750 mg and 1000 mg*	Acceptable
Available units (e.g., bottles of 100 tablets)	60 tablets per blister card*	Acceptable (in NDA, [redacted] tablet. Applicant will be notified to use the correct dosage form name)
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	See above reproduced label text	Acceptable
Special handling (e.g., protect from light, do not freeze)	None	Acceptable
Storage conditions	Store at room temperature 25°C (77°F); excursions permitted to 15°C to 30°C (59°F and 86°F) .	Acceptable
		* See above reproduced label text.

Manufacturer/distributor name listed at the end of PI, following Section #17

SPRITAM is manufactured by

Aprecia Pharmaceuticals Company, East Windsor NJ 08520

SPRITAM® is a registered trademark of Aprecia Pharmaceuticals Company.

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	See above reproduced label text	Acceptable

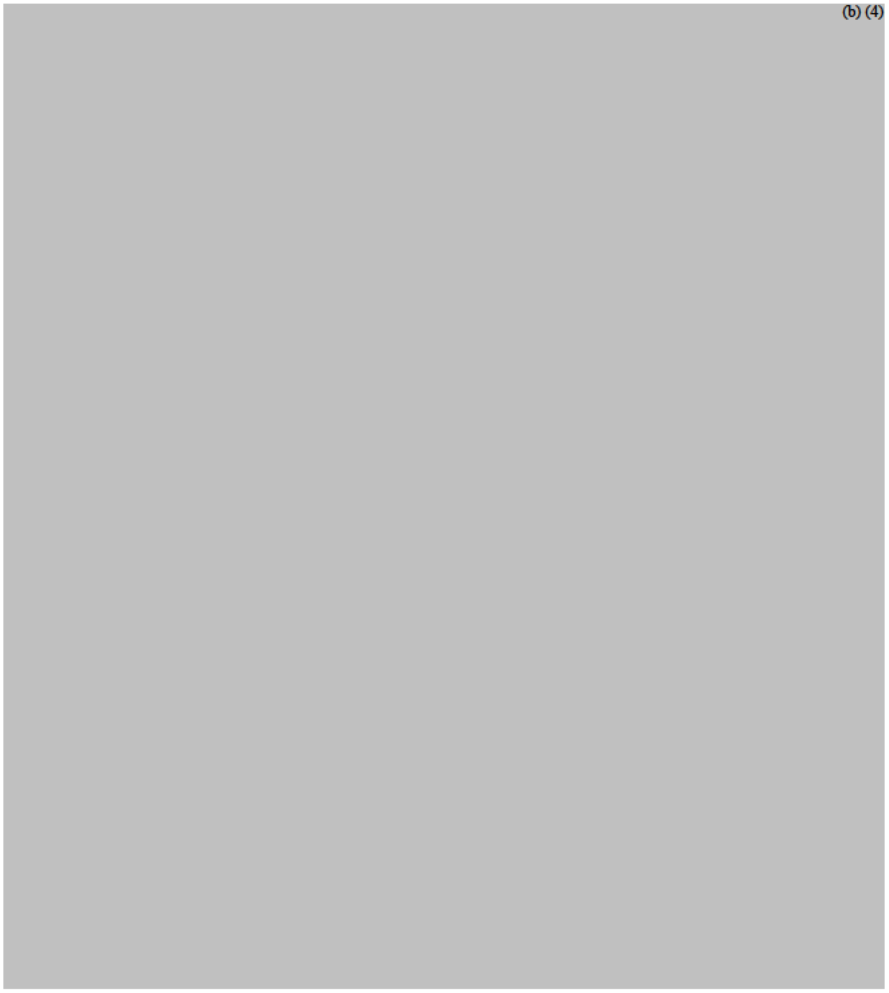
Conclusion: Acceptable. Final package insert language will be finalized with other review disciplines during labeling meetings.

2. Labels

1) Immediate Container Label

Below is the blister label for the 1000-mg strength tablet. The blister labels for 750-, 500-, and 250-mg are the same as the 1000-mg strength tablet with the exception of strength identification and NDC number. Note: in NDA (b) (4) instead of tablet. Applicant will be notified to use the correct dosage form name.

(b) (4)



Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The font size and prominence of both proprietary and establish name is adequate.	Final decisions will be made jointly with DMEPA
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Expression of all strengths is acceptable (see comment on the package insert highlight section of Dosage Forms and Strengths).	Final decisions will be made jointly with DMEPA
Net contents (21 CFR 201.51(a))	N/A blister	
Lot number per 21 CFR 201.18	Space is provided for entry.	Acceptable
Expiration date per 21 CFR 201.17	Space is provided for entry.	Acceptable
"Rx only" statement per 21 CFR 201.100(b)(1)	No "Rx only" statement	Will discuss during labeling meeting
Storage (not required)	Not required. Stated in blister pack	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC number for each strength is printed on the back of the blister	Acceptable
Bar Code per 21 CFR 201.25(c)(2)**	Printed on the label	Acceptable
Name of manufacturer/distributor	Printed on the label	Acceptable
Others	Area for bending and peeling of the blister is provided on the back of the blister.	Acceptable

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: **Acceptable. Final container label will be finalized with other review disciplines during labeling meetings.** Note: in NDA, (b) (4) instead of tablet. Applicant will be notified to use the correct dosage form name.

2) Cartons

QUALITY ASSESSMENT

Below is the carton label for the 1000-mg strength tablet. The carton labels for 750-, 500-, and 250-mg are the same as the 1000-mg strength tablet with the exception of strength identification and NDC number.

(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	The font size and prominence of both proprietary and establish name is adequate.	Final decisions will be made jointly with DMEPA
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Expression of all strengths is acceptable (see comment on the package insert highlight section of Dosage Forms and Strengths).	Final decisions will be made jointly with DMEPA
Net contents (21 CFR 201.51(a))	Label stated 60 tablets (6 tablets per blister card x 10 cards).	Final decisions will be made jointly with DMEPA
Lot number per 21 CFR 201.18	Space is provided for entry.	Acceptable
Expiration date per 21 CFR 201.17	Space is provided for entry.	Acceptable
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	All inactive ingredients are stated correctly.	Acceptable
Sterility Information (if applicable)	N/A oral product	Acceptable
"Rx only" statement per 21 CFR 201.100(b)(1)	Statement is in label	Acceptable
Storage Conditions	Store at room temperature 25°C (77°F); excursions permitted to 15°C to 30°C (59°F and 86°F). Protect from light.	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC number for each strength tablet is printed on the container label.	Acceptable
Bar Code per 21 CFR 201.25(c)(2)**	Bar code printed on side panel of the carton label	Acceptable
Name of manufacturer/distributor	Printed on the label	Acceptable
"See package insert for dosage information" (21 CFR 201.55)	"Dispense accompanying Medication Guide to each patient" is printed on the carton label.	Acceptable
"Keep out of reach of children" (optional for Rx, required for OTC)	No such precaution statement is printed on the carton label.	Acceptable
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	Instructions with figures for patient use are printed on the carton label.	Acceptable

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:

Andrei Ponta, Ph.D., ONDP/Division of New Drug Products I/Branch I

Conclusion: Acceptable. Final container label will be finalized with other review disciplines during labeling meetings.

Secondary Review Comments and Concurrence:

Wendy I. Wilson-Lee, Ph.D.
Acting Branch Chief
Division New Drug Products I
OPQ/ONDP

II. List of Deficiencies To Be Communicated

None.

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Disintegration	Excipients, manufacturing process	H	Disintegration test	Acceptable	