

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207958Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 207958

SUPPL #

HFD #

Trade Name SPRITAM

Generic Name levetiracetam

Applicant Name Aprecia Pharmaceutical Company

Approval Date, If Known PDUFA due 8.1.15

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES X NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505b2 (RLD to Keppra 21035)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO X

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

SPRITAM (levetiracetam oral product) is an easy-to-swallow formulation that quickly disperses in the mouth with a sip of liquid. SPRITAM can provide an alternative to high-dose traditional Keppra tablets, which aid in patient compliance and ease of dosing for those who have difficulty swallowing large traditional tablets or capsules.

The sponsor submitted the NDA under 505(b)(2) using Keppra (levetiracetam) immediate release (IR) tablets as the reference listed drug (RLD). In this submission, without conducting efficacy trial, the sponsor submitted two clinical pharmacology studies to

support its approval: a BA/BE study (Study LVA-P3-439/CL-LEV-001-R001) bridging SPRITAM and the RLD, and a PK study (Study CL-LEV-003/ Novum 11369701) evaluating levetiracetam PK following administration of SPRITAM without taking water.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity? YES  NO X

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?  
RLD Expired 6.16.15 YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade? YES  NO X

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**  
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES X      NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21035 Keppra Tabs  
21872 Keppra INJ  
22285 Keppra XR

## 2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES       NO X

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

### **PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO X

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

YES  NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

YES

NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

!

IND #

YES

!

! NO

! Explain:

Investigation #2

!

!

IND #

YES

! NO

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

!

!

YES

! NO

Explain:

! Explain:

Investigation #2

!

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

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Name of person completing form: Cathy Michaloski  
Title: Sr. Regulatory Project Manager  
Date: 7.29.15

Name of Office/Division Director signing form: Billy Dunn, MD  
Title: Director, Division of Neurology Products, ODE I

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CATHLEEN B MICHALOSKI  
07/29/2015

WILLIAM H Dunn  
07/31/2015

1.3 Administrative Information

**3. DEBARMENT CERTIFICATION**

Aprecia Pharmaceuticals Company (Aprecia) hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Rob Williford, COO

Aprecia Pharmaceuticals Company

19 Sep 2014

Date

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 207958 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Spritam (Spree-tam) Established/Proper Name: Dosage Form: 250, 500, 750 and 1,000 mg oral tablet		Applicant: Aprecia Pharmaceuticals Company. Agent for Applicant (if applicable):
RPM: Cathleen Michaloski		Division: Division of Neurology Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b></li> </ul> <p><input type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check: 6.18.15            B2 clearance – 6.18.15</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>August 1, 2015</u></li> </ul>		X AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		X None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only):  
*(confirm chemical classification at time of approval)*

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (CDER APPROVALS)
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) 7.31.15
Labeling	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	X Included 6.30.15
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	X Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	X Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	X Included
❖ Proprietary Name <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> </ul>	12.12.14
❖ Labeling reviews ( <i>indicate dates of reviews</i> )	RPM: X None DMEPA: X None DMPP/PLT (DRISK): X None OPDP: X None SEALD: <input type="checkbox"/> None CSS: <input type="checkbox"/> None Product Quality X None Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting ( <i>indicate date of each review</i> )	11/14/14
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2) cleared 6.18.15
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	X Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes X No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>7.17.13 and 10.17.14</u> If PeRC review not necessary, explain: _____</li> </ul> </li> </ul>	
<ul style="list-style-type: none"> <li>❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)</li> </ul>	Information request email (C. Michaloski 7/7/15) Information request letter (B. Dunn 3/25/15) Information request email (C. Michaloski 2/11/15) Proprietary Name Granted Letter (T. Bridges 12/22/14) Information request email (C. Michaloski 12/9/14) Filing Communication (E. Bastings 12/4/14)
<ul style="list-style-type: none"> <li>❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg    5/8/14
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	No mtg    3/28/13
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Advisory Committee Meeting(s)</li> </ul>	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	
<b>Decisional and Summary Memos</b>	
<ul style="list-style-type: none"> <li>❖ Office Director Decisional Memo (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None    7.31.15
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None    7.23.15
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical</b>	
<ul style="list-style-type: none"> <li>❖ Clinical Reviews</li> </ul>	
<ul style="list-style-type: none"> <li>• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	No separate review
<ul style="list-style-type: none"> <li>• Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	7.28.15; 7.24.15 (2 reviews)
<ul style="list-style-type: none"> <li>• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	7.28.15
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None Peds 6.16.15
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	X N/A
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	X None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	X None requested consult to BE/BA OTS (no inspection required due to sites already inspected with last 4 years)
<b>Clinical Microbiology</b> X None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> X None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	X No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review 7.24.15
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 6.5.15; 7.22.15
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	X None requested
<b>Nonclinical</b> X None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input type="checkbox"/> None requested

<b>Product Quality</b> <input type="checkbox"/> None	
❖ <b>Product Quality Discipline Reviews</b>	
• Tertiary review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 7.1.15 (comprehensive review)
• Secondary review (e.g., Branch Chief) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team ( <i>indicate date of each review</i> )	<input type="checkbox"/> None
❖ <b>Environmental Assessment (check one) (original and supplemental applications)</b>	
<input type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ <b>Facilities Review/Inspection</b>	
<input type="checkbox"/> Facilities inspections ( <i>action must be taken prior to the re-evaluation date</i> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> )	<b>X</b> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input type="checkbox"/> Done ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul>	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input type="checkbox"/> Done

## Michaloski, Cathleen

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**From:** Michaloski, Cathleen  
**Sent:** Tuesday, July 07, 2015 9:40 AM  
**To:** sanjay sehgal (sanjay.sehgal@aprecia.com)  
**Subject:** Carton and Container recommendations 207958

**Importance:** High

Dear Dr. Sehgal,

We have the following recommendations from the labeling reviewer for NDA 207958:

### Carton Labeling: Physician Samples Carton and Commercial Carton:

1. We note the use of the colors blue and orange for the carton labeling trade dress. Blue and orange are also used as font and graphic colors to denote the statements of strengths (b) (4) carton labeling. These colors overlap with the trade dress and decrease the prominence of the strength statement. The purple color used for the 500 mg strength does not provide adequate differentiation from the 250 mg (blue) strength. To minimize the potential risk of dispensing errors, we recommend revision of the colors to provide adequate differentiation between strengths. We recommend that the colors used to denote the statement of strength do not overlap with the carton trade dress.
2. In accordance with the draft guidance "*Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*", relocate the designated finished dosage form to be either in the same line as the active ingredient (established name) or directly below the active ingredient (established name).
3. Consider revising the text of the unit of measure, "mg", to be the same font size as the statement of strength to improve readability.
4. Consider revising the statements of strength to read "XXX mg per (b) (4) to clarify the strength per unit and minimize the potential for wrong dose errors.

### Blister Packs: Physician Samples and Commercial

1. In accordance with the draft guidance "*Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*", relocate the designated finished dosage form to be either in the same line as the active ingredient (established name) or directly below the active ingredient (established name).
2. Consider revising the text of the unit of measure, "mg", to be the same font size as the statement of strength.
3. The blister labels (sample and commercial) contain several instructional statements including "Bend and Tear", "Bend and Peel" and "Do Not Push or Crush". We are concerned that the presence of all three statements contribute to label clutter and may cause confusion. Consider removing the statement "Bend and Tear" to minimize confusion.

### Physician Sample Carton Labeling only:

1. Revise the net quantity statement to read: 6 (b) (4) (6 (b) (4) per blister card x 1

card)

Please amend the application within 7-10 days (COB 7/16/15) with revised container labeling.

Thank you.

***Cathleen Michaloski, BSN, MPH, RAC***

*Sr. Regulatory Project Manager  
Division of Neurology Products  
ODE I/OND/CDER  
Food and Drug Administration  
Bldg. 22, Room 4342  
10903 New Hampshire Ave  
Silver Spring, MD 20993  
[Cathleen.michaloski@fda.hhs.gov](mailto:Cathleen.michaloski@fda.hhs.gov)  
301-796-1123*

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/s/  
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CATHLEEN B MICHALOSKI  
07/07/2015

**PeRC Meeting Minutes  
June 10, 2015**

**PeRC Members Attending:**

Wiley Chambers  
George Greeley  
Freeda Crooner  
Kristiana Brugger  
Tom Smith  
Daiva Shetty  
Peter Starke  
Lily Mulugeta  
Robert "Skip" Nelson  
Kevin Krudys  
Shrikant Pagay  
Rosemary Addy  
Greg Reaman  
Linda Lewis

**Agenda**

9:00	IND	NON-RESPONSIVE		
9:20	NDA			
9:30	IND			
9:50	IND			
10:10	IND			
10:30	BLA			
10:40	NDA			
10:50	NDA	NON-RESPONSIVE		
11:00	IND			
	IND			
11:20	NDA			
11:30	NDA			
11:40	BLA			
11:50	BLA			
	<i>IND</i>			

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

NON-RESPONSIVE

**Spritam (levetiracetam) Partial Waiver/Assessment**

- Proposed Indications: Treatment of partial onset seizures, myoclonic seizures in patients with juvenile myoclonic epilepsy and primary generalized tonic-clonic seizures.
- The PeRC noted that the plan to support approval of this product is the same as the one agreed upon in the Agreed iPSP for this product.
- The PeRC agreed with the plan as established in the Agreed iPSP.
- *PeRC Recommendations:*
  - The PeRC agreed to the partial waiver in pediatric patients with partial onset seizures under age 4, juvenile myoclonic epilepsy below 12 years of age, primary generalized tonic-clonic seizures less than (b)  
(4) years of age, and to the assessment presented in pediatric patients.

NON-RESPONSIVE

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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GETTIE AUDAIN  
06/23/2015



NDA 207958

**INFORMATION REQUEST/ADVICE**

Apreece Pharmaceuticals Company  
89 Twin Rivers Drive  
East Windsor, NJ 08520

Attention: Robert C. Williford  
Chief Operating Officer

Dear Mr. Williford:

Please refer to your New Drug Application (NDA) dated October 1, 2014, received October 1, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for SPRITAM (levetiracetam), 250 mg, 500 mg, 750 mg, 1000 mg, solid oral product.

We also refer to your February 27, 2015, amendment, including unsolicited chemistry issues, in response to our December 4, 2014, Filing Communication (74-Day letter).

We have reviewed the referenced material and have the following comments/recommendations:

1. In addition to responses to information requests communicated in the December 4, 2014, Filing Communication (74-Day letter), the amendment provides for two unsolicited changes to the pending application. Specifically, you propose:
  - Inclusion of a comparability protocol for a post-approval manufacturing site transfer of the levetiracetam drug substance from (b) (4)
  - Inclusion of SSCI (b) (4) as an additional drug substance testing site.

We are unable to add additional resources to review the changes identified above within this review cycle. Additionally, we are unable to review only selected portions of an amendment. Therefore, we recommend that you withdraw Amendment #0008 and submit the remaining information without the proposed changes. If this is done in a timely manner, we will be able to complete our review of the 74-Day Letter responses.

2. We have reviewed the pre-submission history for your product and note that in the March 28, 2014, pre-NDA meeting package you indicated that (b) (4) had already made a decision to transfer production of levetiracetam to the (b) (4) facility. You also indicated that you intended to use (b) (4)-sourced API for commercial launch and we advised you of the information required to support approval of the (b) (4) facility. In order to establish that you have a viable manufacturer to support commercial production, provide confirmation from (b) (4) that the (b) (4) facility is still manufacturing bulk levetiracetam and

will not stop production of the API prior to the PDUFA goal date for your application (August 1, 2015).

In addition, we ask that you clearly identify all proposed changes in each amendment in that amendment's cover letter or other summary document.

If you have any questions, contact Cathy Michaloski, Sr. Regulatory Project Manager, at (301) 796-1123 or by email [Cathleen.michaloski@fda.hhs.gov](mailto:Cathleen.michaloski@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Billy Dunn, M.D.  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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WILLIAM H Dunn  
03/25/2015

## Michaloski, Cathleen

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**From:** Michaloski, Cathleen  
**Sent:** Wednesday, February 11, 2015 2:22 PM  
**To:** lisa.stoecklin@aprecia.com  
**Subject:** Information request (IR) Spritam 207958 (patent certification related)

**Importance:** High

Good Afternoon Lisa,

Our ORP/OCC staff have reviewed your December 19, 2014 correspondence and has the following response:

We continue to conclude that your paragraph IV certification and accompanying statement are not in the form specified in the regulations at 21 CFR 314.50(i)(1)(i)(A)(4). This regulation describes the specific title of the certification, "Paragraph IV Certification," and that this type of patent certification "shall be submitted in the following form":

I, (name of applicant), certify that Patent No. \_\_\_\_\_ (is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of) (name of proposed drug product) for which this application is submitted.

Please provide a revised patent certification that complies with the form specified in the regulation.

Also, the statement that accompanies your paragraph IV certification commits to notify a specific entity (UCB). This is not consistent with the regulations that require the paragraph IV certification to "be accompanied by a statement that the applicant will comply with the requirements under § 314.52(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the drug product which is claimed by the patent or a use of which is claimed by the patent . . ." See 21 CFR 314.50(i)(1)(i)(A)(4). Please provide a revised statement that is consistent with the language in the regulations.

Finally, we do not agree that amending your certification and statement would require additional notice to the NDA holder and patent owner. Provided the entity you have notified constitutes "each owner of the patent . . . and the holder of the approved application for the drug product which is claimed by the patent or a use of which is claimed by the patent," there is no need to re-notify or amend your previous notification to that entity.

Please amend the application to be in conformance to this language.

Thank you.

**Cathleen Michaloski, BSN, MPH, RAC**

*Sr. Regulatory Project Manager  
Division of Neurology Products  
ODE I/OND/CDER  
Food and Drug Administration  
Bldg. 22, Room 4342  
10903 New Hampshire Ave  
Silver Spring, MD 20993  
[Cathleen.michaloski@fda.hhs.gov](mailto:Cathleen.michaloski@fda.hhs.gov)  
301-796-1123*

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/s/  
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CATHLEEN B MICHALOSKI  
02/11/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 207958

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Apreece Pharmaceuticals Company  
89 Twin Rivers Drive  
East Windsor, NJ 08520

ATTENTION: Rob Williford  
Chief Operating Officer

Dear Mr. Williford:

Please refer to your New Drug Application (NDA) dated and received October 1, 2014, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Levetiracetam (b)(4) 250 mg, 500mg, 750 mg, 1000mg.

We also refer to your correspondence, dated and received October 9, 2014, requesting review of your proposed proprietary name, Spritam.

We have completed our review of the proposed proprietary name, Spritam and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your October 9, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application, contact Cathleen Michaloski, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1123.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh  
Deputy Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES  
12/22/2014

## Michaloski, Cathleen

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**From:** Michaloski, Cathleen  
**Sent:** Tuesday, December 09, 2014 12:41 PM  
**To:** lisa.stoecklin@aprecia.com  
**Subject:** Information request (IR) Spritam 207958 (patent certification related)

**Importance:** High

Good Afternoon Lisa,

The paragraph IV patent certification and accompanying statement you have provided to address U.S. Patent No. 8,802,142 does not meet the regulatory requirements of 21 CFR 314.50(i)(1)(i)(A)(4). Please provide a revised patent certification and accompanying statement.

You added a disclaimer/caveat, (b) (4) to the template language; which should be removed. Similarly, in the accompanying statement about notifying the patent owner/NDA owner, you provide a name of a company, instead of committing to notify "each owner of the patent or their representatives and the holder of the approved application for the drug product which is claimed by the patent or a use of which is claimed by the patent." You have omitted the clause "or a use of which is claimed by the patent". This should be corrected to follow the regulations, as well.

Please submit the corrected certification and statement with 7-10 days.

Please call me if you have any questions.

Thank you.

**Cathleen Michaloski, BSN, MPH, RAC**

*Sr. Regulatory Project Manager  
Division of Neurology Products  
ODE I/OND/CDER  
Food and Drug Administration  
Bldg. 22, Room 4342  
10903 New Hampshire Ave  
Silver Spring, MD 20993  
[Cathleen.michaloski@fda.hhs.gov](mailto:Cathleen.michaloski@fda.hhs.gov)  
301-796-1123*

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/s/  
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CATHLEEN B MICHALOSKI  
12/09/2014



**NDA 207958**

**FILING COMMUNICATION –  
NO FILING REVIEW ISSUES IDENTIFIED**

Apreece Pharmaceuticals Company  
89 Twin Rivers Drive  
East Windsor, NJ 08520

Attention: Robert C. Williford  
Chief Operating Officer

Dear Mr. Williford:

Please refer to your New Drug Application (NDA) dated October 1, 2014, received October 1, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for SPRITAM (levetiracetam), 250 mg, 500 mg, 750 mg, 1000 mg, solid oral product.

We also refer to your amendment dated November 12, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is August 1, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 15, 2015.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

At this time, however, we request that you submit the following information:

**Chemistry, Manufacturing and Controls**

1. Revise the Aprecia specification for levetiracetam to include adequate tests and analytical procedures to allow verification of the results for each parameter reported on the manufacturer's certificate of analysis, regardless of whether the test is performed routinely on lot receipt or periodically for vendor requalification. We specifically refer to Identification C and the additional Heavy Metals test with acceptance criteria not more than 0.001%.
2. We recommend that you revise the acceptance criteria for Levetiracetam acid and (b) (4) of levetiracetam in the Aprecia specification to be consistent with your supplier's specification.
3. As bulk density and particle size are critical to manufacturability and product performance, we recommend testing each drug substance lot on receipt.
4. Provide data or justification in section 3.2.P.2. to ensure that the printing orientation, device fatigue, and design envelop issues (e.g., tablet thickness, geometry, and hardness) are well understood and controlled so that the quality and performance of the final product in commercial production is not compromised.
5. In your quality overall summary (2.3.P, page 7 of 59), you have indicated that the target dosage form was designed and developed using the three-dimensional printing (3DP) technology to create a porous dosage form that would rapidly disperse in the mouth after dosing with a sip of (b) (4) liquid. While the agency concurs with such scientific rationale to support the "rapidly dispersed dosage form once administered into mouth", we could not locate any data on porosity and pore size distribution of the developed product and relevant critical process parameters that can affect such an important physical characteristic of the product during manufacture. Therefore, provide such data and the list of critical process parameters that control the porosity of the drug product. Also, since (b) (4) was used for powder as opposed to (b) (4), please clarify as to why it is a 3D printing (b) (4).
6. Provide full details of the statistically-designed experiments (e.g., number of factors chosen, response evaluated, number of runs and batch sizes) conducted on the individual unit operations including (b) (4). Additionally provide your risk assessment outcome to show how you have identified certain process parameters that are needed to be included in the design of experiments.

7. Tablet (b) (4)  

8. The agency recognizes that yo (b) (4)  

9. The drug product has (b) (4)  
 Provide data from a shipment study to show that product's physical integrity will be maintained during actual commercial distribution.
10. Indicate how the (b) (4) drug product was optimized using the selected formulation. Also, provide information as to how the product is to be administered to the lowest age group pediatric population.
11. Dissolution of drug (b) (4)  

12. Provide data or justification to demonstrate that the stability, surface tension, and viscosity are consistently maintained (b) (4) for the duration of use.
13. The initial NDA contains nine months of long-term stability data with a requested 24 month shelf life. We remind you that, as discussed during the May 8, 2014, pre-NDA meeting, we may review additional stability data received by the end of January 2015, if resources allow.
14. Submit a revised Form 356h that includes all facilities, proposed for commercial manufacture, testing, or packaging of the bulk drug substance (API) and the finished product. For testing facilities, include the specific material(s) tested and the test(s) performed. Facilities that were only used during product development should be listed in appropriate CTD modules but not on the Form 356h. Accordingly, revise the CTD Modules 3.2.S.2.1 and 3.2.P.3.1 to clearly identify role and responsibilities of all facilities, including those used for product development (e.g., registration batches) as well as those intended for commercial manufacture of the drug substance and the finished product.

CMC General Comment

15. We remind you that the designation of your product's dosage form will be determined during the course of review and we do not accept "[REDACTED] (b) (4)" as the dosage form at this time. As a working definition, "solid oral product" may be used.

Biopharmaceutics

16. We acknowledge that the NDA submission specifies USP <701> for the disintegration test method. Provide a complete report detailing instrumentation and determination (and accuracy) of the disintegration end time point.
17. With reference to Question 10 of the official minutes for the type B pre-IND meeting on March 28, 2013 (Module 1.6.3), the meeting minutes discussion states "The sponsor stated that the changes in hardness of the product resulted in changes in disintegration time but had no impact on dissolution." Provide supporting data demonstrating the sensitivity of the disintegration test to critical product quality attributes (including hardness).

Microbiology

18. Please provide the following information or a reference to its location in the subject submission. We refer to Module 3.2.P.5 Table 2 that indicates microbiological testing will not occur at release. This proposal may be acceptable provided adequate [REDACTED] (b) (4) controls are established and documented. More information on your process is needed. Address the following points.
- a. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product. Include a description of [REDACTED] (b) (4)  
[REDACTED]
  - b. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.
  - c. Describe activities taken when microbiological acceptance criteria are not met at control points.
  - d. In addition to these points, provide the results of microbial limits testing performed on exhibit or stability batches of the drug product. We note that registration batches were manufactured using [REDACTED] (b) (4)  
[REDACTED]

19. We refer to Table 1 in Module 3.2.P.8. Clarify whether the microbiological testing (USP<61><62>) will occur at time zero on stability or only at 12 and 24 months.
20. Provide a more detailed summary of the USP<51> test for the spearmint-flavored (b) (4) Include a summary of the method and results.

### **CMC- Office of Compliance**

21. Submit a revised Form 356h that includes all facilities, proposed for commercial manufacture, testing, or packaging of the bulk drug substance (API) and the finished product. For testing facilities, include the specific material(s) tested and the test(s) performed. Facilities that were only used during product development should be listed in appropriate CTD modules but not on the Form 356h. Accordingly, revise the CTD Modules 3.2.S.2.1 and 3.2.P.3.1 to clearly identify role and responsibilities of all facilities, those used for product development (e.g., registration batches) as well as those intended for commercial manufacture of the drug substance and the finished product.

### **PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified labeling (format) issues. Please make the following corrections:

1. Remove extra white space in Highlights section (see Reference Drug Keppra label).
2. Edit Section 17 in Highlights to read:  
**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**
3. Remove extra 'periods' in TOC section (after each subsection).
4. Provide a Word version document of the Medication Guide.
5. Carton and Container Labeling: Please confirm whether the Levetiracetam (b) (4) 1000 mg blister package sample (lot number LV-13-001) provided during the May 8, 2014, meeting with the FDA is the final version intended for market. If not, please submit 3 samples to the Agency for review.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by January 8, 2015. The resubmitted labeling will be used for further labeling discussions. Use the

SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and Medication Guide and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult The Division of Neurology Products or the Project Manager. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

This drug may be appropriately labeled for use in some pediatric patients. We will notify you if the current pediatric labeling for that age group is not adequate.

If you have any questions, contact Cathy Michaloski, Sr. Regulatory Project Manager, by email at [Cathleen.michaloski@fda.hhs.gov](mailto:Cathleen.michaloski@fda.hhs.gov) or by phone at (301) 796-1123.

Sincerely,

*{See appended electronic signature page}*

Eric P. Bastings, M.D.  
Deputy Division Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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ERIC P BASTINGS  
12/04/2014



NDA 207958

**NDA ACKNOWLEDGMENT**

Apreece Pharmaceuticals Company  
89 Twin Rivers Drive  
East Windsor, NJ 08520

Attention: Robert C. Williford, COO

Dear Mr. Williford:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: SPRITAM (levetiracetam), 250 mg, 500 mg, 750 mg, and 1000 mg  
(b) (4) tablets

Date of Application: October 1, 2014

Date of Receipt: October 1, 2014

Our Reference Number: NDA 207958

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 30, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Neurology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, contact me by email [Cathleen.michaloski@fda.hhs.gov](mailto:Cathleen.michaloski@fda.hhs.gov) or by phone at, (301) 796- 1123.

Sincerely,

*{See appended electronic signature page}*

Cathleen Michaloski, BSN, MPH, RAC  
Sr. Regulatory Project Manager  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CATHLEEN B MICHALOSKI  
10/10/2014

### CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

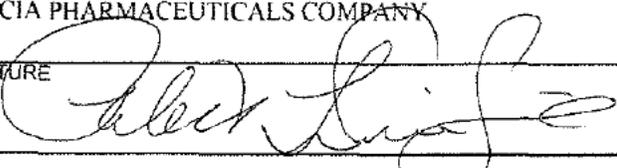
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable check box.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See Attached List	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME ROB WILLIFORD	TITLE CHIEF OPERATING OFFICER
FIRM/ORGANIZATION APRECIA PHARMACEUTICALS COMPANY	
SIGNATURE 	DATE (mm/dd/yyyy) 10/01/2014

**This section applies only to the requirements of the Paperwork Reduction Act of 1995.**

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

*"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."*

**Do NOT send your completed form to the PRA Staff email address below.**

Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer  
PRAStaff@fda.hhs.gov



PIND 117613

**MEETING MINUTES**

Apria Pharmaceuticals Company  
Attention: Rob Williford  
Chief Operating Officer  
2010 Cabot Blvd, West – Suite F  
Langhorne, PA 19047

Dear Mr. Williford:

Please refer to your Pre-Investigational New Drug Application (PIND) file for levetiracetam

(b) (4)

We also refer to the meeting between representatives of your firm and the FDA on May 8, 2014. The purpose of the meeting was to discuss your submission plans for a 505(b)(2) New Drug Application for the levetiracetam (b) (4) dosage form.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or [fannie.choy@fda.hhs.gov](mailto:fannie.choy@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Billy Dunn, M.D.  
Acting Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA meeting

**Meeting Date and Time:** May 8, 2014 at 2:00 P.M. EST  
**Meeting Location:** FDA White Oak Campus, Building 22, Rm. 1315

**Application Number:** PIND 117613  
**Product Name:** Levetiracetam (b) (4)

**Indication:** Partial Onset Seizures  
Myoclonic Seizures in patients with juvenile myoclonic epilepsy  
Primary Generalized Tonic-Clonic Seizures

**Sponsor/Applicant Name:** Aprecia Pharmaceuticals

**Meeting Chair:** Billy Dunn, M.D.  
**Meeting Recorder:** Fannie Choy, R.Ph.

**FDA ATTENDEES**

Division of Neurology Products

Billy Dunn, MD, Acting Director  
Norman Hershkowitz, MD, PhD, Clinical Team Leader  
Fannie Choy, RPh, Regulatory Project Manager  
Aaron Sherman, Consumer Safety Technician  
Rainer Paine, MD, PhD, NIH Visiting Fellow

Office of New Drug Quality Assessment

Martha Heimann, PhD, Neurology CMC Lead  
Rao Kambhampati, PhD, Quality Reviewer

Office of Clinical Pharmacology

Angela Men, MD, PhD, Clinical Pharmacology Team Leader  
Bei Yu, PhD, Clinical Pharmacology Reviewer

Office of Manufacturing and Product Quality

Vibhakar Shah, PhD, Senior Policy Advisor (via teleconference)

Division of Medication Error Prevention and Analysis, OSE

Julie Neshiewat, PharmD, Team Leader  
Tingting Gao, PharmD, Team Leader  
Millie Brahmhatt, PharmD, ORISE Fellow

**SPONSOR ATTENDEES**

Apria Pharmaceuticals

Don Wetherhold, CEO  
Rob Williford, Chief Operations Officer  
Lisa Stoecklin, Regulatory Affairs  
John Engel, Regulatory Advisor  
[REDACTED]<sup>(b) (4)</sup>, R&D Consultant  
[REDACTED]<sup>(b) (4)</sup>, Regulatory Consultant

## 1.0 BACKGROUND

Aprecia Pharmaceuticals has requested the pre-NDA meeting to discuss the submission plans for a new drug application (NDA) under section 505(b)(2) for the levetiracetam (b)(4) dosage form. The 505(b)(2) application is expected to rely upon the reference listed drug (RLD) Keppra tablet (NDA 021035).

On March 28, 2013, an end-of-phase 2 (EOP2) meeting was held between the Agency and the sponsor.

The purpose of the pre-NDA meeting is to provide the Agency an update on the development program since the EOP2 meeting. The sponsor would like to discuss the expected format and content of the NDA, and to obtain FDA guidance on their proposed submission plan and strategy related to preclinical, CMC, clinical and administrative.

Aprecia is currently anticipating the NDA submission in the 3Q2014 – 4Q2014.

## 2.0 DISCUSSION

### 2.1. Preclinical

#### Question #1:

We believe that FDA's prior finding of safety and efficacy for Keppra embodying as it does all the pre-clinical trials supporting the approval of Keppra NDA are acceptable for the reference and approval of a 505(b)(2) application seeking approval of the same indications and labeling approved for the RLD. Does the Agency agree?

#### FDA Preliminary Response to Question 1:

We agree that no additional nonclinical studies will be needed, provided there are no safety concerns (e.g., related to impurities or excipients) that would require nonclinical studies.

#### Meeting Discussion:

*There was no discussion at the meeting.*

### 2.2. Drug Product Development

#### Question #2:

We have been informed by our raw material supplier (b)(4) API that they will be shifting the commercial production of levetiracetam from (b)(4). They have

updated their DMF and have performed validation and comparability studies on the API from the new manufacturing site. We will include the open part of these studies in our NDA. Apreece will show comparability of levetiracetam (b) (4) manufactured with API from the (b) (4) site by comparing release testing of this material to registration batches. As part of our market life stability, we commit to placing the first batch using this material on stability. Upon FDA approval of our NDA we will launch using the (b) (4) API manufactured in (b) (4). Does the Agency agree with this approach?

### **FDA Preliminary Response to Question 2:**

If you plan to launch the drug product batches using the (b) (4) API manufactured in (b) (4), we expect you to provide in the NDA at least 3 months of accelerated and long-term stability study results for the drug product batches manufactured using the (b) (4) API from the (b) (4) site. In addition, please include the following information in the NDA:

- Batch analysis results and COAs for the levetiracetam drug substance batches that are used in the manufacturing of all drug product batches.
- Batch analysis results and COAs for the drug product batches that are manufactured by using levetiracetam drug substance batches from the (b) (4) site in (b) (4).

From a CGMP standpoint, you need to identify the role and responsibilities of all facilities that are/will be involved in the manufacturing of the drug substance and the drug product and ensure that they are ready for inspection at the time of NDA submission. As a result, FDA expects the new Chinese facility for the manufacture of the drug substance to be ready for inspection at the time of NDA submission.

### **Meeting Discussion:**

*There was no discussion at the meeting.*

## **2.3. Drug Product Manufacture and Control**

### **Question #3:**

We are not planning on providing the batch records and other documents for batches LV-13-004 and LV-13-005 as part of our NDA, but will provide a summary of the inadvertent loss of the packaging record documentation in our NDA submitted to the Agency. Is this acceptable to the Agency? If not, what additional data regarding these two batches would the Agency expect to be submitted in the NDA?

### **FDA Preliminary Response to Question 3:**

We normally expect batch records for the bioavailability/bioequivalence study batches and representative registration stability batches. If LV-13-004 and LV-13-005 were not

used in the bioavailability/bioequivalence study or registration stability studies, we do not expect you to submit the batch records. However, we expect you to include all other available relevant information. Additionally, note that the Agency expects availability of all executed batch records supporting the bioavailability/bioequivalence studies, stability studies, and the commercial manufacturing process, if requested for audit on inspection.

**Meeting Discussion:**

*There was no discussion at the meeting.*

**2.4. Drug Product Stability**

**Question #4:**

We believe that the demonstrated stability of levetiracetam in other FDA approved oral products (including ready to use oral solutions) is well established. We believe that the stability observed in our registration batches confirms the stability demonstrated in our development batches. Aprecia is proposing NDA submission with 9 months room temperature data and 6 month accelerated data on 1000 and 250 mg strength on 3 batches each and 6-month room temperature and 6 month accelerated data on the 500 mg and 750 mg batches. Twelve month stability data will be provided within 120 days of acceptance of the application. Does the FDA agree with this proposed stability plan to support submission of the NDA for filing, review, and approvability?

**FDA Preliminary Response to Question 4:**

We normally expect 12 months of long-term and 6 months of accelerated stability data for registration drug product stability batches that are packaged in the proposed commercial blister packaging system. You may submit the stability update during the NDA review; however, first cycle review of the additional data will depend upon the resources available at that time.

**Sponsor submitted discussion points (May 8, 2014):**

- We acknowledge the Agency's commitment to maintain the first cycle review clock.
- Aprecia currently plans on submission of the application in October 2014.
- Aprecia will provide 12 month stability data on all registration batch strengths by the end of January 2015.
- We believe submission of the data at that time will be within approximately 30 days of the filing acceptance decision.

**Meeting Discussion:**

*The sponsor was informed that it may submit the NDA in October 2014 by including the proposed stability data in Question 4 and they may provide additional stability data by the end of January 2015; however, review of the additional data will depend on the resources available at that time.*

## 2.5. Clinical Pharmacology – Pharmacokinetics

### Question #5:

We believe the summary data from the comparative bioavailability study, included in this briefing book, which compared the 1000 mg Keppra tablets to our 1000 mg SPRITAM™ (b) (4) are consistent with the prespecified criteria in the protocol and the comments received during our EOP II meeting. Does the Agency agree that summary data comply with the prespecified criteria outlined in the protocol and our EOP II meeting agreements?

### FDA Preliminary Response to Question 5:

Based on the material from the meeting package, this seems reasonable.

#### Meeting Discussion:

*There was no discussion at the meeting.*

### Question #6:

We believe that the summary data from the comparative bioavailability study are scientifically appropriate and sufficient to establish a PK bridge between our proposed 1000 mg drug product and KEPPRA, the RLD and thereby allow the reliance on FDA's finding of safety and/or effectiveness for the listed drug. Does the Agency agree?

### FDA Preliminary Response to Question 6:

In the NDA submission, you will need to provide an adequate justification to support the contention that a high as well as a low extreme interpretation of "a sip of (b) (4)" has no significant impact on the PK profile. For example, a large "sip" may constitute as much as a cup of (b) (4).

### Sponsor submitted discussion points (May 8, 2014):

- Aprecia would like to understand the considerations underlying the Agency's comment with the respect to "a large 'sip' may constitute as much as a cup of (b) (4)."

#### Meeting Discussion:

*The sponsor stated the facts that the bioavailability of Keppra tablet is ~100%, that the levetiracetam tablet and solution are bioequivalent, and that levetiracetam is a highly soluble drug in water, indicate that large volumes of water (e.g., 8 oz. water) will not affect the drug bioavailability. The Agency acknowledged this rationale as reasonable and noted that a clearly stated discussion and justification that large quantities of water would not affect absorption should be included in the NDA submission. The sponsor acknowledged the Agency's request.*

**Question #7:**

We believe that the results of our second bioavailability study, dosing the (b) (4) with no water, address the previously stated Agency concern about the effect of dosing SPRITAM with less than the recommended amount of liquid or no liquid, on its bioavailability. Does the Agency agree?

**FDA Preliminary Response to Question 7:**

Yes. Please also see our comments for Q6.

**Meeting Discussion:**

*There was no discussion at the meeting.*

**Question #8:**

We believe that the PK bridging data on 1000 mg SPRITAM (b) (4) and KEPPRA tablet and the dissolution testing conducted per the agreement from the EOP II meeting provide a scientifically appropriate and sufficient data set to allow for a biowaiver for the proportionally-similar 250 mg, 500 mg, and 750 mg strengths of SPRITAM (b) (4) that will be included in the NDA. Does the Agency agree that the proposed SPRITAM formulations fulfill the criteria for the biowaiver of the 250, 500 and 750 mg strengths and would be eligible to obtain a bio-study waiver?

**FDA Preliminary Response to Question 8:**

Yes, the data provided appear to support a BA/BE waiver for the lower strengths. Note that the final decision will be made during NDA review. Provide the complete supporting data in the NDA submission.

**Meeting Discussion:**

*There was no discussion at the meeting.*

**2.6. Clinical**

**Question #9:**

We believe that FDA's prior finding of safety and efficacy for Keppra embodying as it does all the clinical trials supporting approval of the Keppra NDA are acceptable for the reference and approval of a 505(b)(2) NDA application seeking approval of the same indications and labeling approved for the RLD. Does the Agency agree?

**FDA Preliminary Response to Question 9:**

The Agency typically does not advise a sponsor on the selection of a particular listed drug that may be relied upon to support approval of a proposed product. However, your proposal to rely on Keppra appears acceptable.

**Meeting Discussion:**

*There was no discussion at the meeting.*

**Question #10:**

As agreed in EOP II meeting we propose to file the 505(b)(2) NDA with the data from the comparative bioavailability and food effect study (Keppra 1000 mg tablets vs. SPRITAM™ 1000 mg (b)(4) Protocol CL-LEV-001-R00 and the PK data from the “no water” administration trial Protocol CL-LEV-003-R00 as the only clinical studies for FDA acceptance for filing, review and approval of our NDA. Does the Agency agree that no additional clinical trials need to be performed?

**FDA Preliminary Response to Question 10:**

As stated at the EOP2 meeting, this is reasonable; however, if there are any unexpected findings (e.g., marked difference in the shape of the absorption curve or a safety signal) additional studies/data may be required.

**Meeting Discussion:**

*There was no discussion at the meeting.*

**Question #11:**

As agreed in EOP II meeting, the bridging study from SPRITAM to the RLD was a comparative bioavailability study in healthy volunteers, and does not include any multi-dose, long-term clinical trials or clinical end-point studies in patients. Accordingly, Aprecia proposes that the Summary of Clinical Efficacy, and Summary of Clinical Safety be excluded from our NDA submission. We propose that the two bioavailability studies performed by Aprecia be included in eCTD section 5.3.1, and that all other portions of Module 5 be excluded from our NDA submission. Does the Agency agree?

**FDA Preliminary Response to Question 11:**

Yes.

**Meeting Discussion:**

*There was no discussion at the meeting.*

## **2.7. Division of Medication Error Prevention and Analysis**

### **Question #12:**

FDA has previously completed a review of the proposed proprietary name SPRITAM and indicated it is conditionally acceptable (9/24/2013). We realize that final approval of our proprietary name will only be granted after review of our NDA. Is the Agency aware of any action in the intervening time since the prior name review that would impact the suitability of "SPRITAM" as our proposed proprietary name for NDA review purposes?

### **FDA Preliminary Response to Question 12:**

Since your question would be considered a review issue under the NDA, we are unable to comment specifically on any actions that may impact the approvability of the proprietary name at this time. We request that you submit your request for proposed proprietary name review for re-evaluation of Spritam at the time of NDA submission.

### **Meeting Discussion:**

*There was no discussion at the meeting.*

## **2.8. PREA Pediatric Study Plan**

### **Question #13:**

We believe that our Pediatric Study Plan submission complies with the Agency requirements and is sufficient to allow the FDA to accept for filing and review our 505(b)(2) application. We realize that final approval of our Pediatric Study Plan will be granted after review of our application. Does the Agency agree?

### **FDA Preliminary Response to Question 13:**

As noted elsewhere in this document, a decision on the filability of an application is not made until the application has been received. In your marketing application, please reference or include a copy of our December 8, 2013, correspondence that confirms our agreement with your Agreed iPSP (submission dated November 4, 2013).

### **Meeting Discussion:**

*There was no discussion at the meeting.*

## 2.9. **Content and Format**

### **Question #14:**

We believe that the NDA content identified to be excluded from our 505(b)(2) NDA either because it is not applicable or is incorporated by reference will still allow a complete overview of our product and sufficient information for the FDA to accept for filing and review our 505(b)(2) NDA. Does the Agency agree? Are there any specific needs the Division requires beyond our proposed content and format?

### **FDA Preliminary Response to Question 14:**

A formal filing decision must await receipt of your application. From a technical standpoint (irrespective of content), the proposed format for the planned NDA is acceptable.

Please see additional comments below:

- Providing a Reviewer's Guide with a high level overview of documents in modules 1 through 5 (with hyperlinks) can be helpful to reviewers. The Reviewer's Guide is usually provided as a separate document in the cover letter section (m1.2), with a clear and descriptive leaf title.
- Do not provide placeholders for sections that will not be submitted (e.g., m1.3.1.1 – 1.3.1.3, etc.), except when requested by the Division.
- A single pdf file can be provided in m1.6.3 (instead of separate pdf files for each document) with proper bookmarks of all correspondence, table of contents, and hyperlinks.
- For archival purposes, submit a pdf file of any labeling document that is also submitted as a word document. Also, make sure the leaf title includes "word", so reviewers can quickly identify the word version of the document.
- The briefing package was not bookmarked. For ease of review, please make sure you provide sufficient navigation for all pdf files (i.e., proper bookmarks, table of contents, and hyperlinks) when submitting your application. Please refer to the PDF Specifications, located at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163565.pdf>.
- With regard to m1.4.4, your options of cross referencing information submitted to another application would be to either place a cross reference document under m1.4.4 (cross reference to other applications), or use cross application links.

1. To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information (eCTD and/or non-eCTD) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) the eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title, and (8) the submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc.) of the referenced document, along with a hypertext link to the location of the information, when possible.
2. To use the second option (cross application links), both applications would need to be in eCTD format and reside on the same server. The applications need to include the appropriate prefix in the href links (e.g., NDA and IND). Also, when cross application links are used, it is strongly recommended that a cross reference document be placed in m1.4.4 in case any of the links do not work. In the leaf titles of the documents, it is recommended that the leaf title indicates the word “cross reference” and application number (e.g., Cross Ref to NDA 123456). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application and the application number that is being referenced.

Prior to using cross application linking in an application, it is recommended that you submit an "eCTD cross application links" sample, to ensure successful use of cross application links.

- To submit an eCTD cross application links sample, you would need to request two sample application numbers from the ESub team (esub@fda.hhs.gov). For more information on an eCTD sample, please refer to the Sample Process web page which is located at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>.

Raw PK data in SAS transport file format should be provided for each study report in the NDA submission. Sufficient hyperlinks for each study report also should be provided.

**Meeting Discussion:**

*There was no discussion at the meeting.*

**Question #15:**

The two studies to be included in the NDA will be submitted in different formats. Study Protocol CL-LEV-003 (no water study) will be submitted SDTM v 3.1.2 compliant and ADaM compliant. Study Protocol CL-LEV-001 (fasted and food effect study) will be

submitted SDS v2.0 compliant with associated submission deliverables. Does the Agency agree?

**FDA Preliminary Response to Question 15:**

Yes, the proposal is acceptable. Please submit data in xpt format, and submit define.xml and define.pdf with the data.

**Meeting Discussion:**

*There was no discussion at the meeting.*

**2.10. REMS (Risk Evaluation and Mitigation Strategies)**

**Question #16:**

Levetiracetam oral and injectable products do not currently have a requirement for REMS. Aprezia's SPRITAM<sup>TM</sup> levetiracetam (b) (4) represents a new immediate release oral dosage form. We believe the change in dosage form does not represent any additional risk beyond that currently associated with the FDA approved levetiracetam dosage forms on the market. Given that our application seeks approval of SPRITAM (b) (4) for the same indications, strengths, dosing frequency, and route of administration as the RLD (immediate release Keppra tablet) with minor modifications to the RLD labelling (including the incorporated Medication Guide), we believe there is no need for a REMS program for SPRITAM levetiracetam (b) (4). Does the Agency agree?

**FDA Preliminary Response to Question 16:**

We do not anticipate a need for a REMS at this time. This could change after review.

**Meeting Discussion:**

*There was no discussion at the meeting.*

**3.0 ADDITIONAL COMMENTS**

**3.1 PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov). For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

### 3.2 **PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

**3.3 MANUFACTURING FACILITIES**

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

**3.4 505(b)(2) REGULATORY PATHWAY**

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing

application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

<b>List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature</b>	
<b>Source of information (e.g., published literature, name of listed drug)</b>	<b>Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)</b>
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

- The discussion should not be presented verbatim and capture only salient and relevant points.
- The summary of the discussion should clearly identify which party, either FDA or sponsor, owned the discussion point. The discussion should not identify individuals.
- If there was no discussion and the sponsor accepted the response as is, then insert a comment, such as, “The sponsor accepted FDA’s response, no discussion occurred.”

- Clearly identify agreements and/or disagreements that were reached by FDA and the sponsor during the discussion related to the specific question.

#### **4.0 ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussion.

#### **5.0 ACTION ITEMS**

There were no action items identified during the meeting.

#### **6.0 ATTACHMENTS AND HANDOUTS**

Sponsor submitted discussion slides titled “Aprecia Pharmaceuticals Company / Levetiracetam <sup>(b) (4)</sup> Pre-NDA Meeting / PIND 117613 / May 8, 2014”.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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WILLIAM H Dunn  
06/06/2014



PIND 117613

**MEETING MINUTES**

Apria Pharmaceuticals  
Attention: Glenn Vraniak  
President, Chief Operating Officer  
2010 Cabot Blvd, West – Suite F  
Langhorne, PA 19047

Dear Mr. Vraniak:

Please refer to your Pre-Investigational New Drug Application (PIND) file for levetiracetam

(b) (4)

We also refer to the meeting between representatives of your firm and the FDA on March 28, 2013. The purpose of the meeting was to discuss your proposed plan for a 505(b)(2) NDA submission for the levetiracetam (b) (4) dosage form.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or [fannie.choy@fda.hhs.gov](mailto:fannie.choy@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Russell G. Katz, M.D.  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-IND meeting

**Meeting Date and Time:** March 28, 2013 3:00 P.M. EST  
**Meeting Location:** FDA White Oak Campus, Building 22, Rm. 1315

**Application Number:** PIND 117613  
**Product Name:** Levetiracetam (b) (4)

**Indication:** Partial Onset Seizures  
Myoclonic Seizures in patients with juvenile myoclonic epilepsy  
Primary Generalized Tonic-Clonic Seizures

**Sponsor/Applicant Name:** Aprecia Pharmaceuticals

**Meeting Chair:** Russell G. Katz, M.D.

**FDA ATTENDEES**

Division of Neurology Products

Russell Katz, MD, Director  
Norman Hershkowitz, MD, PhD, Clinical Team Leader  
Fannie Choy, RPh, Regulatory Project Manager

Office of New Drug Quality Assessment

Martha Heimann, PhD, Neurology CMC Lead  
Deepika Lakhani, PhD, Biopharmaceutic Reviewer

Office of Clinical Pharmacology

Angela Men, MD, PhD, Clinical Pharmacology Team Leader  
Bei Yu, PhD, Clinical Pharmacology Reviewer

Division of Medication Error Prevention and Analysis, OSE

Irene Z. Chan, PharmD, BCPS, Team Leader  
Julie Neshiewat, PharmD, Safety Reviewer

**SPONSOR ATTENDEES**

**Aprecia Pharmaceuticals**

Rob Williford, Chief Operations Officer

Cheryl Zwirgzdas, Vice President Technical Operations

Jules Jacob, Senior Director product Development

Thomas Bradbury, Vice President, Research and Engineering

Nemichand Jain, PhD, R&D Consultant

Lisa Stoecklin, Regulatory Affairs

John Engel, Regulatory Advisor

(b) (4) Clinical Consultant

(b) (4) Regulatory

(b) (4) Regulatory Consultant

## 1.0 BACKGROUND

Apreece Pharmaceuticals has requested the Type B meeting to discuss their overall development plan for the new levetiracetam oral dosage preparation.

Apreece stated that they have designed a new levetiracetam product, an oral easy-to-swallow formulation that disperses in the mouth in under (b) (4) seconds with a sip of (b) (4). The sponsor is proposing to submit a new drug application (NDA) under section 505(b)(2) for the new levetiracetam product. The 505(b)(2) application is expected to rely upon the reference listed drug (RLD) Keppra tablet (NDA 021035).

The purpose of this meeting is to obtain the Agency's guidance on the following issues:

- the sponsor's overall plan of the pivotal studies as set forth in the protocol outlines for the comparative bioavailability studies, and to ensure that there is no need for additional pre-clinical data or clinical data beyond the proposed studies
- the appropriateness of the comparative bioavailability studies to allow for bridging of data from the RLD to the sponsor's product
- the appropriateness of the in vitro dissolution testing to support a biowaiver request
- the proposed stability plan for pivotal NDA batches
- the general content of the proposed 505(b)(2) application.

## 2.0 DISCUSSION

### 2.1 PROCEDURAL/LABELING

#### Question 1:

We have omitted proposed labeling regarding a sub-set of the approved population for the RLD KEPPRA tablet relating to its use as an adjunctive therapy in the treatment of partial onset seizures in children 1 month to less than 4 years old, because these aspects of the RLD's labeling are protected by regulatory exclusivity until June 16, 2015. Does the Agency agree?

#### FDA Preliminary Response to Question 1:

The carve-out of protected pediatric use information is a review issue for both 505j and 505(b)(2) products.

#### Meeting Discussion:

*There was no discussion at the meeting.*

**Question 2:**

Based on the KEPPRA labeling, exclusivity designations, and approval letter dated Dec 16, 2011, Aprecia believes that there are sound bases for omitting the RLD label sections (as shown herein for discussion purposes) that are specific to use of KEPPRA as an adjunctive therapy in the treatment of partial onset seizures in children 1 month to less than 4 years. Does the Agency agree?

**FDA Preliminary Response to Question 2:**

Please see above. The carve-out of protected pediatric use information is a review issue for both 505j and 505(b)(2) products.

**Meeting Discussion:**

*There was no discussion at the meeting.*

**Question 3:**

Does the Agency agree that the description, data, and proposed studies outlined in this Briefing Book (e.g., Section 10) are sufficient to support approval of the proposed labeling for SPRITAM (b)(4) as outlined in the Target Product Profile and Appendix C (Section 13.3)?

**FDA Preliminary Response to Question 3**

Please refer to Questions 7 and 9.

**Meeting Discussion:**

*There was no discussion at the meeting.*

**2.2 DRUG PRODUCT DEVELOPMENT, MANUFACTURE AND CONTROL**

**Question 4:**

Does the Agency agree with Aprecia's proposal for packaging registration batches that will be used for pivotal stability studies?

**FDA Preliminary Response to Question 4:**

You indicate that there will be differences in seal strength (b)(4) for institutional use and the child resistant (CR) blisters. However, you have not provided any data that would support reliance on stability data for tablets packaged (b)(4) to establish an expiration dating period for the CR

packaging. [REDACTED] (b) (4)

**Meeting Discussion:**

*There was no formal discussion at the meeting. However, during the demonstration of the packaging and product [REDACTED] (b) (4)*

**Question 5:**

Does the Agency agree with the planned registration batch size which will also be used for the pivotal stability and comparative bioavailability studies?

**FDA Preliminary Response to Question 5:**

Based on the commercial batch sizes proposed, yes, we agree.

**Meeting Discussion:**

*There was no discussion at the meeting.*

**2.3 DRUG PRODUCT STABILITY**

**Question 6:**

Does the Agency agree with Aprecia's proposal for the stability and bracketing approach to determine the stability and expiration dating of all four strengths of levetiracetam [REDACTED] (b) (4)

**FDA Preliminary Response to Question 6:**

The proposed bracketing strategy is acceptable. Based on the information available at this time, the test parameters and stability test schedule appear adequate.

**Meeting Discussion:**

*There was no discussion at the meeting.*

## 2.4 CLINICAL – BIOWAIVER

### Question 7:

We believe the bioavailability study protocol outline, which compares our 1000 mg levetiracetam (b) (4) with the 1000 mg Keppra tablet, is consistent with the Agency's current bioequivalence guideline for levetiracetam products. Does the Agency agree that the biopharmaceutic principles laid down in the current guideline apply to our NDA application?

### FDA Preliminary Response to Question 7:

On face, it's acceptable. Alternatively, you can conduct a single dose, 3-arm, 3-way cross-over study to compare the drug bioavailability to support your NDA application. The 3 arms are: 1000 mg levetiracetam (b) (4) under fasted conditions, 1000 mg Keppra IR tablet under fasted conditions, and 1000 mg levetiracetam (b) (4) under fed conditions.

### Meeting Discussion:

*There was no discussion at the meeting.*

### Question 8:

We believe that the proposed protocol outline for the comparative bioavailability study is scientifically appropriate and sufficient to establish a bridge between our proposed 1000 mg drug product and the listed RLD, and thereby allow the reliance on FDA's finding of safety and/or effectiveness for the listed drug and if successful, will support a 505(b)2 approval without the need for any additional clinical data. Does the Agency agree?

### FDA Preliminary Response to Question 8:

The protocol is adequate, as described in the answer for Question 7. However, if there is any unexpected finding (e.g. marked difference in the shape of the absorption curve or a safety signal) additional clinical studies/data will be required.

### Meeting Discussion:

*There was no discussion at the meeting.*

### Question 9:

Aprécia believes that the proposed study design, where SPRITAM will be given with 15 ml (b) (4) of water, supports the proposed label where SPRITAM will be given with 15 ml of water, only. Does the Agency agree?

**FDA Preliminary Response to Question 9:**

No. The administration in the study should be exactly the same as the proposed label. Thus, levetiracetam (b) (4) should be administered in the proposed studies solely with a sip of water, (b) (4).

Additionally, your proposed labeling indicated that “Each SPRITAM (b) (4)

(b) (4) There will be some other practical scenarios for patients, such as swallowing it immediately (b) (4) or taking the drug with plenty of (b) (4) etc. You need to provide sufficient data or justification to show that these different administration scenarios will not have impact on the bioavailability of the drug absorption.

**Meeting Discussion:**

*The sponsor will follow the Agency’s recommendation to administer levetiracetam (b) (4) solely with 15 mL of water in the proposed studies. For the other potential practical scenarios of taking the product with less or more water, the sponsor will provide a justification in their NDA submission to demonstrate that such conditions will not have an impact on the bioavailability of their product based on the available data, e.g., high solubility, high permeability, 100% bioavailability of the levetiracetam tablets, bioequivalence between tablets and oral solution of levetiracetam, no food effect, etc.*

*The Agency expressed concern that levetiracetam (b) (4) may be administered by patients in a manner similar to orally disintegrating products, by allowing it to dissolve on the tongue without the aid of water. This concern partially stems from the proposed labeling of taking it with only a sip of water. The Agency also questioned whether the marketing plan would include emphasis on the dispersion properties of the product, which may possibly cause some consumers to also misinterpret the product as an orally disintegrating product.*

**Question 10:**

Apreece believes that the proposed comparative dissolution studies are appropriate and sufficient, in combination with acceptable comparative bioavailability studies on the 1000 mg strength, to support a waiver of in vivo bioequivalence studies for 250 mg, 500 mg, and 750 mg strengths of levetiracetam (b) (4). Does the Agency agree?

**FDA Preliminary Response to Question 10:**

The CFR’s BA/BE requirements for the lower strengths of your proposed product may be waived if the following criteria are met:

- a. You include a biowaiver request in the NDA submission for all the proposed strengths not tested clinically.
- b. There is acceptable BA/BE data for the highest strength.
- c. All the strengths have the same manufacturing process.
- d. The lower strengths and higher strength products have the same dosage form.
- e. The lower strengths are proportionally similar in their active and inactive ingredients to the highest strength product.
- f. Dissolution profile comparisons between the highest and lower strengths meet the  $f_2$  similarity requirements in three different media (i.e., pH 1.2, 4.5, 6.8) using the same dissolution testing conditions. For the estimation of the  $f_2$  value(s), the highest strength used in the BA/BE study should be the reference product.

Note our following recommendations for development and validation of a dissolution method for the proposed product:

**Dissolution Test:** The dissolution method report supporting the selection of the proposed dissolution test should be provided in the NDA. The dissolution report should include the following information:

- a. Solubility data for the drug substance covering the pH range;
- b. Detailed description of the dissolution test being proposed for the evaluation of the proposed drug product and the developmental parameters used to select the proposed dissolution method as the optimal test for the proposed product (i.e., selection of the equipment/ apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.). If a surfactant was used, the data supporting the selection of the type and amount of surfactant should be included. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend that at least twelve samples be used per testing variable;
- c. Provide the complete dissolution profile data (individual, mean, SD, profiles) for the proposed drug product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim); and
- d. Include the complete dissolution data for the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.). In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with *meaningful variations* (i.e. aberrant formulations and manufacturing conditions) for the most relevant critical manufacturing variables. In addition if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent.

**Dissolution Acceptance Criterion:** For the setting of the dissolution acceptance criterion(a) of your proposed drug product, the following points should be considered:

- a. The dissolution profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criterion of your proposed drug product [i.e., specification-sampling time point and specification value].
- b. The selection of the specification time point should be where  $Q = 80\%$  dissolution occurs.
- c. The dissolution acceptance criterion should be based on average in vitro dissolution data (n=12).

Note that the final determination on the acceptability of the proposed acceptance criterion for your proposed product will be made during NDA review process based on the provided data.

**Meeting Discussion:**

*The sponsor provided data showing that levetiracetam is a highly soluble drug and 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 suggested that the sponsor must submit all the dissolution method validation data in the NDA to support the lack of discriminating ability of the method. The sponsor 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 sponsor 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 sponsor is planning on submitting a biowaiver request for the lower strengths of the drug product, dissolution data must be submitted as stated in the FDA's response to question 10. With an understanding of the very high solubility and permeability of the drug, the FDA advised the sponsor that they may seek approval of BCS Class 1 classification of the drug substance by the BCS-committee. To accomplish this they are required to submit solubility and permeability data.*

**POST MEETING COMMENT:**

*If you decide to seek approval of a BCS Class 1 classification, please refer to the BCS guidance. Also, the attached "BCS Question Based Approach" document describes the information/data that should be submitted to FDA (under the IND) to support a BCS-Class 1 classification for your levetiracetam drug substance/drug product.*

## 2.5 ADMINISTRATIVE – USER FEE

### Question 11:

Does the Agency agree that Aprecia is eligible for a waiver of the user fee for this NDA?

#### FDA Preliminary Response to Question 11:

We neither agree or disagree whether Aprecia is eligible for a small business waiver under section 736(d)(1)(D) of the Food, Drug, and Cosmetic Act. However, if you believe that Aprecia is eligible, and meets all the criteria, you may consider requesting a waiver. Please refer to FDA's guidance for industry *User Fee Waivers, Reductions, and Refunds for Drug and Biologic Products* for details on the criteria for, and how to apply for a waiver. If you have further questions on waivers, please contact Michael Jones, Office of Management, at 301-796-3602.

#### Meeting Discussion:

*There was no discussion at the meeting.*

## 2.6 OTHER

### Question 12:

Based on the data and information presented in the Briefing Book, are there any other issues, items missed or things to consider for a successful application?

#### FDA Preliminary Response to Question 12:

#### **Recommendations for sponsors considering the submission of an application through the 505(b)(2) regulatory pathway**

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s).

You should establish a “bridge” (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely on the Agency’s finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA’s finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency’s regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the “listed drug for which FDA has made a finding of safety and effectiveness,” and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, you should include a copy of the article(s) in your submission.

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

**Meeting Discussion:**

*There was no discussion at the meeting.*

## Nomenclature

Although a definitive designation of the dosage form will not be made prior to review of the NDA, we remind you FDA currently considers the most appropriate designation to be (b) (4) tablet, (b) (4).

### **Meeting Discussion:**

*There was no discussion at the meeting*

## 3.0 ADDITIONAL COMMENTS

### 3.1 **DIVISION OF MEDICATION ERROR PREVENTION AND ANALYSIS**

In your briefing packet, you describe that the product will be packaged in child resistant (b) (4) blister packs with peelable lidding. Please bring functional prototypes of the blister packs (b) (4) to the meeting scheduled on March 28, 2013. We request a blister pack of each strength and request that the blister cavities be filled with active product or placebo that is comparable in friability to your proposed product. We would like to determine whether the dosage form can be easily retrieved from the blister cavities without damaging the product.

We note you referred to this product as “Spritam” in the briefing packet. If this proprietary name is intended for use, please submit a formal request for proprietary name review at your earliest convenience.

Please see the Guidance for Industry: Contents of a Complete Submission for the Evaluation of Proprietary Names available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>.

### **Meeting Discussion:**

*The sponsor provided functional blister packs (b) (4) child resistant packaging. The FDA noted that the child resistant packaging seemed difficult to open. The sponsor explained that peeling around the edging of the seal in a circle could help make it easier to open the blister. The sponsor further clarified that the blister packs are early prototypes, and they anticipate changes to the blister pack presentations to address the Agency’s concerns regarding being able to open the packaging without damaging the tablets.*

### 3.2 **PREA PEDIATRIC STUDY PLAN**

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-

of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. For additional guidance on submission of the PSP, including a PSP Template, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm> . In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email [pdit@fda.hhs.gov](mailto:pdit@fda.hhs.gov).

**Meeting Discussion:**

*There was no discussion at the meeting.*

### **3.3 DATA STANDARDS FOR STUDIES**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

**Meeting Discussion:**

*There was no discussion at the meeting.*

#### **4.0 ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussion.

#### **5.0 ACTION ITEMS**

There were no action items identified during the meeting.

#### **6.0 ATTACHMENTS AND HANDOUTS**

- Attachment 1: General recommendations to support the BCS Class 1 Classification
- Sponsor submitted slides for presentation and discussion: Aprecia Pharmaceuticals Company, Levetiracetam (b) (4) Type B Meeting, PIND 117613, March 28, 2013.

**Attachment 1**

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**BIOPHARMACEUTICS CLASSIFICATION SYSTEM\***

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**QUESTION BASED APPROACH**

**To support the BCS Class 1 Classification for: 1) Drug Substance, and/or 2) Drug Product, and/or 3) BCS-Biowaiver Request for a Drug Product, the applicants should provide the information being requested in each question.**

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*\*Guidance for industry on Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (BCS), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070246.pdf>*

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## QUESTION BASED APPROACH

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### 1. INFORMATION NEEDED TO SUPPORT A BCS CLASS 1 DRUG SUBSTANCE

The complete information addressing the following questions should be provided to support a BCS Class 1 classification request for a drug substance.

#### 1.1. Determination of Drug Substance Solubility Class

- 1.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance?
- 1.1.2. What is the nature of the drug substance (acid, base, amphoteric, or neutral)? What is the dissociation constant(s), PKa(s) of the drug substance?
- 1.1.3. What is the solubility profile of the drug substance under physiological pH conditions (i.e., pH range 1-7.5 at 37°C in aqueous media)?
- 1.1.4. Were five pH conditions used to define the solubility pH profile? How many replicate determinations of solubility of the drug substance at each pH condition were performed?
- 1.1.5. What type of buffer solutions were used to define the solubility profile? What are the compositions of the buffer solutions? How they were prepared?
- 1.1.6. Was the buffer solution's pH verified after the addition of the drug substance to the buffer?
- 1.1.7. What type of method was selected to evaluate the equilibrium solubility of the drug substance? What are the specific experimental testing conditions?
- 1.1.8. What analytical method was used to determine the concentration of the drug substance in the selected buffers (or pH conditions)? What data support the validation of the assay?
- 1.1.9. What are the solubility pH profile results (individual, mean, standard deviation, coefficient of variation, and graphics)?
- 1.1.10. Is the highest dose strength of the proposed drug-product soluble in 250 ml of aqueous media over the pH range of 1 to 7.5?
- 1.1.11. Is the overall solubility information supportive of a BCS high soluble Class 1 classification for the drug substance?

## 1. 2. Determination of Drug Substance Permeability Class

- 1.2.1. What approach was used to determine the permeability class of the drug substance (*i.e., in vivo mass balance or absolute BA or intestinal permeability*)? If more than one method was used to demonstrate permeability classification, what is the other(s) approach?
- 1.2.2. For human pharmacokinetic approaches - Which approach was selected (*i.e., mass balance and/or absolute BA*)? What is the information describing the study design, methods, results, etc?
- 1.2.3. For the intestinal permeability approaches – Which method was selected (*i.e., 1) in vivo intestinal perfusion studies in humans; 2) in vivo or in situ intestinal perfusion studies using suitable animal models; 3) in vitro permeation studies using excised human or animal intestinal tissues; or 4) in vitro permeation studies across a monolayer of cultured epithelial cells*) and what is the rationale for its selection?
- 1.2.4. Is the drug substance being testing a passively transported drug? What is the information supporting this assumption?
- 1.2.5. Was the linear relationship between the dose and measures of bioavailability (*humans*) demonstrated?
- 1.2.6. Was there a lack of dependency of the measured in vitro permeability of the test article on initial drug concentration or transport direction (*no difference in the rate of transport between the apical-to-basolateral and basolateral-to-apical direction*) using a suitable in vitro cell culture method. What is the supportive information?
- 1.2.7. For the in vivo-human perfusion studies, in vivo or in situ-animal intestinal perfusion studies or in vitro cell culture methods, how many model drugs were used? What model drugs were selected and did they represent a range of absorption values? What are the permeability values for each model drug (mean, SD, CV) and what is the permeability class of each model drug?
- 1.2.8. What information supports the suitability of the selected method (*i.e., description of the study, criteria for the selected approach, analytical method, method used to estimate the extent of absorption, (where appropriate, efflux potential), results (individual, mean, SD, coefficient of variation), etc.*)? Were the results tabulated? Was the suitability of the selected permeability method(s) adequately demonstrated?
- 1.2.9. What drugs were selected as low and high permeability internal standards? What is the high permeability internal standard used for the permeability classification?
- 1.2.10. What is the information supporting the high permeability of the drug substance (*i.e., permeability methods permeability data on the test drug substance and internal standards (mean, SD, & CV), data supporting classification and passive transport mechanism*)?
- 1.2.11. What is the graphic representation of the extent of absorption as a function of permeability (*mean  $\pm$ SD or 95% CI*) with low/high permeability class boundary and selected internal

standard(s). What is the rank-order relationship between test permeability values and the extent of drug absorption values?

- 1.2.12. Is the overall information supporting a BCS - high permeable Class 1 classification for the drug substance?

### **1.3. Gastric Stability**

- 1.3.1. What is the information supporting the stability of the drug substance/drug product in the GI tract?
- 1.3.2. What are the experimental conditions used during the gastric stability experiments?
- 1.3.3. Were simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) used to generate the chemical stability data or human fluid? What are the compositions of the SGF and SIF solutions?
- 1.3.4. What is the validation information for the analytical method? What is a validated stability-indicating assay?
- 1.3.5. What are the SGF and SIF stability results (mean, SD, CV)? Are the results tabulated?
- 1.3.6. Is the overall information supportive of gastric stability?

## **2. INFORMATION TO SUPPORT A BCS CLASS 1 – DRUG PRODUCT**

The complete information addressing the following questions should be provided to support a BCS Class 1 classification request for a drug product.

### **2.1. Determination of the Drug Substance Solubility Class (same as 1.1).**

### **2.2. Determination of the Drug Substance Permeability Class (same as 2.1).**

### **2.3 Determination of the Dissolution Characteristics of the Drug Product**

- 2.3.1 What is the information describing the drug product used for dissolution testing (*i.e., batch/ lot No., expiry date, lot size, strength, etc.*)?
- 2.3.2 What are the selected dissolution testing conditions (*i.e., apparatus, rotation speed, dissolution media, temperature, and volume*)?
- 2.3.3 What is the sampling schedule? Does the sampling schedule adequately characterize the complete dissolution profile? Were twelve dosage units per experiment tested?
- 2.3.4 What is the information supporting the validation of the dissolution methodology (robustness, etc.).
- 2.3.5 What is the analytical method(s) used to determine the concentration of the drug in the dissolution samples? What is the validation information for the analytical method? Was it a validated assay?
- 2.3.6 Was the dissolution of the drug product characterized in three different pH media? What are the compositions of the buffer solutions? How they were prepared? What are the dissolution characteristics in these media?
- 2.3.7 What are the dissolution results (*i.e., individual, mean, SD, CV, and graphics*) in the different media? Are the results tabulated? Are the dissolution profile data reported in percent of label claim?
- 2.3.8 Is the drug product showing fast dissolution in the different pH media? Is more than 85% of drug being dissolved in 15-30 minutes in each medium?
- 2.3.9 Does the overall dissolution data support a rapid/fast dissolving designation for the drug product?

### **3. DATA SUPPORTING A REQUEST FOR A BIOWAIVER(s)**

Sponsor requesting a biowaiver(s) for a drug products based on the BCS should submit complete information addressing the following questions.

#### **3.1. Data Supporting High Solubility for the Drug Substance (same as 1.1).**

#### **3.2. Data Supporting High Permeability for the Drug Substance (same as 1.2).**

#### **3.3. Data Supporting Gastric Stability (same as 1.3).**

#### **3.4. Data Supporting Rapid Dissolution for the Drug Product (same as 2.3).**

#### **3.5 Data Supporting Similar Dissolution for the Test and Reference Products**

- 3.5.1. What is the information describing the test and reference products used for dissolution testing (*i.e., batch/ lot No., expiry date, lot size, dimensions, strength, weight, etc.*)?
- 3.5.2. What are the methodology and conditions used for the dissolution testing of the test and reference products? Does the sampling schedule include adequate frequency and sampling times to characterize the complete dissolution profile?
- 3.5.3. Were the dissolution profiles of the drug product and reference product characterized in different pH media? What are those media and how they were prepared?
- 3.5.4. What are the dissolution testing results (*individual, mean, range, SD, coefficient of variation*) for the test and reference products in the different dissolution media? Are the dissolution profile comparison data at each tested interval reported in percent of label claim? Was the overall dissolution data tabulated?
- 3.5.5. What is the graphic representation of the mean dissolution profiles for the test and reference products in the different dissolution media?
- 3.5.6. Was the similarity f<sub>2</sub> metric for the dissolution profiles of the test and reference products estimated? What are the similarity f<sub>2</sub> values for each tested media?
- 3.5.7. Are the overall dissolution profile comparison data and f<sub>2</sub> values supporting the biowaiver(s) request?

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RUSSELL G KATZ  
04/26/2013