

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208277Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 208277

SUPPL #

HFD #

Trade Name Fycompa

Generic Name perampanel

Applicant Name Eisai, Inc.

Approval Date, If Known 4/29/16

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 ☒

NO ☐

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

505(b)(1)

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 ☒

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.

The study used to support the NDA was a bioavailability study, because it compared equivalent doses of the approved tablet formulation and the proposed oral suspension formulation in healthy adult volunteers, primary outcome measures were pharmacokinetic parameters, and efficacy was not assessed. Safety of patients in the study was evaluated. In their Statement of Claimed Exclusivity, the sponsor states that Study E2007-A001-048 met the definition of "new clinical investigation" as defined in 21 CFR 314.108(a). However, CFR 314.108(a) clearly states "Clinical investigation means any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects." As this is a bioavailability study, the

sponsor's claim that their study is a new clinical investigation is incorrect.

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:

N/A

c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3

d) Has pediatric exclusivity been granted for this Active Moiety?

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?

N/A

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 ☒

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 ☒ NO ☐

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

NDA# 202834

NDA#

NDA#

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 ☐

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 ☒

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:

N/A

(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:

N/A

=====

Name of person completing form: Stephanie N. Parncutt, MHA
Title: Senior Regulatory Health Project Manager

Date: April 21, 2016

Name of Office/Division Director signing form: Billy Dunn, M.D.

Title: Director, DNP

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

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

/s/

STEPHANIE N PARNCUTT
04/28/2016

WILLIAM H Dunn
04/28/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208277 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: Fycompa Established/Proper Name: perampanel Dosage Form: Oral Suspension		Applicant: Eisai, Inc. Agent for Applicant (if applicable): Heather A. Bradley, MPH
RPM: Stephanie N. Parncutt		Division: Division of Neurology Products
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> - Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. - Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☐ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: <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>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>April 30, 2016</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ 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 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received
❖ Application Characteristics ³		

¹ 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.

² 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).

³ 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): 1
 (confirm chemical classification at time of approval)

- | | |
|---|---|
| ☐ Fast Track | ☐ Rx-to-OTC full switch |
| ☐ Rolling Review | ☐ Rx-to-OTC partial switch |
| ☐ Orphan drug designation | ☐ Direct-to-OTC |
| ☐ Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
 Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

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

Action Letters [TAB F]	
❖ Copies of all action letters (including approval letter with final labeling)	Approval: April 29, 2016
Labeling [TAB G]	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
• Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	☒ Medication Guide ☐ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included (See Package Insert)
• Original applicant-proposed labeling	☒ Included (See Package Insert)
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
• Most-recent draft labeling	☒ Included (6/30/15; 3/10/16)
❖ Proprietary Name	Acceptability Letter: November 9, 2015 Review: November 4, 2015
• Acceptability/non-acceptability letter(s) (indicate date(s))	
• Review(s) (indicate date(s))	
❖ Labeling reviews (indicate dates of reviews)	RPM: ☒ September 1, 2015 DMEPA: ☒ March 2, 2016; March 23, 2016 DMPP/PLT: ☒ April 21, 2016 OPDP: ☒ April 21, 2016 SEALD: None CSS: ☒ See Primary Review PLLR: See Maternal Health Review: 4/4/16
Administrative / Regulatory Documents [TAB H]	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	Clinical Pharmacology Filing Review: September 8, 2015
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	RPM Filing Review: October 29, 2015
	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary (signed by Division Director)	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	

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

• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No N/A N/A ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) • Date reviewed by PeRC <u>February 24, 2016</u> If PeRC review not necessary, explain: <u>N/A</u>	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	N/A
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	N/A
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)	N/A
❖ 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, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	sNDA Acknowledgement letter: 7/22/15 Information Request: 08/11/15 Information Request: 08/26/15 No Filing Review Issues Identified: 9/11/15 CMC Information Request: 12/15/15 Information Request: 02/29/16 Information Request: 03/07/16 Information Request: 03/29/16
❖ 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)	OPDP Consult: 7/29/15 Patient Labeling Consult: 07/29/15 Pediatric & Maternal Health Consult: 07/30/15 CSS Consult: 07/30/15 Biopharmaceuticals Inspections Request: 9/8/15 Memorandum: 12/28/15 PeRC Meeting Minutes: 3/18/16
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	N/A
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☒ 4/30/15
• EOP2 meeting (<i>indicate date of mtg</i>)	No mtg

• Mid-cycle Communication (<i>indicate date of mtg</i>)	N/A
• Late-cycle Meeting (<i>indicate date of mtg</i>)	N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	Type C Guidance Meeting: 5/27/14
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	N/A
Decisional and Summary Memos [TAB I]	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	☒ April 29, 2016
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☒ April 29, 2016
PMR/PMC Development Templates (<i>indicate total number</i>)	☒ April 28, 2016
Clinical [TAB J]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ April 28, 2016
• Clinical review(s) (<i>indicate date for each review</i>)	March 31, 2016
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Clinical Review: 03/31/16
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵	☒ Pediatric Review 3/24/16 Maternal Health Review: 4/4/16 DPV I Review: 2/8/16
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ 2/25/16; 4/4/16
❖ Risk Management	
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)	N/A
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	N/A
• 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>)	☒ None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	None requested

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☐ No separate review
Clinical Microbiology Review(s) (indicate date for each review)	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	☐ No separate review
Statistical Team Leader Review(s) (indicate date for each review)	☐ No separate review
Statistical Review(s) (indicate date for each review)	☐ None
Clinical Pharmacology [TAB K] ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☒ See Clinical Pharmacology review
Clinical Pharmacology review(s) (indicate date for each review)	☒ April 26, 2016
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	☒ 1/19/16; 2/24/16
Nonclinical ☒ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☒ No separate review
• Supervisory Review(s) (indicate date for each review)	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	No carc
❖ ECAC/CAC report/memo of meeting	None
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	None requested
Product Quality [TAB L] ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (indicate date for each review)	See Integrated Quality Assessment
• Secondary review (e.g., Branch Chief) (indicate date for each review)	See Integrated Quality Assessment
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)	☒ April 26, 2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)	None

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	See Integrated Quality Assessment
☐ Review & FONSI (<i>indicate date of review</i>)	N/A
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	N/A
❖ Facilities Review/Inspection	
☒ 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>)	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ 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	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

From: Heather_Bradley@Eisai.com
To: Parncutt_Stephanie
Subject: Re: NDA 208277 Maternal Health Information Request
Date: Tuesday, March 29, 2016 10:47:45 AM

Dear Stephanie,
Received, thank you. We are working on a response to be submitted within 3 business days, ie by 31 Mar 2016.

Heather A. Bradley, MPH
Director, Global Regulatory Affairs

Eisai Inc.
155 Tice Boulevard
Woodcliff Lake, NJ 07677
Tel: 201-949-4691
Cell: 201-699-6714
Fax: 201-949-4595
heather_bradley@eisai.com

From: "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>
To: "Heather_Bradley@Eisai.com" <Heather_Bradley@Eisai.com>
Date: 03/28/2016 01:15 PM
Subject: NDA 208277 Maternal Health Information Request

Heather,

Please see the following IR from the Maternal Health team:

We would like to request additional safety information on the neonatal death case that is included in your summary report (attached). Please provide additional details that you may have, including the timing of exposure in pregnancy, dose, duration of exposure, pregnancy complications, concomitant medications, comorbidities, exposures to alcohol smoking, drugs, etc., details on the neonatal death, and your assessment regarding whether you think the neonatal death may have been associated with exposure to Fycompa.

Please confirm receipt, and provide a response within 1-3 business days.

Thank you,

~~~~~  
Stephanie N. Parncutt, MHA  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4165  
Silver Spring, MD 20993-0002  
phone: 301-796-4098  
email: [stephanie.parncutt@fda.hhs.gov](mailto:stephanie.parncutt@fda.hhs.gov)

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[attachment "(3-28-16)Safety Information Amendment.pdf" deleted by Heather Bradley/RIG/EisaiInc] [attachment "emfinfo.txt" deleted by Heather Bradley/RIG/EisaiInc]

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Please refer to the [30 Jun 2015 NDA 208277/s0000](#) submission of perampanel oral suspension as an alternative formulation to perampanel tablets for all approved indications of Fycompa.

Please also refer to the Filing Communication letter received on 11 Sep 2015. This Safety Information Amendment contains responses to the request made by the Maternal Health Division.

## TABLE OF CONTENTS

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| CLINICAL SAFETY INFORMATION REQUEST (11 SEP 2015) ..... | 1 |
|---------------------------------------------------------|---|

## LIST OF IN-TEXT TABLES

|                                                                                                     |                   |
|-----------------------------------------------------------------------------------------------------|-------------------|
| <a href="#">Table 1 Cumulative Summary of Reports of Perampanel Exposure During Pregnancy .....</a> | <a href="#">2</a> |
|-----------------------------------------------------------------------------------------------------|-------------------|

## CLINICAL SAFETY INFORMATION REQUEST (11 Sep 2015)

Together with submission of the proposed labeling for PLLR compliance, applicants should provide the following information to support the labeling content: a review and summary of the relevant published literature, summary of cases reported in the pharmacovigilance database, interim ongoing or final report on a closed pregnancy registry (if applicable).

During our preliminary review of your submitted labeling, you did not provide a review and summary of the available literature to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. Thus, your proposed PLLR labeling changes cannot be agreed upon until this information request is fulfilled. No partial PLLR conversions may be made.

Resubmit the following information on perampanel use in pregnant and lactating women by Nov 11, 2015:

- A review and summary of all available published literature regarding [drug name],
- A review and summary from your pharmacovigilance database,
- Interim report from the ongoing pregnancy registry.

### Company Response:

A cumulative search of the clinical trial and post-marketing perampanel adverse event database for events coded to the MedDRA (version 18.0) HLG of Pregnancy, labour,

delivery and postpartum conditions and the Standardized MedDRA Query (SMQ) term of Congenital, Familiar and Genetic Disorders was performed. Searches were cumulative through September 15, 2015. These cases were then reviewed to identify cases meeting the FDA criteria.

The search revealed a total of 36 reports of drug exposure during pregnancy. Of the 36 reports, 24 were from perampanel clinical trials, 11 were spontaneous reports and 1 report was a solicited report from an extended access program. Of the 36 reports, 18 reports were received since market approval; 11 spontaneous reports, 6 reports from perampanel clinical trials and 1 solicited report. The reports of exposure to perampanel during pregnancy are characterized in the Table 1.

**Table 1 Cumulative Summary of Reports of Perampanel Exposure During Pregnancy**

| <b>Total Pregnancies: 36</b> | <b>Maternal Exposures: 35<sup>1</sup></b> | <b>Paternal Exposures: 1</b> |
|------------------------------|-------------------------------------------|------------------------------|
|                              | Maternal Exposures Outcomes               | Paternal Exposures Outcomes  |
|                              | Healthy Babies: 10                        | Healthy Babies: 1            |
|                              | Elective Abortion: 11                     |                              |
|                              | Spontaneous Abortion: 6                   |                              |
|                              | Neonatal death: 1                         |                              |
|                              | Unknown: 7                                |                              |

<sup>1</sup> One report of a single exposure of perampanel 12 mg prior to pregnancy

Eisai has not received any reports from any pregnancy registries, epidemiological studies or from published literature. A letter received from the North American AED Pregnancy Registry noted that as of January 1, 2015 there were no women enrolled who had taken perampanel as monotherapy and that no major malformations were identified in infants exposed to perampanel.

Given the number of individuals exposed post-marketing (approximately 6.1 million patient days of exposure) and the number of clinical trial subjects who have received perampanel (approximately 6,500 subjects), there have been relatively few pregnancy cases. Of the pregnancies reported there have been no reports of an associated birth defect. These findings support the updates in sections 8.1, 8.2, and 8.3 to comply with PLLR guidance.

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/s/  
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STEPHANIE N PARNCUTT  
03/29/2016

**PeRC Meeting Minutes**  
**February 24, 2016**

**PeRC Members Attending:**

Lynne Yao

Ikram Elayan

Kevin Krudys

Gettie Audain

Daiva Shetty

Meshaun Payne

Gerri Baer

Wiley Chambers

Julia Pinto

Maura O'Leary ((b) (4)) Perampanel, ((b) (4))  
((b) (4))

Lili Mulugeta

Peter Starke

Ruthanna Davi

Raquel Tapia

Greg Reaman

Dionna Green

Barbara Buch

Rachel Witten

Michelle Roth-Kline

George Greeley

## Agenda

|       |            |                                                                                                 |         |       |                                   |                                                                                                                                                                                                                   |
|-------|------------|-------------------------------------------------------------------------------------------------|---------|-------|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 9:00  | (b) (4)    |                                                                                                 |         | DNP   | Nahleen Lopez                     | (b) (4)                                                                                                                                                                                                           |
| 9:20  | NDA 208277 | Fycompa (perampanel) Oral Suspension (Partial Waiver/Deferral Plan/Assessment) with Agreed iPSP | (b) (4) | DNP   | Stephanie Parncutt                | Adjunctive therapy in the treatment of partial-onset seizures with or without secondarily generalized seizures and primarily generalized tonic-clonic seizures in patients with epilepsy aged 12 years and older. |
| 9:30  | (b) (4)    |                                                                                                 |         | DMIP  | Su Lin Sun                        | (b) (4)                                                                                                                                                                                                           |
| 9:40  |            |                                                                                                 |         | DPARP | Angela Ramsey                     |                                                                                                                                                                                                                   |
| 10:40 |            |                                                                                                 |         | DGIEP | Mary Chung                        |                                                                                                                                                                                                                   |
| 11:00 |            |                                                                                                 |         | DGIEP | Kelly Richards/<br>Allan Lawrence |                                                                                                                                                                                                                   |
| 11:00 |            |                                                                                                 |         | DGIEP | Kelly Richards/<br>Allan Lawrence |                                                                                                                                                                                                                   |
| 11:10 |            |                                                                                                 |         | DPP   | Simran Parihar                    |                                                                                                                                                                                                                   |
| 11:20 |            |                                                                                                 |         | DPARP | Nina Ton                          |                                                                                                                                                                                                                   |
| 11:35 |            |                                                                                                 |         | DNP   | Lana Chen                         |                                                                                                                                                                                                                   |
| 11:45 |            |                                                                                                 |         | DHP   | Kimberly Scott                    |                                                                                                                                                                                                                   |
|       |            |                                                                                                 |         | DNDP  | Alina Salvatore                   |                                                                                                                                                                                                                   |
|       |            |                                                                                                 |         | DOP1  | Charlene Wheeler                  |                                                                                                                                                                                                                   |
|       |            |                                                                                                 |         | DPP   | Brendan Muoio                     |                                                                                                                                                                                                                   |
|       |            |                                                                                                 |         | DAVP  | Elizabeth Thompson                |                                                                                                                                                                                                                   |
|       |            |                                                                                                 |         | DPARP | Sadaf Nabavian                    |                                                                                                                                                                                                                   |

**Fycompa Oral Suspension Partial Waiver/Deferral with Agreed iPSP**

- Indication: Adjunctive therapy in the treatment of partial-onset seizures with or without secondarily generalized seizures and primarily generalized tonic-clonic seizures in patients with epilepsy aged 12 years and older.
- This product triggers PREA as a new dosage form and has a PDUFA goal date of April 30, 2016.
- The division notes that the pediatric plan is consistent with the agreed iPSP except that the division now has determined that extrapolation is acceptable for POS in patients 4 to less than 12 years of age. Therefore, an adequate and well-controlled study will no longer be required.
- The PeRC recommended that a single PK PMR could be conducted to include all patients 1 month to 12 years of age rather than 2 separate PK studies.
- The division specified the waivers for POS and PGTC seizures as follows:
  - POS: Ages less than one month old because necessary studies are impossible or highly impracticable due to difficulties in diagnostic.
  - PGTC seizures: Birth to less than 24 months of age because necessary studies are impossible or highly impracticable.
- *PeRC Recommendations:*
  - The PeRC also recommends that the Division add dates for the PMRs.
  - See additional comments provided in the PeRC Template for the division on February 24, 2016.

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/s/  
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GETTIE AUDAIN  
03/18/2016

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt, Stephanie](#)  
**Subject:** RE: NDA 208277 Advice/Information Request: DMEPA  
**Date:** Monday, March 07, 2016 6:55:21 AM

---

Received, thank you Stephanie.

Heather A. Bradley, MPH  
Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: 201-699-6714  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

From: "Parncutt, Stephanie" <[Stephanie.Parncutt@fda.hhs.gov](mailto:Stephanie.Parncutt@fda.hhs.gov)>  
To: "Heather\_Bradley@Eisai.com" <[Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)>  
Date: 03/05/2016 01:59 AM  
Subject: RE: NDA 208277 Advice/Information Request: DMEPA

---

Heather,

Please see the response from DMEPA:

**The Sponsor can submit all of the carton and container changes at once, including their proposal below and the revisions DMEPA requested. We will review them all at once to determine acceptability.**

Please confirm receipt.

Thank you,

Stephanie

**From:** Heather\_Bradley@Eisai.com [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Thursday, March 03, 2016 12:25 PM  
**To:** Parncutt, Stephanie  
**Subject:** Re: NDA 208277 Advice/Information Request: DMEPA  
**Importance:** High

Dear Stephanie,  
Received, thank you. We were just about to submit a labeling amendment for the carton and container to reflect the oral suspension fill volume rather than the bottle size. Is it possible for DMEPA to comment on this proposed change by tomorrow? If acceptable, we will incorporate all changes (fill volume and today's requests) into one response to the NDA next week. Attached is a mock-up of the changes we intended file to show fill volume rather than bottle size.

To clarify, these attached files are **not** our response to today's DMEPA recommendations. We intend also to carry this revision over to the USPI but will defer that revision until the FDA Round 1 edits are received.

Heather A. Bradley, MPH  
Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: 201-699-6714  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

From: "Parncutt, Stephanie" <[Stephanie.Parncutt@fda.hhs.gov](mailto:Stephanie.Parncutt@fda.hhs.gov)>  
To: "[Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)" <[Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)>  
Date: 03/03/2016 11:49 AM  
Subject: NDA 208277 Advice/Information Request: DMEPA

---

Heather,

Please see the attached recommendations from DMEPA, regarding Carton & Container labeling. Please provide a response submission within 5-7 business days.

Please confirm receipt of this submission.

Thank you,

~~~~~  
Stephanie N. Parncutt, MHA
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4165
Silver Spring, MD 20993-0002
phone: 301-796-4098
email: stephanie.parncutt@fda.hhs.gov

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/s/

STEPHANIE N PARNCUTT
03/07/2016

From: Heather_Bradley@Eisai.com
To: Parncutt_Stephanie
Subject: Re: NDA 208277 - IR for withdrawal AEs for perampanel for post-marketing period
Date: Monday, February 29, 2016 10:15:33 AM

Dear Stephanie,
Received, thank you. Do you have a response deadline for this IR?

Heather A. Bradley, MPH
Director, Global Regulatory Affairs

Eisai Inc.
155 Tice Boulevard
Woodcliff Lake, NJ 07677
Tel: 201-949-4691
Cell: 201-699-6714
Fax: 201-949-4595
heather_bradley@eisai.com

From: "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>
To: "Heather_Bradley@Eisai.com" <Heather_Bradley@Eisai.com>
Date: 02/28/2016 10:04 PM
Subject: NDA 208277 - IR for withdrawal AEs for perampanel for post-marketing period

Heather,

Please see the following IR from our CSS team:

CSS would like to request detailed information/CFRs for adverse events of drug withdrawal convulsions, drug dependence, overdoses intentional and not intentional that occurred during the whole post-marketing period.

Please confirm receipt.

Thank you,

~~~~~

Stephanie N. Parncutt, MHA  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4165  
Silver Spring, MD 20993-0002  
phone: 301-796-4098  
email: [stephanie.parncutt@fda.hhs.gov](mailto:stephanie.parncutt@fda.hhs.gov)

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/s/  
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STEPHANIE N PARNCUTT  
02/29/2016



Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**Memorandum of NDA - Initiated in Vivo Bioequivalence Inspection Assignment**

**Date:** December 21, 2015

**From:** Charles R. Bonapace, Pharm.D.  
Director  
Division of New Drug Bioequivalence Evaluation (DNDBE)  
Office of Study Integrity and Surveillance (OSIS)  
Office of Translational Sciences  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**To:** [ORAPHIBIMO@fda.hhs.gov](mailto:ORAPHIBIMO@fda.hhs.gov)

**Subject:** Premarket Original Surveillance BIMO Inspection Assignment

**Preannounce:** No

**Compliance Program:** 7348.001  
**PAC Code:** 48001A  
**Priority:** High  
**Operation Code:** 12 (Domestic Inspection)

**Application Number:** NDA 208277  
**Product Name:** Perampanel Oral Suspension  
**Sponsor:** Eisai Inc.

**Protocol Number:** E2007-A001-048

**Inspection Date:** (b) (4)  
**EIR Due Date:** (b) (4)

**Center Participation:** Yes  
**Joint Regulatory Agency Participation:** No

| Establishment<br>for inspection | FEI Number | FACTS Number |
|---------------------------------|------------|--------------|
| (b) (4)                         | (b) (4)    | (b) (4)      |

|             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Note</b> | <p>Please contact the POC <b>Yiyue Zhang</b> by sending an email to <a href="mailto:yiyue.zhang@fda.hhs.gov">yiyue.zhang@fda.hhs.gov</a> prior to the beginning of the inspection or during the inspection to verify the focus and intent of the inspection. We frequently receive real-time information from the review team that may change the focus of the inspection.</p> <p>Please follow the compliance program with emphasis on the specific instructions in the memorandum.</p> <p>If significant deviations are found during the inspection that may have impact on the safety of study subjects or accuracy and reliability of the data, we request that you expand the scope of your inspection as necessary and contact me immediately.</p> <p>At the end of the inspection, send an e-mail to <a href="mailto:yiyue.zhang@fda.hhs.gov">yiyue.zhang@fda.hhs.gov</a> with any inspection findings and copy of FDA-483 issued. Forward the EIR and exhibits to the contact address mentioned in the inspection memo.</p> <p><b>Important:</b> Forward any post-inspection correspondence from the establishment to Yiyue Zhang and <a href="mailto:CDER.OSIS.BEQ@fda.hhs.gov">CDER.OSIS.BEQ@fda.hhs.gov</a> as soon as possible. All post-inspection correspondence must be reviewed prior to issuing any post-inspection notification of compliance status.</p> |
|-------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

(b) (4)

This memo requests an inspection of the analytical portion of the following in vivo bioequivalence (BE) study. Background

(b) (4)

(b) (4)

**Do not reveal the applicant/sponsor, application number, study to be inspected, drug name, or the study investigator to the site prior to the start of the inspection.** The site will receive this information during the inspection opening meeting. The inspection will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

**Study Number:** E2007-A001-048

**Study Title:** "A Randomized, Open-Label, Crossover Study to Demonstrate Bioequivalence Between a 12-mg Dose of an Oral Suspension Formulation of Perampanel and a 12-mg Tablet Formulation of Perampanel Under Fasted and Fed Conditions in Healthy Subjects"

**Analytical Site:**

(b) (4)

**Investigator:**

**Methodology:**

(b) (4)

**During the analytical site inspection, please:**

☐ Examine all pertinent items related to the analytical method used for the measurement of analyte concentrations in human plasma.

☐ Compare the accuracy of the analytical data in the NDA submission against the original documents at the site.

☐ Determine if the site employed a validated analytical method to analyze the subject samples.

☐ Compare the assay parameters (such as variability between and

(b) (4)

within runs, accuracy and precision, etc.) observed during the study sample analysis with those obtained during method validation.

☐ Confirm that the accuracy and precision in matrix were determined using standards and QCs prepared from separate stock solutions.

☐ Determine if the subject samples were analyzed within the conditions and times of demonstrated stability. Note that

(b) (4) extended the validation of pera (b) (4) stability following a previous inspection. [FACTS (b) (4)]

☐ Confirm that freshly made calibrators and/or freshly made QCs were used for stability evaluations during method validation.

☐ Scrutinize the number of repeat assays of the subject plasma samples, the reason for such repetitions, the SOP(s) for repeat assays, and if relevant stability criteria (e.g., number of freeze-thaw cycles) sufficiently covered the stability of reanalyzed subject samples.

☐ Examine correspondence files between the analytical site and the Applicant for their content.

Draft: ZY 12/17/2015

Edit: MFS 12/18/2015, CB 12/21/2015

Email cc:

OSIS/Kassim/Taylor/Fenty-Stewart/Nkah/Kadavil/Miller

OSIS/DNDBE/Bonapace/Dasgupta/Cho/Zhang

OSI (b) (4) y/Choi

ORA (b) (4) /Campbell/Despins

OGR

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laborat E Program/Analytical  
Sites/ (b) (4)

BE file (b) (4)

**FACTS:** (b) (4)

Yiyue Zhang -S

Digitally signed by Yiyue Zhang -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yiyue Zhang -S,  
0.9.2342.19200300.100.1.1=2001741289  
Date: 2015.12.21 14:08:21 -05'00'

Yiyue Zhang, Ph.D.  
Division of New Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance

Charles R. Bonapace  
-A

Digitally signed by Charles R. Bonapace -A  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,  
ou=People, 0.9.2342.19200300.100.1.1=1300156609,  
cn=Charles R. Bonapace -A  
Date: 2015.12.21 14:26:36 -05'00'

Charles R. Bonapace, Pharm.D.  
Division of New Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance

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/s/  
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YIYUE ZHANG  
12/28/2015



NDA 208277

**INFORMATION REQUEST**

Eisai Inc.  
Attention: Heather Bradley, MPH  
Director, Regulatory Affairs  
155 Tice Blvd  
Woodcliff Lake, NJ 07677

Dear Ms. Bradley:

Please refer to your New Drug Application (NDA) dated 30 June 2015, received 30 June 2015, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Fycompa (perampanel) Oral Suspension 0.5 mg/mL.

We are reviewing the Chemistry Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA by Thursday, 31 December 2015.

**Drug Product:**

1. The drug product specification is devoid of tests for redispersibility and particle size. Update the drug product specification to include these tests or provide adequate justification for the exclusion of these tests
2. Confirm that the polymorphic form [REDACTED] (b) (4)

**Biopharmaceutics:**

1. Provide a list of critical material attributes (CMA) and critical process parameters (CPP) affecting dissolution and demonstrate the discriminating ability of the proposed dissolution method with regard to these CMAs and CPPs.
2. Refer to Table 3.2.P.2.3-10, Test results of [REDACTED] (b) (4) using your proposed method and submit the results to the NDA. We note that the particle size of perampanel

drug substance (D<sub>90</sub>) is (b) (4) μm; however, data presented in the table indicate that the particle size (b) (4) μm) at almost all (b) (4) times. Explain the

Drug Process:

1. We were unable to find any discussion regarding the order of addition and its impact on the CQA of the drug product. Please describe how the particular order of addition was selected for the manufacturing process.

6. Please provide statement of compliance for CFR regulations for direct food contact, or other justification, for the components which comes in direct contact during the manufacturing of the drug product.

(b) (4)

If you have any questions, please contact Dahlia A. Woody, Regulatory Business Process Manager, at (301) 796-8427

Sincerely,

**Martha R.  
Heimann -S**

Digitally signed by Martha R. Heimann -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,  
ou=People,  
0.9.2342.19200300.100.1.1=1300091527,  
cn=Martha R. Heimann -S  
Date: 2015.12.15 11:37:05 -05'00'

Martha R. Heimann, Ph.D.  
CMC Lead, Neurology Products  
Branch I, Division of New Drug Products I  
Office of New Drug Products  
Office of Pharmaceutical Quality



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 208277

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677

ATTENTION: Heather Bradley, MPH  
Director, Global Regulatory Affairs

Dear Ms. Bradley:

Please refer to your New Drug Application (NDA) dated and received June 30, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Perampanel Oral Suspension, 0.5 mg/mL.

We also refer to your correspondence dated and received September 9, 2015, requesting review of your proposed proprietary name, Fycompa.

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

If any of the proposed product characteristics as stated in your September 9, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,  
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact CDR 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 Stephanie Parncutt, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4098.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh

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  
11/09/2015



NDA 208277

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

Eisai Inc.  
Attention: Heather Bradley, MPH  
Director, Global Regulatory Affairs  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677

Dear Ms. Bradley:

Please refer to your New Drug Application (NDA) dated June 30, 2015, received June 30, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for FYCOMPA (perampanel) Oral Suspension.

We also refer to your amendments dated July 20, 2015; August 17, 2015; and August 28, 2015.

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 **April 30, 2016**.

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 **March 30, 2016**.

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.

We request that you submit the following information:

**Controlled Substance Staff**

1. Perampanel is listed in Schedule III of the Controlled Substances Act (CSA) (Dec 2013). The Schedule III recommendation applies to all mixtures, compounds, and preparations that contain any quantity of perampanel. If data on actual abuse show that Schedule III is not adequate to prevent abuse and diversion of the product, its schedule placement will be revisited. Thus far, there is insufficient marketing history to determine if Schedule III is inadequate.
2. You claim that the oral suspension has similar PK profile as the tablet formulation. PK data alone are usually insufficient for assessing abuse liability of a drug.
3. You should perform a dependence study in juvenile animals to be able to extrapolate the results from the adult dependence study.
4. You should continue to monitor for abuse and inappropriate use of the tablet and other approved formulations.

**Microbiology**

Non-sterile aqueous drug products may potentially be contaminated with organisms in the *Burkholderia cepacia* complex (BCC). BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate (b) (4)

(b) (4)  
For a recent review of FDA's perspective on BCC, please see *PDA J Pharm Sci Tech* 2011; 65(5): 535-43.

(b) (4)  
As there are currently no compendial methods for detection of BCC, we have provided suggestions for a potential validation approach and some points to consider when designing your validation studies. However, any validated method capable of detecting BCC organisms would be adequate. (b) (4)

(b) (4)  
Your submission should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated

organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to insure that the proposed recovery methods are adequate to recover organisms potentially present in the environment. For more information, we refer you to *Envir Microbiol* 2011; 13(1):1-12 and *J. Appl Microbiol* 1997; 83(3):322-6.

### **Maternal Health**

Together with submission of the proposed labeling for PLLR compliance, applicants should provide the following information to support the labeling content: a review and summary of the relevant published literature, summary of cases reported in the pharmacovigilance database, interim ongoing or final report on a closed pregnancy registry (if applicable).

During our preliminary review of your submitted labeling, you did not provide a review and summary of the available literature to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. Thus, your proposed PLLR labeling changes cannot be agreed upon until this information request is fulfilled. No partial PLLR conversions may be made.

Resubmit the following information on perampanel use in pregnant and lactating women by Nov 11, 2015:

- A review and summary of all available published literature regarding [drug name],
- A review and summary from your pharmacovigilance database,

Interim report from the ongoing pregnancy registry Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>). Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

### **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](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

### **Dosage Forms and Strengths in Highlights**

1. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by **October 2, 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:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

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.

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.

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

If you have any questions, call Stephanie N. Parncutt, M.H.A., Regulatory Health Project Manager, at (301) 796-4098.

Sincerely,

*{See appended electronic signature page}*

Eric Bastings, M.D.  
Deputy 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

09/11/2015

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)  
**To:** [Parncutt, Stephanie](#)  
**Subject:** RE: NDA 208277 Information Request - Clinical Pharmacology  
**Date:** Tuesday, August 25, 2015 3:24:03 PM

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Thank you, we are preparing the response, I'll update you when I know of a confirmed submission date, hopefully end of this week or early next week.

Heather

Heather A. Bradley, MPH  
Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677  
Tel: 201-949-4691  
Cell: 201-699-6714  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

From: "Parncutt, Stephanie" <[Stephanie.Parncutt@fda.hhs.gov](mailto:Stephanie.Parncutt@fda.hhs.gov)>  
To: "Heather\_Bradley@Eisai.com" <[Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)>  
Date: 08/25/2015 01:53 PM  
Subject: RE: NDA 208277 Information Request - Clinical Pharmacology

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No, your response will not influence the filing decision. However, please submit the response as soon as possible.

[Stephanie](#)

**From:** [Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com) [[mailto:Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)]  
**Sent:** Tuesday, August 25, 2015 12:59 PM  
**To:** Parncutt, Stephanie  
**Subject:** Re: NDA 208277 Information Request - Clinical Pharmacology

Dear Stephanie,  
Received, thank you. We are approaching the Day 60 filing determination date of 29 Aug 2015 for this NDA. Will the timing of our response to this IR influence the filing decision (i.e. is a response due on or before EOB on Friday August 28th in order to complete the filing acceptance determination)?

Regards,  
Heather

Heather A. Bradley, MPH  
Director, Global Regulatory Affairs

Eisai Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677

Tel: 201-949-4691  
Cell: 201-699-6714  
Fax: 201-949-4595  
[heather\\_bradley@eisai.com](mailto:heather_bradley@eisai.com)

From: "Parncutt, Stephanie" <[Stephanie.Parncutt@fda.hhs.gov](mailto:Stephanie.Parncutt@fda.hhs.gov)>  
To: "[Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)" <[Heather\\_Bradley@Eisai.com](mailto:Heather_Bradley@Eisai.com)>  
Date: 08/25/2015 12:42 PM  
Subject: NDA 208277 Information Request - Clinical Pharmacology

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Heather,

Please see the following IR from our Clinical Pharmacology team:

*You only provided the study report for population PK analysis (CPMS-E2007-010R). You need to provide files for dataset (with .xpt extension), model codes or control streams, and output listings (with .txt extension) for base structural model, final model, and simulations you conducted.*

Please confirm receipt.

Thank you,

~~~~~  
Stephanie N. Parncutt, MHA
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4165
Silver Spring, MD 20993-0002
phone: 301-796-4098
email: stephanie.parncutt@fda.hhs.gov

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[attachment "emfinfo.txt" deleted by Heather Bradley/RIG/EisaiInc]

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APPEARS THIS WAY ON ORIGINAL

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/s/

STEPHANIE N PARNCUTT
08/26/2015

From: Heather_Bradley@Eisai.com
To: [Parncutt, Stephanie](#)
Subject: Re: NDA 208277 FYCOMPA (perampanel) PLLR IR
Date: Wednesday, August 05, 2015 1:36:03 PM

Dear Stephanie,
Received, thank you.

Heather A. Bradley, MPH
Director, Global Regulatory Affairs

Eisai Inc.
155 Tice Boulevard
Woodcliff Lake, NJ 07677
Tel: 201-949-4691
Cell: 201-699-6714
Fax: 201-949-4595
heather_bradley@eisai.com

From: "Parncutt, Stephanie" <Stephanie.Parncutt@fda.hhs.gov>
To: "Heather_Bradley@Eisai.com" <Heather_Bradley@Eisai.com>
Date: 08/05/2015 01:23 PM
Subject: NDA 208277 FYCOMPA (perampanel) PLLR IR

Heather,

Please see the following IR from our Maternal Health Staff:

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) does not conform to the content and format requirements of the Pregnancy and Lactation Labeling Rule (PLLR) which implemented June 30, 2015. You must conform 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](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances, and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Please submit revised labeling on or before August 17, 2015.

Please confirm receipt.

~~~~~

Stephanie N. Parncutt, MHA  
Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4165  
Silver Spring, MD 20993-0002  
phone: 301-796-4098  
email: [stephanie.parncutt@fda.hhs.gov](mailto:stephanie.parncutt@fda.hhs.gov)

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[attachment "emfinfo.txt" deleted by Heather Bradley/RIG/EisaiInc]

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/s/  
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STEPHANIE N PARNCUTT  
08/11/2015

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|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |                                              | <b>PEDIATRIC AND MATERNAL HEALTH<br/>STAFF REQUEST FOR CONSULTATION</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                       |
| TO: CDER Pediatric and Maternal Health Staff <i>(please check)</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |         |                                              | FROM <i>(Name, Office/Division, and Phone Number of Requestor)</i> :<br>Billy Dunn, MD, Division of Neurology Products                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                       |
| Pediatrics <input checked="" type="checkbox"/> Maternal Health <input checked="" type="checkbox"/> Both <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                       |
| DATE<br>July 29, 2015                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | IND NO. | NDA/BLA NO.<br>208277                        | TYPE OF DOCUMENT<br>New NDA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | DATE OF DOCUMENT<br>June 30, 2015                     |
| NAME OF DRUG<br>FYCOMPA (perapanel)<br>Oral Suspension                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |         | NAME OF FIRM<br>Eisai, Inc.                  | CLASSIFICATION OF DRUG<br>Type 5 – New Formulation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | PDUFA Goal Date<br>PDUFA goal date = 4/30/16          |
| <b>Requested Consult</b><br><b>Completion Date: 8/29/15 - 4/30/16</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |         | <input type="checkbox"/> Urgent* (< 14 days) | <input type="checkbox"/> Priority (14-29 days)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <input checked="" type="checkbox"/> Routine ≥ 30 days |
| <p>*Note: Any consult requests with a desired completion date of &lt; 14 days from receipt must receive prior approval from PMHS team leaders. <b>Also, please check one of the three boxes above and also put in a due date.</b></p>                                                                                                                                                                                                                                                                                                                             |         |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                       |
| <b>REASON FOR REQUEST</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |         |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                       |
| <b>Pediatrics:</b><br><br><input checked="" type="checkbox"/> Labeling Review<br><input type="checkbox"/> Written Request/PPSR<br><input type="checkbox"/> PREA PMR/General Regulatory Question<br><input type="checkbox"/> SPA<br><input type="checkbox"/> Action Letter Review<br><input type="checkbox"/> 30-day IND Review<br><input type="checkbox"/> Other Protocol Review<br><input checked="" type="checkbox"/> Meeting Attendance<br><input checked="" type="checkbox"/> PeRC Preparation Assistance<br><input type="checkbox"/> Other (please explain): |         |                                              | <b>Maternal Health Team:</b><br><br><input checked="" type="checkbox"/> Labeling Review<br><input type="checkbox"/> Pregnancy Exposure Registry (protocol or report)<br><input type="checkbox"/> Clinical Lactation Study (protocol or report)<br><input type="checkbox"/> Pregnancy PK (protocol or report)<br><input type="checkbox"/> 30-day IND Review<br><input type="checkbox"/> Risk Management – Pregnancy Prevention and Planning<br><input type="checkbox"/> Evaluation of possible safety signal<br><input type="checkbox"/> Guidance development<br><input type="checkbox"/> Other (please explain): |                                                       |
| Link to electronic submission (if available):<br>EDR Location:<br><a href="\\CDSESUB1\evsprod\NDA208277\208277.enx">\\CDSESUB1\evsprod\NDA208277\208277.enx</a>                                                                                                                                                                                                                                                                                                                                                                                                   |         |                                              | <b>Materials to be reviewed:</b><br>The Pediatric information can be found in m1.9 for the supplement. You will also find that the sponsor has submitted Waiver and Deferral requests.                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                       |
| 1. Please briefly describe the submission including drug's indication(s):<br><b>NDA 208277</b><br><br><b>NEW NDA – New formulation of oral suspension for the adjunctive treatment of partial-onset seizures (POS) with or without secondarily generalized seizures and for primary generalized tonic-clonic (PGTC) seizures in patients with epilepsy aged 12 years and older.</b><br><br>FDA Stamp Date: 6/30/15<br>PDUFA Action Date: 4/30/16<br>Filing Date: 08/29/15<br>74 day letter date: 09/12/15                                                         |         |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                       |
| 2. Describe in detail the reason for your consult. Include specific questions:<br>Please make the necessary reviewer assignments for this New NDA. I need your reviewer assignments ASAP in order to include the reviewers in upcoming meetings.<br>Also, the Sponsor did not comply with PLLR, so MH will need to provide language for the Sponsor, in order to submit corrected labeling prior to Filing.                                                                                                                                                       |         |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                       |
| 3. Meeting dates:<br><b>August 29, 2015 - (FILING/PLANNING MEETING)</b><br><br><b>*** Additional team meetings and labeling meetings will be scheduled soon.</b>                                                                                                                                                                                                                                                                                                                                                                                                  |         |                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                       |

4. DARRTS Reference ID # for Prior Peds or Maternal Health consults for this product (within the last 3 years):

Review team:

Project Manager: Stephanie N. Parncutt, MHA

Clinical reviewer & Team Leader: Norm Hershkowitz/Natalie Getzoff

Pharmacology/Toxicology reviewer & Team Leader: Lois Freed/Christopher Toscano

Clinical Pharmacology reviewer & Team Leader: Angela Men/Xinning Yang

Other:

PRINTED NAME or SIGNATURE OF REQUESTOR:

Stephanie Parncutt, Regulatory Project Manager, DNP  
Food and Drug Administration

Phone: 301-796-4098

Email: [stephanie.parncutt@fda.hhs.gov](mailto:stephanie.parncutt@fda.hhs.gov)

METHOD OF DELIVERY (Please check)

☒ DARRTS ☐ EMAIL ☐ HAND ☐ OTHER

Version: [DARRTS 06/01/2011](#)

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/s/  
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STEPHANIE N PARNCUTT  
07/30/2015

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|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------------------------------------------|--------------------------------------------------------------------------------------------------------------------|------------------------------------------|---------------------------------------------------|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |         | <b>REQUEST FOR CONSULTATION</b>           |                                                                                                                    |                                          |                                                   |
| TO (Office/Division): <b>HFD-009/Controlled Substances Staff</b><br><b>Attention: Corinne Moody/ Michael Klein</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |         |                                           | FROM (Name, Office/Division, and Phone Number of Requestor): <b>Billy Dunn, MD, Division of Neurology Products</b> |                                          |                                                   |
| DATE<br><b>July 30, 2015</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | IND NO. | NDA NO.<br><b>208277</b>                  | TYPE OF DOCUMENT<br><b>New NDA</b>                                                                                 | DATE OF DOCUMENT<br><b>June 30, 2015</b> |                                                   |
| NAME OF DRUG<br><b>Fycompa (perampanel) Oral Suspension</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |         | PRIORITY CONSIDERATION<br><b>Standard</b> | CLASSIFICATION OF DRUG<br><b>5 - New Formulation</b>                                                               |                                          | DESIRED COMPLETION DATE<br><b>August 29, 2015</b> |
| NAME OF FIRM: <b>Eisai, Inc.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |         |                                           |                                                                                                                    |                                          |                                                   |
| <b>REASON FOR REQUEST</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         |                                           |                                                                                                                    |                                          |                                                   |
| <b>I. GENERAL</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |         |                                           |                                                                                                                    |                                          |                                                   |
| <div style="display: flex; flex-wrap: wrap;"> <div style="width: 33%;"> <input type="checkbox"/> NEW PROTOCOL<br/> <input type="checkbox"/> PROGRESS REPORT<br/> <input type="checkbox"/> NEW CORRESPONDENCE<br/> <input type="checkbox"/> DRUG ADVERTISING<br/> <input type="checkbox"/> ADVERSE REACTION REPORT<br/> <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION<br/> <input type="checkbox"/> MEETING PLANNED BY         </div> <div style="width: 33%;"> <input type="checkbox"/> PRE-NDA MEETING<br/> <input type="checkbox"/> END-OF-PHASE 2a MEETING<br/> <input type="checkbox"/> END-OF-PHASE 2 MEETING<br/> <input type="checkbox"/> RESUBMISSION<br/> <input type="checkbox"/> SAFETY / EFFICACY<br/> <input type="checkbox"/> PAPER NDA<br/> <input type="checkbox"/> CONTROL SUPPLEMENT         </div> <div style="width: 33%;"> <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br/> <input type="checkbox"/> FINAL PRINTED LABELING<br/> <input type="checkbox"/> LABELING REVISION<br/> <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br/> <input type="checkbox"/> FORMULATIVE REVIEW<br/> <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):         </div> </div> |         |                                           |                                                                                                                    |                                          |                                                   |
| <b>II. BIOMETRICS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |         |                                           |                                                                                                                    |                                          |                                                   |
| <div style="display: flex; flex-wrap: wrap;"> <div style="width: 50%;"> <input type="checkbox"/> PRIORITY P NDA REVIEW<br/> <input type="checkbox"/> END-OF-PHASE 2 MEETING<br/> <input type="checkbox"/> CONTROLLED STUDIES<br/> <input type="checkbox"/> PROTOCOL REVIEW<br/> <input type="checkbox"/> OTHER (SPECIFY BELOW):         </div> <div style="width: 50%;"> <input type="checkbox"/> CHEMISTRY REVIEW<br/> <input type="checkbox"/> PHARMACOLOGY<br/> <input type="checkbox"/> BIOPHARMACEUTICS<br/> <input type="checkbox"/> OTHER (SPECIFY BELOW):         </div> </div>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |         |                                           |                                                                                                                    |                                          |                                                   |
| <b>III. BIOPHARMACEUTICS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |         |                                           |                                                                                                                    |                                          |                                                   |
| <div style="display: flex; flex-wrap: wrap;"> <div style="width: 50%;"> <input type="checkbox"/> DISSOLUTION<br/> <input type="checkbox"/> BIOAVAILABILITY STUDIES<br/> <input type="checkbox"/> PHASE 4 STUDIES         </div> <div style="width: 50%;"> <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br/> <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS<br/> <input type="checkbox"/> IN-VIVO WAIVER REQUEST         </div> </div>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |         |                                           |                                                                                                                    |                                          |                                                   |
| <b>IV. DRUG SAFETY</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |                                           |                                                                                                                    |                                          |                                                   |
| <div style="display: flex; flex-wrap: wrap;"> <div style="width: 50%;"> <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br/> <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br/> <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br/> <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         </div> <div style="width: 50%;"> <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br/> <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br/> <input type="checkbox"/> POISON RISK ANALYSIS         </div> </div>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |         |                                           |                                                                                                                    |                                          |                                                   |
| <b>V. SCIENTIFIC INVESTIGATIONS</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |         |                                           |                                                                                                                    |                                          |                                                   |
| <div style="display: flex; flex-wrap: wrap;"> <div style="width: 50%;"> <input type="checkbox"/> CLINICAL         </div> <div style="width: 50%;"> <input type="checkbox"/> NONCLINICAL         </div> </div>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |         |                                           |                                                                                                                    |                                          |                                                   |
| <b>COMMENTS / SPECIAL INSTRUCTIONS:</b><br><p><b>NEW NDA – New formulation of oral suspension for the adjunctive treatment of partial-onset seizures (POS) with or without secondarily generalized seizures and for primary generalized tonic-clonic (PGTC) seizures in patients with epilepsy aged 12 years and older.</b></p> <p>FDA Stamp Date: 6/30/15<br/>         PDUFA Action Date: 4/30/16<br/>         Filing Date: 08/29/15<br/>         74 day letter date: 09/12/15</p> <p>EDR Location: \\CDSESUB1\evsprod\NDA208277\208277.enx</p> <p>DNP would like to know if a CSS review would be needed for the Oral Suspension formulation, since the Tablet formulation is already scheduled? Please see submission link and advise as to your reviewer assignments for the</p>                                                                                                                                                                                                                                                                                                                                                                                                                                    |         |                                           |                                                                                                                    |                                          |                                                   |

Filing/Planning meeting on August 29, 2015, from 10-11am.

SIGNATURE OF REQUESTOR

Stephanie Parncutt, Regulatory Project Manager, DNP  
Food and Drug Administration  
Phone: 301-796-4098  
Email: stephanie.parncutt@fda.hhs.gov

METHOD OF DELIVERY (Check one)

☐ DFS

☒ EMAIL

☐ MAIL

☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/  
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STEPHANIE N PARNCUTT  
07/30/2015

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| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                   | <b>REQUEST FOR PATIENT LABELING REVIEW CONSULTATION</b>                                                                                |                                                                                                                                       |                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                        |
| TO:<br><b>CDER-DMPP-PatientLabelingTeam</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                   | FROM: (Name/Title, Office/Division/Phone number of requestor) <b>Billy Dunn,<br/>MD, Division of Neurology Products</b>                |                                                                                                                                       |                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                        |
| REQUEST DATE:<br><b>July 29, 2015</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | NDA/BLA NO.:<br><b>208277</b>                                                                                                                                                                                                                                                                                                                     | TYPE OF DOCUMENTS:<br>(PLEASE CHECK OFF BELOW)                                                                                         |                                                                                                                                       |                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                        |
| NAME OF DRUG:<br><b>Fycompa (perampanel) Oral<br/>Suspension</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | PRIORITY CONSIDERATION:<br><b>Standard</b>                                                                                                                                                                                                                                                                                                        | CLASSIFICATION OF DRUG:<br><b>Type 5 – New<br/>Formulation</b>                                                                         | DESIRED COMPLETION DATE<br>(Generally 2 Weeks after receiving substantially<br>complete labeling)<br><br><b>Before March 30, 2016</b> |                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                        |
| SPONSOR:<br><b>Eisai, Inc.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                   | PDUFA Date: 4/30/16                                                                                                                    |                                                                                                                                       |                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                        |
| <b>TYPE OF LABEL TO REVIEW</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                        |                                                                                                                                       |                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                        |
| <table border="0"> <tr> <td> <b>TYPE OF LABELING:</b><br/>           (Check all that apply)<br/> <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI)<br/> <input checked="" type="checkbox"/> MEDICATION GUIDE<br/> <input type="checkbox"/> INSTRUCTIONS FOR USE (IFU)         </td> <td> <b>TYPE OF APPLICATION/SUBMISSION</b><br/> <input checked="" type="checkbox"/> ORIGINAL NDA/BLA<br/> <input type="checkbox"/> EFFICACY SUPPLEMENT<br/> <input type="checkbox"/> SAFETY SUPPLEMENT<br/> <input type="checkbox"/> LABELING SUPPLEMENT<br/> <input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT<br/> <input type="checkbox"/> PLR CONVERSION         </td> <td> <b>REASON FOR LABELING CONSULT</b><br/> <input type="checkbox"/> INITIAL PROPOSED LABELING<br/> <input type="checkbox"/> LABELING REVISION         </td> </tr> </table> |                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                        |                                                                                                                                       | <b>TYPE OF LABELING:</b><br>(Check all that apply)<br><input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI)<br><input checked="" type="checkbox"/> MEDICATION GUIDE<br><input type="checkbox"/> INSTRUCTIONS FOR USE (IFU) | <b>TYPE OF APPLICATION/SUBMISSION</b><br><input checked="" type="checkbox"/> ORIGINAL NDA/BLA<br><input type="checkbox"/> EFFICACY SUPPLEMENT<br><input type="checkbox"/> SAFETY SUPPLEMENT<br><input type="checkbox"/> LABELING SUPPLEMENT<br><input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT<br><input type="checkbox"/> PLR CONVERSION | <b>REASON FOR LABELING CONSULT</b><br><input type="checkbox"/> INITIAL PROPOSED LABELING<br><input type="checkbox"/> LABELING REVISION |
| <b>TYPE OF LABELING:</b><br>(Check all that apply)<br><input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI)<br><input checked="" type="checkbox"/> MEDICATION GUIDE<br><input type="checkbox"/> INSTRUCTIONS FOR USE (IFU)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <b>TYPE OF APPLICATION/SUBMISSION</b><br><input checked="" type="checkbox"/> ORIGINAL NDA/BLA<br><input type="checkbox"/> EFFICACY SUPPLEMENT<br><input type="checkbox"/> SAFETY SUPPLEMENT<br><input type="checkbox"/> LABELING SUPPLEMENT<br><input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT<br><input type="checkbox"/> PLR CONVERSION | <b>REASON FOR LABELING CONSULT</b><br><input type="checkbox"/> INITIAL PROPOSED LABELING<br><input type="checkbox"/> LABELING REVISION |                                                                                                                                       |                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                        |
| <b>EDR link to submission:</b><br>EDR Location: <a href="\\CDSESUB1\evsprod\NDA208277\208277.enx">\\CDSESUB1\evsprod\NDA208277\208277.enx</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                        |                                                                                                                                       |                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                        |
| <b>Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                        |                                                                                                                                       |                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                        |
| <b>COMMENTS/SPECIAL INSTRUCTIONS:</b><br>Please make the necessary reviewer assignments for this New NDA. I need your reviewer assignments ASAP in order to add your attendee to the Filing/Planning meeting.<br><br><b>Filing/Planning Meeting: August 29, 2015</b><br><br>Mid-Cycle Meeting: TBA<br><br>Labeling Meetings: TBA<br><br>Wrap-Up Meeting: TBA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                        |                                                                                                                                       |                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                        |
| SIGNATURE OF REQUESTER<br><b>Stephanie Parncutt, Regulatory Project Manager, DNP</b><br><b>Food and Drug Administration</b><br><b>Phone: 301-796-4098</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                        |                                                                                                                                       |                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                        |

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| Email: stephanie.parncutt@fda.hhs.gov |                                                                                              |
| SIGNATURE OF RECEIVER                 | METHOD OF DELIVERY (Check one)<br><input type="checkbox"/> eMAIL (BLAs Only) <b>X DARRTS</b> |

Version: 12/9/2011

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/s/  
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STEPHANIE N PARNCUTT  
07/29/2015

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| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                        | <b>REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION</b><br><br><b>**Please send immediately following the Filing/Planning meeting**</b>                                                |                                                                                                                  |                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                        |
| TO:<br><br><b>CDER-OPDP-RPM</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                        | FROM: (Name/Title, Office/Division/Phone number of requestor) <b>Billy Dunn, MD, Division of Neurology Products</b>                                                                                    |                                                                                                                  |                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                        |
| REQUEST DATE<br><b>07/29/15</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | IND NO.                                                                                                                                                                                                                                                                                                                | NDA/BLA NO.<br><b>208277</b>                                                                                                                                                                           | TYPE OF DOCUMENTS<br>(PLEASE CHECK OFF BELOW)                                                                    |                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                        |
| NAME OF DRUG<br><br><b>Fycompa (perampanel) Oral Suspension</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | PRIORITY CONSIDERATION<br><br><b>Standard</b>                                                                                                                                                                                                                                                                          | CLASSIFICATION OF DRUG<br><br><b>Type 5: New Formulation</b>                                                                                                                                           | DESIRED COMPLETION DATE<br>(Generally 1 week before the wrap-up meeting)<br><br><b>Goal Date: March 30, 2016</b> |                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                        |
| NAME OF FIRM:<br><br><b>Eisai, Inc.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                        | PDUFA Date: <b>April 30, 2016</b>                                                                                                                                                                      |                                                                                                                  |                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                        |
| <b>TYPE OF LABEL TO REVIEW</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                        |                                                                                                                  |                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                        |
| <table style="width: 100%; border: none;"> <tr> <td style="width: 33%; vertical-align: top;"> <b>TYPE OF LABELING:</b><br/>           (Check all that apply)<br/> <input type="checkbox"/> PACKAGE INSERT (PI)<br/> <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI)<br/> <input type="checkbox"/> CARTON/CONTAINER LABELING<br/> <input type="checkbox"/> MEDICATION GUIDE<br/> <input type="checkbox"/> INSTRUCTIONS FOR USE (IFU)         </td> <td style="width: 33%; vertical-align: top;"> <b>TYPE OF APPLICATION/SUBMISSION</b><br/> <input checked="" type="checkbox"/> ORIGINAL NDA/BLA<br/> <input type="checkbox"/> IND<br/> <input type="checkbox"/> EFFICACY SUPPLEMENT<br/> <input type="checkbox"/> SAFETY SUPPLEMENT<br/> <input type="checkbox"/> LABELING SUPPLEMENT<br/> <input type="checkbox"/> PLR CONVERSION         </td> <td style="width: 33%; vertical-align: top;"> <b>REASON FOR LABELING CONSULT</b><br/> <input type="checkbox"/> INITIAL PROPOSED LABELING<br/> <input type="checkbox"/> LABELING REVISION<br/><br/> <b>For OSE USE ONLY</b><br/> <input type="checkbox"/> REMS         </td> </tr> </table> |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                        |                                                                                                                  | <b>TYPE OF LABELING:</b><br>(Check all that apply)<br><input type="checkbox"/> PACKAGE INSERT (PI)<br><input type="checkbox"/> PATIENT PACKAGE INSERT (PPI)<br><input type="checkbox"/> CARTON/CONTAINER LABELING<br><input type="checkbox"/> MEDICATION GUIDE<br><input type="checkbox"/> INSTRUCTIONS FOR USE (IFU) | <b>TYPE OF APPLICATION/SUBMISSION</b><br><input checked="" type="checkbox"/> ORIGINAL NDA/BLA<br><input type="checkbox"/> IND<br><input type="checkbox"/> EFFICACY SUPPLEMENT<br><input type="checkbox"/> SAFETY SUPPLEMENT<br><input type="checkbox"/> LABELING SUPPLEMENT<br><input type="checkbox"/> PLR CONVERSION | <b>REASON FOR LABELING CONSULT</b><br><input type="checkbox"/> INITIAL PROPOSED LABELING<br><input type="checkbox"/> LABELING REVISION<br><br><b>For OSE USE ONLY</b><br><input type="checkbox"/> REMS |
| <b>TYPE OF LABELING:</b><br>(Check all that apply)<br><input type="checkbox"/> PACKAGE INSERT (PI)<br><input type="checkbox"/> PATIENT PACKAGE INSERT (PPI)<br><input type="checkbox"/> CARTON/CONTAINER LABELING<br><input type="checkbox"/> MEDICATION GUIDE<br><input type="checkbox"/> INSTRUCTIONS FOR USE (IFU)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | <b>TYPE OF APPLICATION/SUBMISSION</b><br><input checked="" type="checkbox"/> ORIGINAL NDA/BLA<br><input type="checkbox"/> IND<br><input type="checkbox"/> EFFICACY SUPPLEMENT<br><input type="checkbox"/> SAFETY SUPPLEMENT<br><input type="checkbox"/> LABELING SUPPLEMENT<br><input type="checkbox"/> PLR CONVERSION | <b>REASON FOR LABELING CONSULT</b><br><input type="checkbox"/> INITIAL PROPOSED LABELING<br><input type="checkbox"/> LABELING REVISION<br><br><b>For OSE USE ONLY</b><br><input type="checkbox"/> REMS |                                                                                                                  |                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                        |
| <b>EDR link to submission:</b> EDR Location: <a href="\\CDSESUB1\evsprod\NDA208277\208277.enx">\\CDSESUB1\evsprod\NDA208277\208277.enx</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                        |                                                                                                                  |                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                        |
| <p><b>Please Note:</b> There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.</p> <p><b>OSE/DRISK ONLY:</b> For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.</p>                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                        |                                                                                                                  |                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                        |
| <b>COMMENTS/SPECIAL INSTRUCTIONS:</b><br>Filing/Planning Meeting: August 29, 2015 (10:00 – 11:00 AM EST)<br>Mid-Cycle Meeting: TBA<br>Labeling Meetings: TBA<br>Wrap-Up Meeting: TBA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                        |                                                                                                                  |                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                        |
| SIGNATURE OF REQUESTER<br><b>Stephanie Parncutt, MHA, Regulatory Project Manager, DNP</b><br><b>Food and Drug Administration</b><br><b>Phone: 301-796-4098</b><br><b>Email: <a href="mailto:stephanie.parncutt@fda.hhs.gov">stephanie.parncutt@fda.hhs.gov</a></b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                        |                                                                                                                  |                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                        |

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| SIGNATURE OF RECEIVER | METHOD OF DELIVERY (Check one)<br><input checked="" type="checkbox"/> eMAIL <input type="checkbox"/> HAND |

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/s/  
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STEPHANIE N PARNCUTT  
07/29/2015



NDA 208277

**NDA ACKNOWLEDGMENT**

Eisai Inc.  
Attention: Heather Bradley, MPH  
Director, Global Regulatory Affairs  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677

Dear Ms. Bradley:

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

Name of Drug Product: FYCOMPA (perampanel) Oral Suspension

Date of Application: June 30, 2015

Date of Receipt: June 30, 2015

Our Reference Number: NDA 208277

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 August 29, 2015, 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

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, call me at (301) 796-4098 or email me at [Stephanie.Parncutt@fda.hhs.gov](mailto:Stephanie.Parncutt@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Stephanie N. Parncutt, MHA  
Regulatory Health Project Manager  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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STEPHANIE N PARNCUTT  
07/22/2015

**Meeting Date:** May 5, 2015**Time:** 11:00 AM– 12:00 PM EST**Meeting Type:** Type B/pre-sNDA meeting**Sponsor:** Eisai, Inc.**Product:** Perampanel (E2007) Oral Suspension**Proposed Use:** Adjunctive therapy for the treatment of primary generalized tonic-clonic seizures in patients with epilepsy aged 12 years and older.

**Introductory Comment:** This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for May 5, 2015 at 11:00 AM– 12:00 PM EST between Eisai, Inc., and the Division of Neurology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

## **SUMMARY OF QUESTIONS AND FDA PRELIMINARY RESPONSES**

### *Clinical Safety – ISS and Cross-Referencing to NDA 202834*

**QUESTION 1:** Can the Division confirm that an Integrated Summary of Safety (ISS) is not required for the OS NDA and that the perampanel tablet NDA 202834 can be cross-referenced in the Summary of Clinical Safety (SCS) for the purpose of establishing the safety of perampanel?

### **FDA Preliminary Response**

*Your plan to cross-reference the perampanel tablet NDA 202834 in the Summary of Clinical Safety (SCS) for the purpose of establishing the safety of perampanel oral solution is acceptable.*

**QUESTION 2:** Can the Division confirm that inclusion of Study (b) (4) is not required for this bioequivalence-based NDA?

**FDA Preliminary Response**

*Inclusion of Study (b) (4) in this NDA is not necessary.*

*Clinical Efficacy –Cross-Referencing to NDA 202834 for Efficacy*

**QUESTION 3:** Can the Division confirm that neither an Integrated Summary of Efficacy (ISE) nor Summary of Clinical Efficacy (SCE) is required for the OS NDA and that the perampanel tablet NDA 202834 can be cross-referenced for the purposes of establishing the efficacy of perampanel?

**FDA Preliminary Response**

*Your plan to include neither an Integrated Summary of Efficacy (ISE) nor Summary of Clinical Efficacy (SCE) but instead to cross-reference the perampanel tablet NDA 202834 for the purpose of establishing the efficacy of perampanel oral solution is acceptable. Safety data should, of course, be contained in all pharmacokinetic study report submitted.*

*Statistical –SDTM Datasets*

**QUESTION 4:** Can the Division confirm that the proposed SDTM dataset submission plans for the two CSRs to be included in the OS NDA are acceptable.

**FDA Preliminary Response**

*Your plan is acceptable.*

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/s/  
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STEPHANIE N PARNCUTT  
04/30/2015



IND 112515

**MEETING REQUEST-  
WRITTEN RESPONSES**

Eisai, Inc.  
155 Tice Boulevard  
Woodcliff Lake, NJ 07677

Attention: Heather Bradley, MPH  
Associate Director, Global Regulatory Affairs

Dear Ms. Bradley:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for perampanel (E2007) adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

We also refer to your submission dated March 17, 2014, containing a Type C meeting request. The purpose of the requested meeting was to discuss a proposed study to establish bioequivalence between perampanel oral suspension and perampanel oral tablets, with the goal of establishing an alternative suspension formulation to the approved indication under NDA 202834.

Further reference is made to our Meeting Granted letter dated March 31, 2014, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your April 24, 2014, background package.

If you have any questions, call Cathleen Michaloski, Sr. Regulatory Project Manager at (301) 796-1123.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure:  
Written Responses



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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## WRITTEN RESPONSES

**Meeting Type:** Meeting Type C  
**Meeting Category:** Guidance

**Application Number:** IND 112515  
**Product Name:** E2007 perampanel (Fycompa) oral suspension (OS)  
**Indication:** adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

**Sponsor/Applicant Name:** Eisai, Inc.

### 1.0 BACKGROUND

Fycompa (perampanel) tablets ranging in strength from 2 to 12 mg are the formulations currently approved under NDA 202834. Eisai intends to submit a New Drug Application (NDA) for perampanel OS as an alternative formulation for perampanel tablets in the approved labeling supported by a pivotal bioequivalence (BE) study between perampanel tablet and OS formulations. The purpose of the meeting/questions is to obtain agreement with the Division on the design and objectives of a proposed pivotal bioequivalence (BE) study and supportive modeling and simulation (if needed) that will be submitted to register perampanel OS as an alternative formulation to perampanel tablets in the Fycompa (perampanel) approved package insert. Chemistry, Manufacturing, and Controls (CMC) considerations for the perampanel OS registration package to accompany the BE study are also included.

### 2.0 QUESTIONS AND RESPONSES

#### 2.1 Category: Clinical Pharmacology

**Question 1:** Proposed Pivotal Bioequivalence Study Design: Can the Division confirm that the proposed Study 048 is sufficient to establish BE between perampanel OS and tablet formulations and to support approval of the OS formulation as an alternative to the currently approved tablet formulation.

#### **FDA Response to Question 1:**

Yes. We also recommend that you include sequence factor as a fixed effect in the mixed linear model to analyze the data.

**Question 2:** Supportive Modeling and Simulation for  $C_{\max}$  Parameter: Can the Division confirm that modeling and simulation analyses can be used to support approval of perampanel OS as a bioequivalent formulation if the rate of absorption in the proposed single-dose BE Study 048 is different between tablet and OS?

**FDA Response to Question 2:**

Besides the analysis you proposed, you also need to evaluate any potential difference in  $C_{\min}$  of perampanel at steady-state under fasted and fed conditions. In addition, you should simulate the scenarios where patients on maintenance doses of perampanel switch from the tablet formulation to the oral suspension formulation and *vice versa*. Comparability of  $C_{\max}$ , AUC, and  $C_{\min}$  of perampanel should be demonstrated in these scenarios (before and after switching). Otherwise, justification for no impact of the PK differences on clinical relevance of perampanel (efficacy and safety) should be provided.

**2.2. Category: Chemistry**

**Question 3:** Supporting Stability for Perampanel OS NDA: Does the Division agree with the proposed drug product stability data package to be filed in the perampanel oral suspension NDA?

**FDA Response to Question 3:**

The FDA recommends that you submit twelve months stability data in your NDA submission to support the shelf life of the product. Submission of less data would not support extrapolation beyond real time. Whether we will review additional data submitted during the same review cycle will be determined based on available resources at the time the data are received.

**Question 4:** Preservative Efficacy Testing (PET): Can the Division confirm that the proposed PET timepoints for perampanel OS NDA is acceptable?

**FDA Response to Question 4:**

The FDA concurs with the proposed time points for stability.

**Additional Biopharmaceutics Comments:**

Based upon the information in this submission, we have the following comments regarding the biopharmaceutics information that should be provided in your NDA.

**1. Data Supporting the Approval of the Lower Strength:** Note, that if you are not planning on evaluating the lower strength of your proposed product in clinical trials, the submission of bioequivalence (BE) and/or bioavailability (BA) information for lower strength (s) of your proposed product may be waived if the following CFR requirements are met:

- a) Inclusion of the biowaiver request as part of the NDA submission;
- b) The lower strength (s) and higher strength products have the same dosage form;
- c) There is BA/BE data for the highest strength;
- d) The lower strength (s) product is proportionally similar in its active and inactive ingredients to the highest strength product;
- e) The lower and highest strength products have the same manufacturing process; and
- f) Dissolution profile comparisons between the highest and lower strengths in three different media meet the similarity requirements.

**2. Dissolution Method:** You must include the dissolution method report supporting the selection of the proposed test. The report should include the following information:

- a) The pH solubility profile;
- b) Detailed description of the dissolution method being proposed for the evaluation of your product and the developmental parameters (*i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.*) used to select the proposed dissolution method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The conditions used for each test should be clearly specified. If possible, the dissolution profile should be complete and cover at least (b)(4) % of drug release of the label amount or whenever a plateau (*i.e., no increase over 3 consecutive time-points*) is reached. We recommend use of at least twelve samples per testing variable;
- c) Provide the complete dissolution profile data (*individual, mean, SD, profiles*) for your product. The dissolution data should be reported as the amount of drug release with time;
- d) Provide data to support the discriminating capability of the proposed dissolution method. 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 manufacturing variables (*e.g. drug substance particle size, drug substance solid state, etc.*). In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent.

Note, that the discriminating ability is not only determined by the dissolution method settings but also by the selected specification-sampling time point and specification value.

### **Additional FDA Advice**

#### **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>

#### **LABORATORY TEST UNITS FOR CLINICAL TRIALS**

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm) (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

#### **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.

|                                                                                                                                                                                                                              |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><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></p> |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

| <b>Source of information<br/>(e.g., published literature, name of<br/>listed drug)</b> | <b>Information Provided<br/>(e.g., specific sections of the 505(b)(2)<br/>application or labeling)</b> |
|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <i>1. Example: Published literature</i>                                                | <i>Nonclinical toxicology</i>                                                                          |
| <i>2. Example: NDA XXXXXX<br/>“TRADENAME”</i>                                          | <i>Previous finding of effectiveness for<br/>indication X</i>                                          |
| <i>3. Example: NDA YYYYYY<br/>“TRADENAME”</i>                                          | <i>Previous finding of safety for<br/>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.

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/s/  
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ERIC P BASTINGS

05/27/2014