CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208277Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval

NDA 208277

Review 1
April 26, 2016

Drug Name/Dosage Form	Fycompa (perampanel)
Strength	0.5 mg/mL
Route of Administration	Oral Suspension
Rx/OTC Dispensed	Rx
Applicant	Eisai Inc.
US agent, if applicable	N/A

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sherita McLamore	Branch 1/DNDP 1/ONDP
Drug Product	Sherita McLamore	Branch 1/DNDP 1/ONDP
Process	Kumar Janoria	Branch VII/DPA3/OPF
Microbiology	Peggy Kriger	Branch 1/DMA/OPF
Facility	Ruo (Rose) Xu	Branch 2/DIA/OPF
Biopharmaceutics	Om Anand	Branch 1/DB/ONDP
Regulatory Business Process Manager	Dahlia Woody	Branch 1/DRBPM1/OPRO
Application Technical Lead	Martha Heimann	Branch 1/DNDP 1/ONDP
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Assessment (EA)	Sherita McLamore	Branch 1/DNDP 1/ONDP

SUBMISSIONS REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	30-Jun-2015	All
Revised 356h with corrected facility information.	20-Jul-2015	RBPM, Facility
Response to IR, stability update	29-Oct-2015	Microbiology, Drug Product
Response to IR	30-Dec-2015	Biopharmaceutics, Drug Product, Process
Response to IR	18-Mar-2016	Drug Product, Process

Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type III		(b) (4)	N/A [1]	N/A [1]	
	Type III			N/A [1]	N/A [1]	
	Type III			N/A [1]	N/A [1]	
	Type III			N/A [1]	N/A [1]	
	Type III			N/A [1]	N/A [1]	

[1] Adequate information provided in application

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	68368	Development of perampanel tablets for epilepsy
IND	112515	Development of perampanel oral suspension
NDA	202834	Approved NDA for Fycompa tablets

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a quality perspective, NDA 208277 for Fycompa® (perampanel) oral suspension is recommended for approval.

The oral suspension is a follow-on product to the approved Fycompa tablets. It offers advantages for patients who are unable to swallow tablets. Additionally, although Fycompa is not currently approved for patients under 12 years old; the oral suspension is a potential dosage form for younger patients.

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

There are no Phase 4 commitments or agreements. The OPQ review team did not identify any issues that would require risk management steps.

II. Summary of Quality Assessments

Perampanel is a first-in-class, selective, non-competitive antagonist of the ionotropic α amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) glutamate receptor. It is thought that activation of AMPA receptors by glutamate is responsible for most fast excitatory synaptic transmission in the brain. In in-vitro studies, perampanel inhibited AMPA-induced increase in intracellular calcium. Perampanel tablets were approved for treatment of epilepsy on 22-Oct-2012.

The current NDA provides for a 0.5 mg/mL oral suspension. The prosed indication and dosing regimen are the same as for the approved tablets.

A. Drug Substance Quality Summary for Perampanel

Information related to the manufacture and control of perampanel bulk drug substance is incorporated by cross-reference to the applicant's NDA 208234. Drug substance used to manufacture Fycompa oral suspension complies with the same requirements, including particle size, as for Fycompa tablets.

B. Drug Product Quality Summary for Fycompa Oral Suspension

Fycompa oral suspension is an aqueous oral suspension containing 0.50 mg of perampanel per mL. The formulation contains compendial excipients, including microcrystalline cellulose and carboxymethylcellulose sodium (b) (4) sorbitol (b) (4) poloxamer (b) (4), simethicone (b) (4) (b) (4) (b) (4) citric acid (b) (4) sodium benzoate (b) (4), and purified water. All excipients meet compendial (USP/NF), and are commonly used in liquid oral dosage forms. The suspension is packaged in an amber polyethylene terephthalate (PETE) bottle containing 340 mL of suspension, with a child-resistant (b) (4) closure and a (b) (4) liner. The product is supplied with two graduated 20 mL oral syringes and a press-in bottle adapter for the oral syringes.

Fycompa oral suspension is manufactured by a contract manufacturer, (b) (4) The manufacturing process uses (b) (4) However, evaluation of the process was problematic due to limited or unclear information provided by the applicant. For example, the applicant did not provide information regarding the order of addition of ingredients, or a rationale for the sequence. As another example, the applicant identified (b) (4). In response to an information request, the applicant clarified that (b) (4) controls did not allow these parameters to be varied beyond pre-set values. Significant deficiencies identified, and adequately addressed by the applicant include absence of suitable in-process controls (IPCs) (b) (4) To address in-process particle size controls, the applicant agreed to conduct an (b) (4)

The specifications for Fycompa oral suspension include appropriate tests for critical quality attributes (CQAs) including appearance, identification by HPLC and UV, assay, dissolution, related substances, (b) (4), pH, and microbial limits. All noncompendial analytical procedures are adequately described and validated.

Based on the available stability data, a 24-month expiration dating period is assigned for unopened product stored at or below 30°C. The product should be used within 90 days after opening the bottle or discarded. The product should not be frozen.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Fycompa
Non Proprietary Name of the Drug Product	Perampanel oral suspension
Non Proprietary Name of the Drug Substance	Perampanel
Proposed Indication(s) including Intended Patient Population	Adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy 12 years of age and older and adjunctive therapy for the treatment of primary generalized tonic-clonic seizures in patients with epilepsy 12 years of age and older.
Duration of Treatment	Chronic
Maximum Daily Dose	12 mg
Alternative Methods of Administration	Tablets

D. Biopharmaceutics Considerations

1. BCS Classification:
   - Drug Substance: An official designation has not been requested, however, perampanel is low solubility drug substance in particular below pH 4.5, therefore, it is potentially BCS Class 2 or class 4 compound.
   - Drug Product: An official designation has not been requested for this suspension formulation containing potentially BCS Class 2 or Class 4 compound
   -
2. Biowaivers/Biostudies
   - PK studies: E2007-A001-048 [bioequivalence (BE) study [Study 048]) (OCP is to review this study)
   - Biowaiver Requests: Not Applicable
   - IVIVC: Not Applicable

3. Dissolution method: **ACCEPTABLE**

The following proposed dissolution method is acceptable:

Apparatus	Speed	Volume and Medium
USP 2 (paddle)	50 rpm	900 mL [890 mL 0.1 M HCl + 10 mL perampanel oral suspension]

4. **Dissolution Acceptance Criterion: ACCEPTABLE**

The dissolution acceptance criterion of Q= (b) (4) at 15 minutes for perampanel is acceptable

The Division of Biopharmaceutics recommends APPROVAL of NDA 208277 for Perampanel Oral Suspension, 0.5 mg/mL.

E. Novel Approaches

The applicant did not employ any novel approaches.

F. Any Special Product Quality Labeling Recommendations

The product should be used within 90 days after opening the bottle or discarded. The product should not be frozen.

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:
The OPQ review team recommends Approval of NDA 208277.

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: 2016.04.26 19:07:13 -04'00'

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(b) (4)

[redacted]

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

Both drug substance and drug product manufacturers are acceptable.

Rose Xu, Facility Reviewer 1/25/2016

Secondary Review Comments and Concurrence:

I concur with this acceptable recommendation.

Christina Capacci-Daniel, PhD – 01April2016
Consumer Safety Officer / Acting QAL, OPQ/OPF/DIA/IABII

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

Review: The Biopharmaceutics review focuses on the evaluation and acceptability of the dissolution method and acceptance criterion.

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

Yes. The in-vitro dissolution test method and acceptance criterion are acceptable.

a. What are the highlights of the chemistry and what are the physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?

Perampanel oral suspension is a white to off white suspension and contains 0.5 mg/mL of perampanel (formulated by anhydrous basis).

Perampanel is practically insoluble in water. The solubility of perampanel in various media at 37 °C and dose solubility volumes for 12 mg (highest dosing) are summarized in Table 38.1. The solubility of perampanel is 0.47 mg/mL in 0.1 mol/L HCl and approximately 0.002 mg/mL in both pH 4.5 USP acetate buffer and pH 7.5 USP phosphate buffer. The pKa value of perampanel is 3.24. Perampanel has five anhydrous forms and one hydrate form. The crystal form of perampanel drug substance selected for manufacturing the oral suspension is the 3/4 hydrate form.

Table 38.1 Solubility of perampanel in various dissolution test media at 37 °C and dose solubility volumes for 12 mg

Media	Solubility (mg/mL)	Dose Solubility Volumes for 12 mg [c] (mL)
0.1 mol/L HCl	0.47	25 [d]
pH 4.5 USP acetate buffer [a]	0.0022	> 5400 [e]
pH 7.5 USP phosphate buffer [b]	0.0018	> 6600 [f]

a: Sodium acetate solution (approximately 0.02 mol/L) adjusted with 2 mol/L acetic acid solution at pH 4.5.

b: Monobasic potassium phosphate solution (approximately 0.05 mol/L) adjusted with 2 mol/L sodium hydroxide solution at pH 7.5.

c: Dose solubility volume means the minimum required amount to solubilize whole drug substance in each test medium

d: [12 mg (highest dosing)]/[0.47 mg/mL (0.1 mol/L HCl, 37°C)] = 25 mL

e: [12 mg (highest dosing)]/[0.0022 mg/mL (pH4.5 USP acetate buffer, 37°C)] > 5400 mL

f: [12 mg (highest dosing)]/[0.0018 mg/mL (pH7.5 USP phosphate buffer, 37°C)] > 6600 mL

b. Is there any information on the BCS classification? What claim did the Applicant make based on BCS classification? What data are available to support this claim?

The Applicant did not provide any BCS related information and made no claim on BCS classification. This Reviewer notes that Perampanel is practically insoluble in water and is rapidly and completely absorbed after oral administration with negligible first-pass metabolism[1]. This information indicates that Perampanel is potentially a BCS class 2 drug substance.

c. Does the proposed product meet the extended release designation claim? What data are provided to support the Applicant's claim?

N/A. Perampanel, Oral Suspension is an immediate-release dosage form.

d. What is the proposed dissolution method?

The Applicant proposed dissolution method parameters are provided below in Table 38.2:

Table 38.2: Proposed in vitro dissolution method

USP apparatus	Apparatus 2 (paddle)
Medium	0.1 mol/L hydrochloric acid[2] (b) (4)
Volume	900 mL [890 mL 0.1 M HCl + 10 mL perampanel oral suspension]
Rotation speed	50 rpm

e. What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?

(b) (4)

(b) (4)

[1] http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202834lbl.pdf

[2] (b) (4)

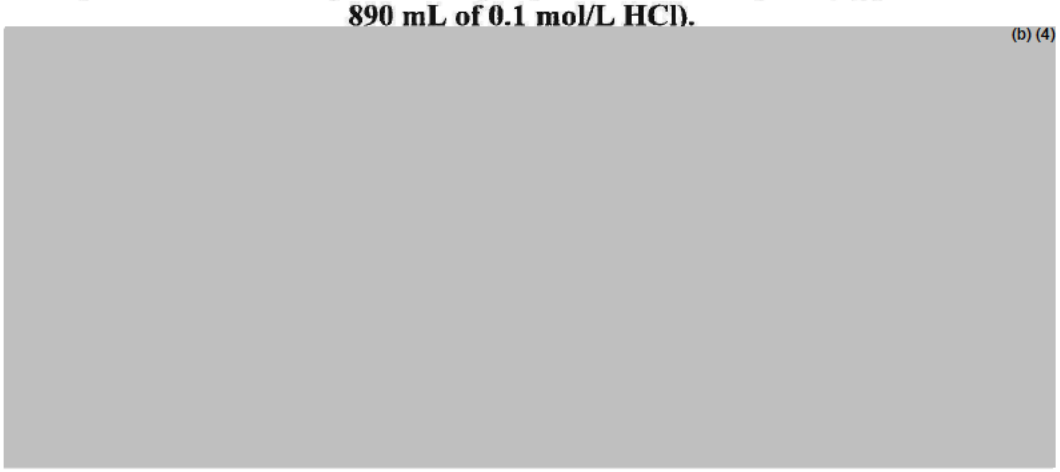
Figure 38.1 Dissolution profiles of perampanel oral suspension (10 mL, (b) (4) (b) (4) in various media (apparatus 2, 50 rpm, 890 ml of medium)

(b) (4)

(b) (4)

50 rpm was selected as the paddle rotation speed.

Figure 38.2 Comparison of dissolution profiles for perampanel oral suspension obtained by (b) (4) 50 rpm paddle rotation speed (Apparatus 2, 890 mL of 0.1 mol/L HCl).



f. What data are available to support the discriminating power of the dissolution method?

A physical mixture of perampanel and placebo suspension, [redacted], was subjected to the dissolution test. [redacted] shown in Figure 38.3, the physical mixture showed delayed dissolution of [redacted]

(b) (4)

[redacted]

Reviewer's Initial Assessment: UNSATISFACTORY: The reviewer disagreed with the Applicant conclusion that the dissolution methods are discriminating. Therefore, in an information request [IR dated 12/15/2015], the Applicant was asked to 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. The Applicant responded on 12/30/2015, the Applicant's response and the reviewer's assessment are presented below.

Information Request [IR dated 12/15/2015]:

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 API particle size during the (b) (4) process. Conduct dissolution testing on batches (b) (4) using your proposed method and submit the results to the NDA. We note that the particle size of perampanel drug substance (b) (4) however, data presented in the table indicate that the particle size increased (b) (4) at almost all (b) (4) times. Explain the observed increase in particle size during (b) (4) and the effect of this change on the dissolution profiles of batches (b) (4).

Applicant's Response [dated: 12/30/2015]: The Applicant provided the following information in response to the IR:

The Applicant provided critical material attributes (CMA) and critical process parameters (CPP) that affect dissolution (see table 38.4).

(b) (4)

(b) (4)

[redacted]

[redacted]

[3] The explanation for the observed differences is described in applicant response: drug product 1 and will be reviewed by the drug product reviewer.

(b) (4)

g. What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?

The method for dissolution testing of perampanel oral suspension has been validated. The method was found to be specific, robust [minor changes in temperature of the dissolution medium and paddle rotation] and provide acceptable precision, linearity, and accuracy over the range of concentrations studied. The validation results demonstrated that the dissolution method is suitable for dissolution testing of perampanel oral suspension.

As detailed in the validation report [Section: 3.2.P.5.3.6 Dissolution], sample solution and the standard solution were demonstrated to be stable (b) (4) A summary of the validation elements and results are presented in table 38.6 below:

(b) (4)

h. What is the proposed dissolution acceptance criterion? Is the proposed dissolution acceptance criterion adequate for assuring the consistent in vitro dissolution of the drug product?

The applicant proposes the following acceptance criterion:

Not less than (b) (4) (Q) in 15 minutes

The Applicant stated that perampanel oral suspension is formulated as an immediate release drug product. Thus, the acceptance criterion is set at not less than (b) (4) (Q) in 15 minutes. The batch analysis data demonstrated that the developed manufacturing process is well controlled and consistent for dissolution characterization of perampanel oral suspension. The drug product also demonstrates a rapid absorption [T_{max} approximately 0.50 to 2.00 h]. The applicant proposed acceptance criterion is acceptable.

i. **Is the proposed dissolution acceptance criterion acceptable? If not, what is the recommended dissolution acceptance criterion? Is the setting of the dissolution acceptance criterion based on data from clinical and registration batches? If not, is the setting based on BE or IVIVC data?**

The proposed dissolution acceptance criterion is acceptable. The dissolution acceptance criterion based on 12 unit data of registration batch (b) (4) Table 38.7] and limited data on other registration batches and the batch [H0001] used in the pivotal BE study [Study 048]).

Table 38.7: Dissolution Profiles of Perampanel Oral Suspension 0.5 mg/mL in 0.1 mol/L HCl[4]

(b) (4)

Paddle rotation speed: 50 rpm
Dissolution medium: 890 mL
Perampanel oral suspension 0.5 mg/mL: 10 mL

24. **Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?**

The Applicant stated that perampanel oral suspension (b) (4) were developed and used in clinical studies with the strength of 0.5 mg/mL perampanel (anhydrous basis). Minor changes were made in the formulation during the product development.

(b) (4) was used in Phase 1 study E2007-A001-048 [bioequivalence (BE) study [Study 048])] and Phase 2 study E2007-G000-238. (b) (4) (b) (4) is the proposed formulation for commercial production.

This application is based on data from a definitive bioequivalence (BE) study (Study E2007-A001-048; [Study 048]) that demonstrated BE between a single 12-mg dose of perampanel oral suspension and a single 12-mg dose of perampanel tablet when administered under fasted conditions in healthy subjects. Perampanel was administered as a single oral dose of a 12-mg tablet (Lot: 005814) and as a single 12-mg dose of an oral suspension (Lot: E127488-0001L001). Table 38.8; summarize the clinical batches, Batch # H0001 of Type (b) (4) of

[4] **Table 3.2.P.2.2-9 in the original submission**

perampanel oral suspension was used in (BE) study (Study E2007-A001-048; [Study 048]).

Table 38.8 Summary of clinical batches

Clinical Study				Drug Product				
Indication	Site of Study	Study Number	Study Title (Nature of Trial)	Dose Concentration	Batch Number of Drug Product	(b) (4)	Batch Size (L) (b) (4)	Batch Number of Drug Substance
-	UK	E2007-E044-028	A Randomized, Open-label, Crossover Study to Compare Relative Bioavailability Between a 4mg Dose of an Oral Suspension of Perampanel and a 4mg Tablet of Perampanel in Healthy Subjects	0.5 mg/mL	P94005ZZA			16091902
Epilepsy	USA	E2007-G000-232	An Open-label Pilot Study with an Extension Phase to Evaluate the Pharmacokinetics, and to Generate Preliminary Safety, Tolerability, and Efficacy of Perampanel (E2007) Oral Suspension when Given as an Adjunctive Therapy in Pediatric Subjects from 2 to less than 12 Years of Age with Epilepsy	0.5 mg/mL	P14007AZA			19030203
					P14010AZA			
					P14013AZA			
					P19016AZA			19072201
					P19019AZA			
					P23013AZA			19071501
					P23016AZA			
					P23019AZA			
				Placebo	P13015AZA			N/A
					P13018AZA			
					P13021AZA			
					P23004AZA			
					P23007AZA			
Epilepsy	USA	E2007-A001-04S	A Randomized, Open-Label Crossover Study to Demonstrate Bioequivalence Between a 12mg Dose of Oral Suspension Formulation of Perampanel and a 12mg Tablet Formulation of Perampanel Under Fasted and Fed Conditions in Healthy Subjects	0.5 mg/mL	H0001			13032801

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

Reviewer's Assessment and Signature:

Dissolution method: ACCEPTABLE

The following proposed dissolution method is acceptable:

Apparatus	Speed	Volume and Medium
USP 2 (paddle)	50 rpm	900 mL [890 mL 0.1 M HCl + 10 mL perampanel oral suspension]

Dissolution Acceptance Criterion: ACCEPTABLE

The Applicant is recommended to implement a dissolution acceptance criterion of Q= (b) (4) at 15 minutes for perampanel oral suspension.

The Division of Biopharmaceutics recommends APPROVAL of NDA 208277 for Perampanel Oral Suspension, 0.5 mg/mL.

03/04/2016

Om Anand, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics/ONDP
Office of Pharmaceutical Quality

Secondary Review Comments and Concurrence:

I concur with Dr. Anand's approval recommendation for NDA 208277.

3/8/2016
Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics/ONDP
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

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

Applicant's Response:

Reviewer's Assessment:

The microbial limits specification for Fycompa (perampanel) Oral Suspension 0.5 mg/mL is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

Fycompa (perampanel) Oral Suspension 0.5 mg/mL is an aqueous suspension for oral administration. The drug product is a multidose liquid formulation containing the (b) (4) Sodium benzoate at (b) (4)

The drug product is tested for microbial limits at release using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The microbial limits acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use). Chapter <1111> recommends that products of aqueous preparations for oral use contain NMT 10^2 CFU/mL total aerobic microbial count, NMT 10^1 CFU/mL total combined yeasts/molds count and that *Escherichia coli* be absent in 1 ml. The release specification for the drug product states that *Staphylococcus aureus* and *Pseudomonas aeruginosa* should also be absent.

The microbial limits test methods were verified, at a (b) (4) of product suspension, to be suitable for use with the drug product following procedures consistent with those in USP Chapter <61> and <62>. Sample testing will be performed by the poured plate microbial enumeration test for total aerobic counts and total yeasts and molds; specified microorganisms testing is by selective media.

As non-sterile aqueous drug products have the potential for contamination with organisms in the *Burkholderia cepacia* complex (BCC), the following information request was submitted to the sponsor on August 20, 2015 regarding risk assessment and testing methods for BCC:

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 in the presence of many traditional (b) (4) *systems. Thus, despite the presence of otherwise adequate* (b) (4) *systems,*

BCC strains can survive and even proliferate in product during storage. For a recent review of FDA's perspective on BCC please see PDA J Pharm Sci Tech 2011; 65(5): 535-43.
In order to control for the presence of BCC in your product you should consider the following:

(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)

In the applicant's response, received on October 29, 2015, a risk assessment and description of the current control strategy was provided, which included the following considerations:

(b) (4)

(b) (4)

Note to reviewer: The strategy used by the sponsor to control microbiological quality of perampanel oral suspension includes (b) (4)

(b) (4)

--

As noted above, the subject drug product is a non-sterile multidose product. (b) (4)

(b) (4)

The proposed shelf life of the product is 24 months. Stability studies currently in-progress for three product exhibit batches are tested for microbial limits, (b) (4) (b) (4) (b) (4) (b) (4) Data from tests performed after the 12 month storage point at the long-term storage conditions (30°C/35% RH) met requirements. The stability study will continue at least 36 months. The drug product will be tested for microbial limits and (b) (4) annually as part of the post-approval stability protocol. The release and stability specification is the same for routine production.

2.3.P.7 Container/Closure System

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

Applicant's Response:

Reviewer's Assessment: Refer to microbiology review in Question 25.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

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

Applicant's Response:

Reviewer's Assessment: N/A.

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

Applicant's Response:

Reviewer's Assessment: N/A.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Adequate
Peggy Kriger, March 3, 2016

Secondary Review Comments and Concurrence:
I concur.
Erika Pfeiler, Ph.D.
03 March 2016

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

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

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

Applicant's Response:
The applicant requested categorical exclusion under 21 CFR25.31 (…entry into the aquatic environment less than 1ppb) and provided the necessary calculations based on a production scale of (b) (4) kg to support this claim. The applicant further indicates that no extraordinary circumstances exist.

Reviewer's Assessment:
With an EIC of 0.002858 ppb, the applicant's claim for categorical exclusion is acceptable and adequate to support the approval of this application.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature: Adequate

Sherita McLamore Hines, Ph.D.

Supervisor Comments and Concurrence: I concur that the information provided is adequate to support approval of the drug product.

Wendy I. Wilson-Lee, Ph.D. 25-APR-2016
Branch Chief (Acting), DNDP1/ONDP

I. Review of Common Technical Document-Quality (CTD-Q) Module 1 Labeling & Package Insert

1. Package Insert

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

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FYCOMPA® safely and effectively. See full prescribing information for FYCOMPA®.

FYCOMPA® (perampanel) tablets, for oral use, CIII
FYCOMPA® (perampanel) Oral Suspension, CIII
Initial U.S. Approval: 2012

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Fycompa (perampanel)	adequate
Dosage form, route of administration	Oral Suspension	adequate
Controlled drug substance symbol (if applicable)	n/a	n/a
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	The drug product is presented as a 0.5 mg/mL oral suspension	adequate

(b) "Full Prescribing Information" Section

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

3 DOSAGE FORMS AND STRENGTHS

Tablets

- 2 mg Tablets: orange, round, debossed with "2" on one side and "€ 275" on the other.
- 4 mg Tablets: red, round, debossed with "4" on one side and "€ 277" on the other.
- 6 mg Tablets: pink, round, debossed with "6" on one side and "€ 294" on the other.
- 8 mg Tablets: purple, round, debossed with "8" on one side and "€ 295" on the other.
- 10 mg Tablets: green, round, debossed with "10" on one side and "€ 296" on the other.
- 12 mg Tablets: blue, round, debossed with "12" on one side and "€ 297" on the other.

Oral Suspension

White to off-white opaque liquid suspension

(b) (4)

[redacted]

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Dosage form included	adequate
Strengths: in metric system	The reviewer notes that the strength is listed in the metric system with an equivalency statement for each of the approved tablet strengths.	adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Full description included	adequate

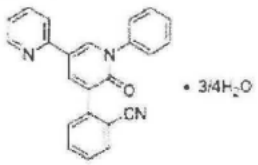
Conclusion: Information for oral suspension was revised to include strength and remove equivalency to tablet doses. Information is adequate to support the approval of application

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

11 DESCRIPTION

FYCOMPA contains perampanel, a non-competitive AMPA receptor antagonist. The chemical name of perampanel is 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl) benzonitrile hydrate (4:3).

The molecular formula is $C_{23}H_{15}N_3O \cdot 3/4H_2O$, and the molecular weight is 362.90 (3/4 hydrate). The chemical structure of perampanel is.



Perampanel is a white to yellowish white powder. It is freely soluble in N-methylpyrrolidone, sparingly soluble in acetonitrile and acetone, slightly soluble in methanol, ethanol and ethyl acetate, very slightly soluble in 1-octanol and diethyl ether, and practically insoluble in heptane and water.

FYCOMPA tablets are round, bi-convex, film-coated tablets containing 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, or 12 mg of perampanel. Tablets contain the following inactive ingredients: lactose monohydrate, low substituted hydroxypropyl cellulose, povidone, microcrystalline cellulose, magnesium stearate, hypromellose, polyethylene glycol, talc, and titanium dioxide. Tablets of different strengths may contain yellow ferric oxide (10 mg and 2 mg), red ferric oxide (2 mg, 4 mg, 6 mg, 8 mg), black ferric oxide (8 mg), and FD&C Blue No. 2 (indigo carmine) aluminum lake (10 mg and 12 mg).

FYCOMPA is also available for oral administration as a white to off-white opaque liquid providing perampanel in a concentration of 0.5 mg/mL. Inactive ingredients are: sorbitol, microcrystalline cellulose, carboxymethyl-cellulose sodium, poloxamer, simethicone, citric acid, sodium benzoate and purified water

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Information included: FYCOMPA	adequate
Dosage form and route of administration	Dosage form described as an opaque liquid-**Inadequate** Dosage form should be updated as a suspension. Route of administration is oral-**adequate**	adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	n/a	n/a
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii), listed by USP/NF names.	Information included: sorbitol, microcrystalline cellulose, carboxymethyl-cellulose sodium, poloxamer, simethicone, citric acid, sodium benzoate and purified water.	n/a
Statement of being sterile (if applicable)	n/a	n/a
Pharmacological/ therapeutic class	Information Included.	adequate
Chemical name, structural formula, molecular weight	Information included	adequate
If radioactive, statement of important nuclear characteristics.	n/a	n/a
Other important chemical or physical properties (such as pKa, solubility, or pH)	n/a	n/a

Conclusion: Information is adequate to support the approval of application

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

FYCOMPA Oral Suspension is supplied in a round amber PET bottle, (b) (4) with a child-resistant closure. It is packaged with a dispenser set that provides two 20-mL graduated oral dosing syringes and a push-in bottle adapter.

Bottle, (b) (4) NDC 62856-290-38

16.2 Storage
Tablets: store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to-86°F). [See USP Controlled Room Temperature]

Oral Suspension: Do not store above 30°C (86°F). Do not freeze. Use within 90 days after the first opening of the bottle.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Dosage form included strength not included	adequate
Available units (e.g., bottles of 100 tablets)	Information included	adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Information included	adequate
Special handling (e.g., protect from light, do not freeze)	Special handling noted: Do not freeze; Use within 90 days after opening	adequate
Storage conditions	adequate	adequate

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

(b) (4) Marketed by Eisai Inc., Woodcliff Lake, NJ 07677

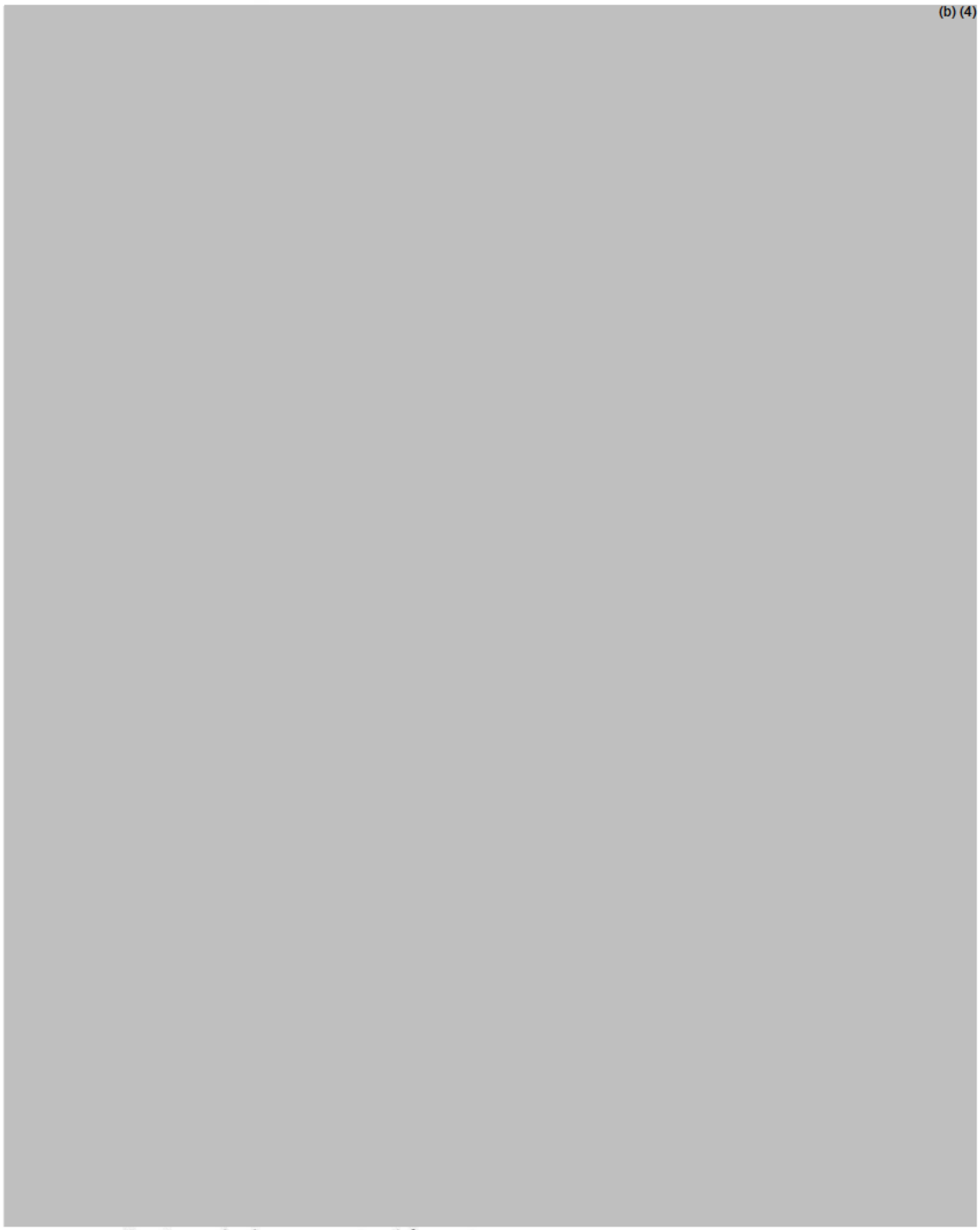
Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Information included	adequate

Conclusion: Revised How Supplied section in draft labeling to indicate oral suspension is supplied as 340 mL per bottle. Applicant incorrectly listed size of bottle (b) (4) not fill volume. Information is adequate to support the approval of application.

2. Labels

1) Immediate Container Label

(b) (4)



Reviewer's Assessment: Adequate

QUALITY ASSESSMENT

NDA 208277

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: Adequate

Sheela McLamore Hines, Ph.D.

Supervisor Comments and Concurrence: I concur that the information provided is adequate to support approval of the drug product.

Wendy I. Wilson-Lee, Ph.D. **25-APR-2016**
Branch Chief (Acting), DNDP1/ONDP

II. List of Deficiencies To Be Communicated

Not applicable

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, Stability	Formulation, raw materials, container closure, process parameters, scale/equipment	L	Drug substance is highly stable. All excipients were evaluated for compatible with .drug substance.	Acceptable	
Physical (solid state) stability	Formulation, process parameters, moisture	L	Most stable form of the drug substance 4:3 hydrate (b) (4) (b) (4)	Acceptable	
Physical stability (phase separation)	Formulation, process parameters	L	Choice of appropriate excipients. (b) (4) (b) (4)	Acceptable	

QUALITY ASSESSMENT

NDA 208277

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
Dosing accuracy	Dosing device, formulation, process parameters, equipment/scale	M	Product will be copackaged with two graduated 20 mL oral syringes and press-in bottle adapter. (b) (4) (b) (4)	Acceptable	
Palatability	Formulation, excipient changes, process parameters	M	Formulation contains sorbitol as (b) (4) Excipients are commonly in oral liquids,	Acceptable	
Leachables	Formulation, raw materials, process parameters	M	Container components are food grade materials suitable for liquids. Product is an aqueous suspension (b) (4) (b) (4)	Acceptable	
Microbial limits	Formulation, raw materials, process parameters, moisture	L	(b) (4) (b) (4) No microbial observed in stability studies.	Acceptable	
Dissolution	Particle size, raw materials, process parameters, scale/equipment	L	The oral suspension is greater than (b) (4) dissolved within 15 minutes. No trends in dissolution test result on stability.	Acceptable	

*Risk ranking applies to product attribute/CQA

**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

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

/s/

ROBYN S JORDON
05/18/2016