CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217684Orig1s000

PRODUCT QUALITY REVIEW(S)

Office of Pharmaceutical Quality

New Drug Application (NDA)
Integrated Quality Assessment

NDA 217684

VIGAFYDE
(vigabatrin oral solution)

NDA Executive Summary

1. Application/Product Information

NDA Number	217684		
Applicant Name	Pyros Pharmaceuticals		
Drug Product Name	Vigafyde (vigabatrin)		
Dosage Form	Solution		
Proposed Strength(s)	100 mg/mL		
NDA Classification	Type 3 - New Dosage Form		
Route of Administration	Oral		
Maximum Daily Dose	2400 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Monotherapy for pediatric patients with infantile spasms 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss.		
Drug Product Description	Clear, colorless to light yellow solution with a peppermint odor		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	20° to 25°C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Jeffrey Medwid	Donna Christner
	Drug Product/ Labeling	Venkateswara Pavuluri	Martha Heimann/ Julia Pinto
	Manufacturing	Yan Xu	Tianhong (Tim) Zhou
	Biopharmaceutics	Jia Leo	Ta-Chen Wu
	Microbiology	Susan Tripathi	Jesse Wells

	Other (specify)	N/A	N/A
	RBPM	Erica Keafer	
	ATL	Martha Heimann	
Consults	N/A		

2. Final Overall Recommendation - Approval

2. Action Letter Information

a. Expiration Dating:

24 months when stored at 20°C to 25°C.

b. Additional Comments for Action

There are no additional comments for the action letter.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The Office of Product Quality (OPQ) review team recommends APPROVAL of NDA 217684 for Vigafyde (vigabatrin) oral solution 100 mg/mL. Based on our evaluation of the available information, the applicant provided sufficient information to support an approval recommendation from the product quality perspective. The applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements. Refer to the individual discipline reviews for additional information.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance - Adequate
Drug Product - Adequate
Quality Labeling - Adequate
Manufacturing - Adequate
Biopharmaceutics - Adequate
Microbiology - Adequate

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: N/A

Comparability Protocols (PACMP): No
Comments: N/A

Additional Lifecycle Comments:

There are no outstanding issues or lifecycle considerations.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.
5/13/2024

Martha Heimann

Digitally signed by Martha Heimann
Date: 5/13/2024 11:34:50AM
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NDA Executive Summary Addendum

This addendum to the Executive Summary for NDA 217684 corrects the individual discipline recommendation for Product Quality Labeling. The final recommendation that NDA 217684 remains APPROVAL.

1. Application/Product Information

NDA Number	217684		
Applicant Name	Pyros Pharmaceuticals		
Drug Product Name	Vigafyde (vigabatrin)		
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NDA Classification	Type 3 - New Dosage Form		
Route of Administration	Oral		
Maximum Daily Dose	2400 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Monotherapy for pediatric patients with infantile spasms 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss.		
Drug Product Description	Clear, colorless to light yellow solution with a peppermint odor		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	20° to 25°C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Jeffrey Medwid	Donna Christner
	Drug Product/ Labeling	Venkateswara Pavuluri	Martha Heimann/ Julia Pinto
	Manufacturing	Yan Xu	Tianhong (Tim) Zhou

	Biopharmaceutics	Jia Leo	Ta-Chen Wu
	Microbiology	Susan Tripathi	Jesse Wells
	Other (specify)	N/A	N/A
	RBPM	Erica Keafer	
	ATL	Martha Heimann	
Consults	N/A		

2. Final Overall Recommendation - Approval

2. Action Letter Information

a. Expiration Dating:

24 months when stored at 20°C to 25°C.

b. Additional Comments for Action

There are no additional comments for the action letter.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The Office of Product Quality (OPQ) review team recommends APPROVAL of NDA 217684 for Vigafyde (vigabatrin) oral solution 100 mg/mL. Based on our evaluation of the available information, the applicant provided sufficient information to support an approval recommendation from the product quality perspective. The applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements. Refer to the individual discipline reviews for additional information.

b. Is the overall recommendation in agreement with the individual discipline recommendations? No

The Product Quality Labeling review deemed the NDA inadequate and recommended revisions that are normally addressed during final labeling negotiations. As the labeling revisions have been made the application is adequate from a product quality perspective.

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: N/A

Comparability Protocols (PACMP): No
Comments: N/A

Additional Lifecycle Comments:

There are no outstanding issues or lifecycle considerations.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.
5/13/2024

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide (OPQ-ALL-WI-0006)

NDA Number	217684
Assessment Cycle Number	01
Drug Product Name	VIGAFYDE™ (vigabatrin) oral solution

Assessment Recommendation: Inadequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Inadequate	
Patient Information	Adequate	eCTD SN 06
Instruction for Use (IFU)	Adequate	eCTD SN 06
Container Labels	Inadequate	
Carton Labeling	Inadequate	

Brief Description of Outstanding Issues: Statements in "How Supplied/Storage and Handling" to be updated in the prescribing information. "Lot / Exp Date" format need to be included on the carton and container labels. Refer to the list of deficiencies below for additional information.

List of Deficiencies:

Highlights of the Prescribing Information

1. Include the four-digit year after "Initial U.S. Approval" indicating the year which FDA initially approved vigabatrin as a new molecular entity (NME).

Section 11 DESCRIPTION

2. Revise the text in 1st paragraph of 11. Description as *"VIGAFYDE (vigabatrin) oral solution, 100 mg/mL, is an oral antiepileptic drug. The clear, colorless to light yellow, peppermint-flavored oral solution in stored a 150 mL bottle."* Add "*Vigabatrin is a racemic mixture of R and S isomers"* at the beginning of 2nd paragraph.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

3. Revise the statement in section 16.1 How supplied to read as *"VIGAFYDETM 100 mg/mL oral solution is a clear, colorless to light yellow, peppermint-flavored oral solution supplied in a white opaque high-density polyethylene (HDPE) 150*

mL bottle with a child-resistant cap and placed in a carton (NDC 80789-003-15).” Delete the sentence (b) (4)

4. In section 16.2 Storage and Handling revise the storage statement as “*Store at room temperature between 68°F to 77°F (20°C to 25°C) with excursions permitted to 59° - 86°F (15°-30°C) [See USP Controlled Room Temperature]. Once opened, store the bottle* (b) (4) *Discard the unused portion 90 days after first opening*.”

Carton and Container labels

5. We took note of the space allotted for Lot/EXP information on all packaging components. For expiration date format, FDA recommends that the expiration date shall appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month.

6. Revise the Instructions to Pharmacist on carton and container labels to read as *“Dispense with Medication Guide and Instructions for Use. Provide with appropriate oral syringe and* (b) (4) *”*

7. Align the statements on the carton and container labels as *“ After first opening, use within 90 days. Discard the unused portion after 90 days.”*

8. Revise the storage statement on carton and container as “*Store at room temperature between 68°F to 77°F (20°C to 25°C) with excursions permitted to 59° - 86°F (15°-30°C) [See USP Controlled Room Temperature]. Once opened, store the bottle* (b) (4) *Discard the unused portion 90 days after first opening.”*

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
eCTD SN 03	17-AUG-2023	Carton and Container Labeling, Prescriber Information
eCTD SN 06	14- MAR-2024	Prescribing Information

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	No USP monograph on Vigabatrin Oral Solution
Route(s) of administration	Adequate	
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Inadequate	To add initial US Approval date of vigabatrin (2009)

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

[2] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)

[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	Adequate	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).[6]	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.[8]	N/A	

Assessment: Inadequate

Refer to deficiency #1 regarding Initial U.S. Approval year (2009) included at the end of this review.

[4] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline
[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>
[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1
[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)
[8] Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>

1.2 FULL PRESCRIBING INFORMATION

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	N/A	Vigabatrin Oral solution is given orally with or without food.
For parenteral products: include statement: *"Parenteral drug*	N/A	

[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)

[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."[11]		
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	Adequate	Vigabatrin Oral Solution has no USP monograph.
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Assessment: Adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

(b) (4)

[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition
[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Solution
Strength(s) in metric system	Adequate	100 mg / mL
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	N/A	Vigabatrin
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable.	Adequate	clear, colorless to light yellow solution with a peppermint odor
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	

Assessment: Adequate

1.2.3 Section 11 (DESCRIPTION)[14]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)[15] [§ 201.57(c)(12)(i)(A)].	Adequate	
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Inadequate	Revise the text in 1st paragraph of 11. Description as *"VIGAFYDE (vigabatrin) oral solution, 100 mg/mL, is an oral antiepileptic drug. The clear, colorless to light yellow, peppermint-flavored oral solution in stored a 150 mL bottle."* Add "*Vigabatrin is a racemic mixture of R and S isomers"* at the beginning of 2nd paragraph.

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)

[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].	N/A	
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Adequate	antiepileptic drug
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	
For oral prescription drug products, include gluten statement[19] (if applicable).	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	No USP monograph

Assessment: Inadequate

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).
[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety. No equivalency statement.	Adequate	Strength is based on vigabatrin content.
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Inadequate	Revise the 1st sentence in 16.1 How Supplied as "*VIGAFYDE (vigabatrin oral solution) contains 100 mg/mL vigabatrin. It is a* (b) (4) *clear, colorless to light yellow, peppermint-flavored solution supplied in a white opaque high-density polyethylene (HDPE) 150 mL bottle with a child-resistant cap and placed in a carton (NDC 80789-003-15).*" Delete the sentence (b) (4)
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	

[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	N/A	Drug product is not light sensitive based on available photostability study.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Inadequate	Revise the storage statements as "*Store at room temperature between 68°F to 77°F (20°C to 25°C) with excursions permitted to 59° - 86°F (15°-30°C) [See USP Controlled Room Temperature]. Once opened, store the bottle* (b) (4) *Discard the unused portion 90 days after first opening."*
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber	N/A	

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*[21]		
Include information about child-resistant packaging[22] (if chosen by manufacturer).	Inadequate	Revise the statement under section 16.1 How supplied to read as " "*VIGAFYDE (vigabatrin oral solution) contains 100 mg/mL vigabatrin. It is a* (b) (4) *clear, colorless to light yellow, peppermint-flavored solution supplied in a white opaque high-density polyethylene (HDPE) 150 mL bottle with a child-resistant cap and placed in a carton (NDC 80789-003-15*)." Delete the sentence (b) (4)

Assessment: Inadequate

Refer to the deficiencies #2 and #3 as listed at the end of this review.

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)
[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)

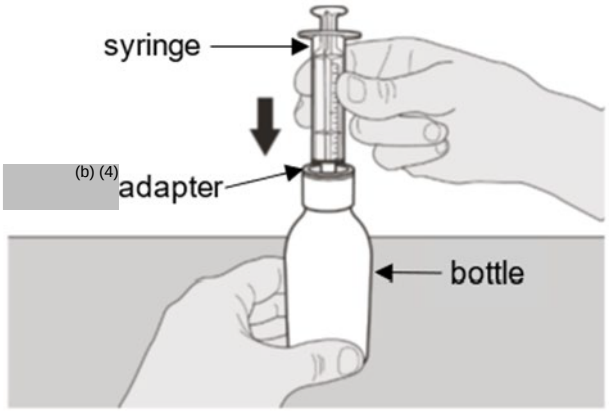
1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.	Adequate	

Assessment: Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[24]	Adequate	
Special preparation instructions (if applicable).	Adequate	
Storage and handling information (if applicable).	Adequate	Store VIGAFYDE at room temperature (b) (4) or in a refrigerator (b) (4) .
If the product contains a desiccant, ensure the desiccant has a warning	N/A	

[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)
[24] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
(e.g., "Do not eat.") and the size and shape of the desiccant differ from the dosage form.		
Active ingredient(s) (if applicable).	Adequate	
Alphabetical listing of inactive ingredients (if applicable).	Adequate	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	

Assessment: Adequate

3.0 CONTAINER AND CARTON LABELING[25]

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

[25] Carton and Container Labeling Resources

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[27], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	Final decision on Front size and prominence deferred to DMEPA
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28]	Adequate	Yes	
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	N/A	Yes	
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29]	Adequate	Yes	
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Yes	
Lot number and expiration date [§ 201.18 & 201.17].	Inadequate	Yes	FDA recommends that the expiration date shall appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month.

[27] Established name = [Drug] [Route of Administration] [Dosage Form]

[28] Express as " XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

[29] § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	Yes	Revise the storage statements as - *Store at room temperature between 68°F to 77°F (20°C to 25°C) with excursions permitted to 59° - 86°F (15°-30°C) [See USP Controlled Room Temperature].* - *Once opened, store the bottle* (b) (4) [redacted] - *Discard the unused portion 90 days after first opening."*
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>).	N/A	Yes	
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5)	Adequate	Yes	

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
or limited space per § 201.10(i)(2)].			
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	Yes	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Yes	
Linear Bar code [§ 201.25(c)(2)].[30]	Adequate	Yes	
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	Yes	
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	Yes	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Inadequate	Yes	Revise the Instructions to Pharmacist to read as " *Dispense with Medication Guide and Instructions for use. Provide with appropriate oral syringe and* (b) (4)"

[30] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Yes	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Yes	No USP monograph.
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.[31]	N/A	Yes	
And others if space is available.	Inadequate	No	Align the statements on the carton and container labels as " After first opening, use within 90 days. Discard the unused portion after 90 days."

Assessment of Carton Labels and Container Labeling: Choose an item.

Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

Please update the following labeling information:

[31] USP General Notices 3.20 Indicating Conformance

Highlights of the Prescribing Information

9. Include the four-digit year after "Initial U.S. Approval" indicating the year which FDA initially approved vigabatrin as a new molecular entity (NME).

Section 11 DESCRIPTION

10. Revise the text in 1st paragraph of 11. Description as *"VIGAFYDE (vigabatrin) oral solution, 100 mg/mL, is an oral antiepileptic drug. The clear, colorless to light yellow, peppermint-flavored oral solution in stored a 150 mL bottle."* Add "*Vigabatrin is a racemic mixture of R and S isomers"* at the beginning of 2nd paragraph.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

11. Revise the statement in section 16.1 How supplied to read as *"VIGAFYDETM 100 mg/mL oral solution is a clear, colorless to light yellow, peppermint-flavored oral solution supplied in a white opaque high-density polyethylene (HDPE) 150 mL bottle with a child-resistant cap and placed in a carton (NDC 80789-003-15)."* Delete the sentence (b) (4)

12. In section 16.2 Storage and Handling revise the storage statement as "*Store at room temperature between 68°F to 77°F (20°C to 25°C) with excursions permitted to 59° - 86°F (15°-30°C) [See USP Controlled Room Temperature]. Once opened, store the bottle* (b) (4) *Discard the unused portion 90 days after first opening*."

Carton and Container labels

13. We took note of the space allotted for Lot/EXP information on all packaging components. For expiration date format, FDA recommends that the expiration date shall appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month.

14. Revise the Instructions to Pharmacist on carton and container labels to read as *"Dispense with Medication Guide and Instructions for Use. Provide with appropriate oral syringe and* (b) (4) *"*

15. Align the statements on the carton and container labels as *" After first opening, use within 90 days. Discard the unused portion after 90 days."*

16. Revise the storage statements on carton and container as "*Store at room temperature between 68°F to 77°F (20°C to 25°C) with excursions permitted to 59° - 86°F (15°-30°C) [See USP Controlled Room Temperature]. Once*

opened, store the bottle (b) (4) *Discard the unused portion 90 days after first opening."*

Recommendation: As of this review, this application is **not deemed ready for approval**, in its present form, per 21 CFR 314.125(b)(8) from the CMC labeling/labels perspective, until the remaining deficiencies (in PI, and Carton and container labels) as listed above are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Venkateswara R. Pavuluri, Ph.D.; R. Ph; 12-APR-2024

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

Julia C. Pinto, Ph. D.; -- -APR-2024.

Venkateswara Pavuluri

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Julia Pinto

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CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

NDA Number	NDA-217684-ORIG-1
Assessment Cycle Number	01
Drug Product Name/ Strength	Vigabatrin Oral Solution 100 mg/mL
Route of Administration	Oral
Applicant Name	Pyros Pharmaceuticals, Incorporated
Therapeutic Classification/ OND Division	Neurologic Disorders /DN2
RLD/RS Number	NDA 022006 Sabril® (Vigabatrin) Powder for oral solution 500 mg/packet
Proposed Indication	monotherapy for pediatric patients with Infantile Spasms (IS) 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss
Primary Reviewer	Jia Leo, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.
Tertiary Reviewer	Okponanabofa Eradiri, Ph.D.

Assessment Recommendation: **Adequate**

Assessment Summary:

The Applicant is seeking approval of vigabatrin oral solution 100 mg/mL via the 505(b)(2) pathway. The listed drug, Sabril® (vigabatrin) powder for oral solution 500 mg/packet, was approved on 8/21/2009 and intended to be reconstituted with 10 mL water for a final concentration of 50 mg/mL immediately prior to administration. As the proposed ready-to-use solution mitigated the potential risk associated with reconstitution, the Office of Orphan Products Development (OOPD) awarded orphan designation status for the proposed drug product.

The Applicant did not conduct any in vivo clinical studies and requested a waiver of in vivo bioavailability studies, which is the focus of this biopharmaceutics review.

Formulation bridging: N/A

Biowaiver Request/Scientific Bridging:
The proposed drug product has different formulation than the LD. Specifically, the proposed drug product does not have povidone (which is present in the LD), and has four new excipients: methylparaben, propylparaben, sucralose, and peppermint flavor. In addition, the results of physiochemical property comparison showed that the pH and viscosity of the proposed drug product are similar to those of the LD, but the osmolality of the proposed drug product is approximately 550

mOsm higher than that of the LD; the observed difference may be attributable, at least in part, to the 2-fold difference in vigabatrin concentration.

The Applicant provided data and justifications that there is 1) no significant impact on the absorption of vigabatrin by the exclusion of povidone and the inclusion of four new excipients and 2) no significant impact on the absorption and bioavailability of vigabatrin due to the higher osmolality of the proposed drug product. The proposed drug product is deemed adequately bridged to the listed drug per 21 CFR 320.24(b)(6).

Recommendation:
From a Biopharmaceutics perspective, NDA 217684 for Vigabatrin Oral Solution 100 mg/mL is ADEQUATE.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Sequence 001 /Original submission	8/17/2023

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

B.12 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

The Applicant did not conduct any in vivo clinical studies. Therefore, there are no clinical batches. The composition of the registration batches is the same as the proposed commercial formulation. Therefore, no in vitro or in vivo formulation bridging study is needed.

Table 1. Composition of vigabatrin oral solution 100 mg/mL

Ingredient	Quality Standard	Function	Quantity	
			mg/mL	% w/w
Vigabatrin	USP	Active	100.0	(b) (4)
Methylparaben	NF			(b) (4)
Propylparaben	NF			
Sucralose	NF			
Peppermint Flavor (b) (4)	In-house			
Purified Water	USP			

B. 13 BIOWAIVER REQUEST/BRIDGING

Assessment: Adequate

The concentration of the active pharmaceutical ingredient (API), vigabatrin, in the proposed drug product is double that in the LD after reconstitution. Therefore, 21

CFR 320.22(3) does not apply. Rather, the data and information submitted by the Applicant support scientific bridging of the proposed drug product to the listed drug after reconstitution per 21 CFR 320.24(b)(6).

The proposed drug product has different formulation than the LD. Specifically, the proposed drug product does not have povidone (which is present in the LD), and has four new excipients: methylparaben, propylparaben, sucralose, and peppermint flavor. Based on the provided data, the maximum daily intake (MDI) of the three new excipients (methylparaben, propylparaben, sucralose) for the proposed infantile spasm (IS) indication is much lower than maximum daily exposure (MDE) in the inactive ingredient database (IID), which support the safety of the three new excipients. Additional reference to an EMA reflection paper, further supported the safety of methylparaben and propylparaben. A reference to the published literature suggests that the presence of sucralose is not expected to adversely impact the absorption of vigabatrin. Regarding peppermint flavor, there is no known data suggests that it will impact the absorption of a drug product. As peppermint flavor is present at a very low concentration ((b) (4) the presence of peppermint flavor is not expected to significantly impact the absorption of the proposed drug product. For povidone, there is also no known data suggest it can impact the absorption of the drug product. Therefore, exclusion of povidone is not expected to significantly impact the absorption of the proposed drug product as well. Overall, the provided justification supports no significant impact on the absorption of vigabatrin by the exclusion of povidone and the inclusion of four new excipients.

The results of physiochemical property comparison showed that the pH and viscosity of the proposed drug product is similar to that of the LD, but the osmolality of the proposed drug product is approximately 550 mOsm higher than that of the LD. The higher osmolality of the proposed drug product is anticipated due to the formulation/composition difference and is mainly attributed to the higher concentration of the drug substance, vigabatrin, in the proposed drug product. The Applicant provided justifications to support the higher osmolality of the proposed drug product is unlikely to have significant impact on the in vivo absorption of the proposed drug product, which include 1) the active transport of vigabatrin by the intestinal hPAT1 transporter plays an important role in the high oral bioavailability of vigabatrin; 2) the small administration volume of the proposed drug product is unlikely to have more than a very brief impact on the overall osmolality of the stomach contents; and 3) The approved label of the LD states that “SABRIL is given orally with or without food and food is known to impact the osmolality of the stomach contents significantly. The above justifications are reasonable and support that the difference in osmolality will not significantly impact the in vivo absorption and bioavailability of the proposed drug product.

Based on the above information, the scientific bridging of the proposed drug product to the listed drug after reconstitution is established per 21 CFR 320.24(b)(6).

Comparison of composition

The proposed drug product is 100 mg/mL ready-to-use vigabatrin oral solution. The listed drug (LD) is Sabril® powder for oral solution 500 mg packet. After reconstitution in 10 mL water, the final concentration of the LD is 50 mg/mL (**Table 2**). In additional to the concentration difference in the API, the proposed drug product and the LD have completely different excipients (**Table 3**).

Table 2. Dosage form and dosing regimen comparison of the proposed vigabatrin oral solution and the reconstituted Sabril® powder for oral solution

	Proposed Product	**Listed Drug (Sabril® Powder for Oral Solution)**
Active ingredient	Vigabatrin	Vigabatrin
Finished Dosage Form	Solution (100 mg/mL)	Solution[1] (50 mg/mL)
Dosing Regimen[2]	The dosing regimen is equivalent to that in the approved LD label. Doses are taken 2 times per day, and the same number of milligrams are provided to the patient for each dose.	
Route of Administration	Oral	Oral
Indication	Infantile Spasms - Monotherapy for pediatric patients with infantile spasms 1 month to 2 years of age for patients for whom the potential benefits outweigh the risk of vision loss.	

Table 3. Composition of the proposed vigabatrin oral solution and the reconstituted Sabril® powder for oral solution

		Quantity/mL (in the final dosage form)	
Ingredient	**Function**	**Sabril® Listed Drug**	**Proposed Drug**
Vigabatrin	Active	50 mg	100 mg
Povidone (b) (4)	(b) (4)	(b) (4)	Not included
Methylparaben		Not included	(b) (4)
Propylparaben		Not included	
Sucralose		Not included	
Peppermint Flavor (b) (4)		Not included	
Purified Water		Not included (added by the consumer)	

Safety of excipients in the proposed drug product

The Applicant evaluated the safety of the excipients by verifying that the quantity of each excipient in the proposed drug product fell within the maximum daily

exposure limits for FDA approved products. As shown in **Table 4**, for both the infantile spasms (IS) and the refractory complex partial seizures (rCPS) indications, the maximum daily intake (MDI) of all the excipients in the proposed drug product is far below the maximum daily exposure (MDE) amount, except for peppermint flavor, which is not in the inactive ingredient database (IID).

Table 4. Excipient safety justification for the infantile spasms (IS) and the refractory complex partial seizures (rCPS) indications

Ingredient	Grade	UNII	Maximum Daily Intake (mg)		IID MDE (mg/day)	Route	Dosage Form
			IS (24 mL)	rCPS (30 mL)			
Methylparaben	NF	A2I8C7HI9T	(b) (4)		346	Oral	(b) (4)
Propylparaben	NF	Z8IX2SC1OH			200	Oral	
Sucralose (b) (4)	NF	96K6UQ3ZD4			800	Oral	
Peppermint Flavor (b) (4)	In-house	(b) (4)			N/A	N/A	N/A

IID: inactive ingredients database; MDE: maximum daily exposure

The Applicant further evaluated the safety of each excipient. The Applicant is only pursuing IS indication. The maximum dose for IS is 150 mg/kg/day given in 2 divided doses (75 mg/kg twice daily).

Methylparaben:

Methylparaben is used as a (b) (4) It is present in the proposed formulation at a concentration of (b) (4), with an expected MDI of (b) (4) for the IS indication. The Applicant referred to the recent EMA reflection paper[1], which concluded that the use of methylparaben in oral formulations up to (b) (4) of the product (corresponding to an MDI of approximately (b) (4)) is not a concern for humans including the pediatric population irrespective of the age group.

Propylparaben:

Propylparaben is used as a (b) (4) It is present in the proposed formulation at a concentration of (b) (4), with an expected MDI of (b) (4) for the IS indication. The Applicant referred to the recent EMA reflection paper, which concluded that a permitted daily exposure (PDE) value of 2 mg/kg/day can be calculated for the use of propylparaben in adults and pediatric patients. If the proposed drug product is dosed at the maximum level of 150 mg vigabatrin/kg/day, it would result in a maximum exposure of propylparaben of (b) (4) (calculated by this reviewer), lower than the calculated PDE.

Sucralose:

[1] \\CDSESUB1\EVSPROD\nda217684\0003\m5\54-lit-ref\ema-reflection-paper-methyl-propylparaben.pdf

Sucralose is used as a [redacted] The Applicant referred to a publication by Abou-Donia et. al.,[2] which reported that sucralose increased intestinal P-gp, CYP3A4, and CYP2D1 levels in male rats. Vigabatrin is not significantly metabolized and is eliminated primarily through renal excretion. In addition, according to Abbot et. al., [3] vigabatrin is a substrate of H^+-coupled amino-acid transporter hPAT1. Therefore, the Applicant concluded that presence of sucralose is not expected to adversely impact the absorption of vigabatrin.

Peppermint flavor:
Peppermint flavor is added to [redacted]. According to the Applicant, this excipient is present at very low levels, and is not expected to adversely affect the rate or extent of absorption of vigabatrin.

Impact of exclusion of povidone
According to the Applicant, povidone [redacted] is biologically inert and unknown to enhance or adversely impact the bioavailability of drug product. The LD contains [redacted] povidone [redacted] packet [redacted]. The proposed drug product is an oral solution and does not require povidone. According to the Applicant, as the level of povidone in LD is low, the exclusion of povidone in the proposed drug product is not anticipated to adversely impact to the bioequivalence.

Comparison of physiochemical properties
The Applicant compared the physiochemical properties (pH, viscosity, and osmolality) of the proposed drug product and the reconstituted LD product (**Table 5**).

Table 5. Comparison of physiochemical properties between the proposed drug product and the reconstituted LD (Sabril® powder for oral solution)

Test Product	Lot	pH	Viscosity (cps)	Osmolality (mOsm/kg)
Vigabatrin Oral Solution (100 mg/mL)	VAL/22/0003	6.9 (6.89, 6.91, 6.91)	1.50 (1.49, 1.51, 1.51)	949 (948, 948, 951)
	VAL/22/0004	6.9 (6.91, 6.91, 6.91)	1.55 (1.54, 1.54, 1.56)	938 (931, 932, 950)
	VAL/22/0005	6.9 (6.91, 6.91, 6.92)	1.54 (1.53, 1.54, 1.55)	963 (959, 962, 968)
Reconstituted Sabril Powder for Oral Solution (50 mg/mL)	3196536A	7.1 (7.07, 7.08, 7.09)	1.24 (1.23, 1.24, 1.24)	398 (397, 398, 398)
	3200160A	7.0 (7.04, 7.04, 7.04)	1.23 (1.23, 1.23, 1.24)	399 (398, 399, 400)
	3200159A	7.0 (7.03, 7.03, 7.04)	1.23 (1.23, 1.23, 1.24)	404 (399, 405, 407)

[2] \\CDSESUB1\EVSPROD\nda217684\0003\m5\54-lit-ref\abou-donia-2008.pdf
[3] \\CDSESUB1\EVSPROD\nda217684\0002\m5\54-lit-ref\abbot-2006.pdf

pH

Based on the provided data, the pH of the proposed drug product (6.89 – 6.92) and the reconstituted LD product (7.03 – 7.09) is similar.

Viscosity

Based on the provided data, the viscosity of the proposed drug product (1.49 – 1.55 cps) and the reconstituted LD product (1.23 – 1.24 cps) is similar.

Osmolality

Based on the provided data, the osmolality of the proposed drug product (931 – 968 mOsm/kg) is higher than that of the reconstituted LD product (397 – 407 mOsm/kg). The higher osmolality of the proposed drug product is anticipated due to the formulation/composition difference and is mainly attributed to the higher concentration of the drug substance, vigabatrin (**Table 6**).

Table 6. Theoretical and measured osmolality of the proposed drug product and reconstituted LD product

Mw (g/mol)	Solute	mg/mL[a]	g /L[b]	Calculated Molarity[c]	Dissociation Factor[d]	Contribution of solute in Osmolarity[e] (mOsm/L)	Calculated Osmolality[f] (mOsm/kg)	Measured Osmolality[g] (mOsm/kg)	Osmolality Difference[h] (mOsm/kg)
Vigabatrin Oral Solution, 100 mg/mL									
129.16	Vigabatrin	100	100	0.774234	1	774.234	778.124		
152.15	Methylparaben	(b) (4)			1	(b) (4)			
180.2	Propylparaben				1				
397.64	Sucralose				1				
	Peppermint Flavor[i]		(b) (4)						
				Total Calc OsM					(b) (4)
Sabril Powder for Oral Solution (Reconstituted to 50 mg/mL)									
129.16	Vigabatrin	50	50	0.387117	1	387.117	389.062		
40000	Povidone	(b) (4)			1	(b) (4)			
				Total Calc OsM					(b) (4)

[a] Per composition of formulation
[b] Converted from mg/mL to g/L
[c] Molarity Calculated (g/L of solute divided by mw of solute)
[d] Dissociation does not occur for any listed solute. Thus, no dissociation factor is required to convert Molarity to Osmolarity.
1 M = 1 OsM
[e] The OsM of solutions were converted to mOsm by multiplying by 1000, and a Total Value was calculated by adding the contribution of each solute.
[f] Osmolality may be calculated from Osmolarity by dividing Osmolarity by 0.995.
https://www.tldrpharmacy.com/content/osmolarity-vs-osmolality-because-youve-probably-forgotten-the-difference
[g] Average Measured Osmolality. See Table 4: PHYSICOCHEMICAL COMPARISON
[h] Difference = Measured Osmolality - Calculated Osmolality
[i] Contribution of Peppermint Flavor components to osmolarity is anticipated to be low due to the small amount of flavor added.

To support that the difference in osmolality will not significantly impact the in vivo absorption of the proposed drug product, the Applicant provided the following justifications:

1) Vigabatrin is a substrate of intestinal transporter hPAT1. hPAT1 plays an important role in vigabatrin oral absorption.[4, 5]

[4] \\CDSESUB1\EVSPROD\nda217684\0002\m5\54-lit-ref\nohr-2014.pdf
[5] \\CDSESUB1\EVSPROD\nda217684\0002\m5\54-lit-ref\abbot-2006.pdf

2) The drug will be diluted by the intestinal fluid and exposed to a high number of hPAT1 transporters. The differences in the concentration or the osmolality between the LD and the proposed product would not be anticipated to make any significant difference since the vigabatrin will be rapidly absorbed. The bioavailability of vigabatrin is 80 – 90%.
3) The administered volume of the proposed drug product will be half of that of the LD. The maximum single dose is 12 mL (1200 mg) to a 16 kg infant. The overall impact of the difference in osmolality for a volume less than or equal to 12 mL (less than a tablespoon) per dose is unlikely to have more than a very brief impact on the overall osmolality of the stomach contents.
4) The approved label of the LD states that "SABRIL is given orally with or without food. Food is known to impact the osmolality of the stomach contents significantly. Therefore, it can be inferred that the higher osmolality of the proposed drug product is unlikely to adversely impact the bioavailability of vigabatrin.

The above justifications are reasonable and support that the differences in osmolality and some excipients are unlikely to significantly impact the in vivo absorption and bioavailability of the proposed drug product.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.

Okponanabofa Eradiri

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Jia Leo

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	217684
Assessment Cycle Number	01
Drug Product Name/ Strength	Vigabatrin Oral Solution, 100 mg?mL
Route of Administration	Oral
Applicant Name	Pyros Pharmaceuticals, Incorporated
Therapeutic Classification/ OND Division	Unknown
Manufacturing Site	(b) (4)
Method of Sterilization	Non-sterile

Assessment Recommendation: **Adequate**

Assessment Summary:
The drug product (DP) is a non-sterile, multi-dose, aqueous, peppermint flavored, ready-to-use oral solution. The DP can be stored at either 20-25°C or 2-8°C.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Original (0003)	08/17/2023
Original (0004)	08/25/2023
Quality/IR Response (0005)	01/30/2024

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: This is an eCTD submission.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): N/A

Supporting Documents: N/A

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** Vigabatrin oral solution 100 mg/mL is an aqueous, non-sterile, clear, colorless to light yellow solution with a peppermint odor indicated for the treatment of infantile spasms.
- **Drug product composition –**

Ingredient	Content % w/w	Function
Vigabatrin, USP	(b) (4)	API
Methylparaben, NF		(b) (4)
Propylparaben, NF		
Sucralose, NF		
Peppermint Flavor (b) (4) In-house		
Purified Water		

- **Description of container closure system –**

Component	Packaging	Description (Gland material code)	Manufacturer
Bottle	Primary	150 mL round white opaque HDPE bottle with (b) (4)	(b) (4)
CR Closure (b) (4)	Primary	Child resistant closure, (b) (4)	

Assessment: *Adequate*
The applicant has adequately described the drug product composition and the container closure system designed to prevent microbial contamination.

(b) (4)

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MICROBIOLOGY LIST OF DEFICIENCIES

N/A

Primary Microbiology Assessor Name and Date: Susan Tripathi, M.Sc., 02/12/2024

Secondary Assessor Name and Date (and Secondary Summary, as needed): Jesse Wells, Ph.D., 02/12/2024

Susan Tripathi

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Jesse Wells

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/s/

MARTHA R HEIMANN
05/13/2024 12:17:41 PM