CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217684Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	June 7, 2024
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 217684
Product Name, Dosage Form, and Strength:	Vigafyde (vigabatrin) oral solution, 100 mg/mL
Applicant Name:	Pyros Pharmaceuticals, Incorporated (Pyros)
FDA Received Date:	May 15, 2024 and June 6, 2024
TTT ID #:	2023-6029-1
DMEPA 2 Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

Pyros Pharmaceuticals, Incorporated submitted revised container label and carton labeling received on May 15, 2024[a] and final label and labeling on June 6, 2024[b], for Vigafyde. The Division of Neurology 2 (DN 2) requested that we review the revised and final container label and carton labeling for Vigafyde (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review[c], as well as in response to comments from other review Divisions (e.g., CMC, OPDP) that were communicated in the correspondence via email dated May 9, 2024.

2 CONCLUSION

We note that the expiration date format is not represented on the container label and carton labeling per our recommendation. However, per the Applicant's response to the Agency's recommendation (see Appendix A) they state that the expiration date will be in the format "YYYY-MMM."

The Applicant implemented all of our recommendations communicated in the Agency's correspondence. We find the final container label and carton labeling acceptable from a medication error perspective and we have no additional recommendations at this time.

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[a] Cover Letter – Labeling (NDA 217684). Parsippany (NJ): Pyros Pharmaceuticals, Inc.; 2024 MAY 15. Available from: \\CDSESUB1\EVSPROD\nda217684\0009\m1\us\12-cover-letters\cover-letter-s0009-2024-05-15.pdf

[b] Cover Letter – Final Labeling (NDA 217684). Parsippany (NJ): Pyros Pharmaceuticals, Inc.; 2024 JUN 06. Available from: \\CDSESUB1\EVSPROD\nda217684\0011\m1\us\12-cover-letters\cover-letter-s0011-2024-06-06.pdf

[c] Weitzman, B. Label and Labeling Review for Vigafyde (NDA 217684). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 APR 22. TTT ID: 2023-6029.

APPENDIX A. LABELS AND LABELING

A.1 List of Label and Labeling Reviewed and Response to Agency's Recommendation

Using the principles of human factors and Failure Mode and Effects Analysis[d], along with postmarket medication error data, we reviewed the following Vigafyde label and labeling submitted by Pyros Pharmaceuticals, Incorporated

- Response to the Agency's recommendations received on May 15, 2024, available from: \\CDSESUB1\EVSPROD\nda217684\0009\m1\us\12-cover-letters\responses-container-carton-label-s0009.pdf
- Final Container and Carton Labeling received on June 6, 2024

A.2 Label and Labeling Images

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	May 9, 2024
To:	Josephine Little Regulatory Project Manager **Division of Neurology II (DN2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia B. Williams, PhD, LCSW-C, BCD Team Leader, Patient Labeling Division of Medical Policy Programs **(DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Lindsay McCann, PharmD, BCCCP **Regulatory Review Officer** **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	VIGAFYDE (vigabatrin)
Dosage Form and Route:	oral solution
Application Type/Number:	NDA 217684
Applicant:	Pyros Pharmaceuticals Inc.

1 INTRODUCTION

On August 17, 2023, Pyros Pharmaceuticals Inc. submitted for the Agency's review, an original New Drug Application (NDA) for VIGAFYDE (vigabatrin) oral solution. The proposed indication for VIGAFYDE is as monotherapy for the treatment of infantile spasms in pediatric patients 1 month to 2 years of age for whom potential benefits outweigh the potential risk of vision loss.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology II (DN2) on September 28, 2023, and September 28, 2023 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for VIGAFYDE (vigabatrin) oral solution.

2 MATERIAL REVIEWED

- Draft VIGAFYDE (vigabatrin) oral solution MG and IFU received on August 17, 2023, revised by the Review Division throughout the review cycle, and received by DMPP on April 24, 2024.
- Draft VIGAFYDE (vigabatrin) oral solution MG and IFU received on August 17, 2023, revised by the Review Division throughout the review cycle, and received by OPDP on April 24, 2024.
- Draft VIGAFYDE (vigabatrin) oral solution Prescribing Information (PI) received on August 17, 2023, revised by the Review Division throughout the review cycle, and received by DMPP April 24, 2024.
- Draft VIGAFYDE (vigabatrin) oral solution Prescribing Information (PI) received on August 17, 2023, Prescribing Information (PI) received on, revised by the Review Division throughout the review cycle, received by OPDP on April 24, 2024.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG and IFU, we have:

- simplified wording and clarified concepts where possible

- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 1, 2024

To: Josephine Little, Regulatory Project Manager, Division of Neurology Products (DN2)

Kevan Vanlandingham, DN2

Tracy Peters, Associate Director for Labeling, DN

From: Lindsay McCann, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, Team Leader, OPDP

Subject: OPDP Labeling Comments for VIGAFYDE (vigabatrin) oral solution

NDA/BLA: 217684

Background: In response to DN2's consult request dated October 2, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), and carton and container labeling for the original NDA 217684 submission for VIGAFYDE.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on April 24, 2024, and our comments are provided below.

Medication Guide/IFU
A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed Medication Guide/IFU, and comments will be sent under separate cover.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on April 30, 2024 and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Lindsay McCann at 301-796-3719 or Lindsay.McCann@fda.hhs.gov.

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LABEL AND LABELING OR LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 22, 2024
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 217684
Product Name, Dosage Form, and Strength:	Vigafyde (vigabatrin) oral solution, 100 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Pyros Pharmaceuticals, Incorporated (Pyros)
FDA Received Date:	August 17, 2023, August 25, 2023, and March 14, 2024
TTT ID #:	2023-6029
DMEPA 2 Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

1 REASON FOR REVIEW

As part of the approval process for Vigafyde (vigabatrin) oral solution (NDA 217684), the Division of Neurology 2 (DN 2) requested that we review the proposed Vigafyde prescribing information (PI), medication guide (MG), instructions for use (IFU) container label and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND/REGULATORY HISTORY

NDA 217684 is a 505(b)(2) NDA and the listed drug product is Sabril, NDA 022006.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Proposed Revisions to Section 17 of PI	E
Applicant's Risk Assessment Table	F
Label and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 ASSESSMENT

Evaluation of the Concentration, Labels, and Labeling

The proposed product Vigafyde (vigabatrin) oral solution concentration of 100 mg/mL is twice the concentration of the currently marketed listed drug product, Sabril (vigabatrin) for oral solution and other generic vigabatrin for oral solution products, which after reconstitution, have a final concentration of 50 mg/mL.

We are concerned that the introduction of the proposed concentration (100 mg/mL) into the marketplace may contribute to wrong dose medication errors, specifically overdose medication errors if healthcare providers prescribe and/or caregivers administer the same volume as the currently available 50 mg/mL after reconstitution vigabatrin products (e.g., two-fold overdose

medication errors). We issued an advice letter on February 28, 2022[a] under IND 157997 requesting the Applicant provide their rationale for the proposed concentration and submit a risk analysis to characterize the risk for confusion and wrong dose medication errors including mitigation strategies. Specifically, we requested the Applicant include a description of the proposed mitigation strategies (e.g., label/labeling differentiation strategies) and how the proposed strategies will address the identified risks and mitigate the potential for errors.

In their response, submitted on November 29, 2022 under IND 157997, the Applicant provided their rationale for the proposed concentration of 100 mg/mL as follows:

- Physician feedback suggests they prefer a concentration that more intuitively aligns the dose in milligrams to the dose in milliliters, and a dose of 100 mg/mL supports this objective.
- Parent feedback revealed that a more concentrated product is desirable as it is difficult to get babies to swallow larger volumes of solution. Internet searches revealed that some parents reduced the volume of water used for reconstitution (on their own, without physician oversight) to provide smaller volumes for each dose so that they could more easily manage getting babies to swallow the complete dose.

In addition, the Applicant provided a risk analysis to characterize the risk for confusion and dosing errors, including their description of their proposed mitigation strategies (i.e., label/labeling differentiation strategies) to address the potential risk associated with prescribing, dispensing and administration of Vigafyde (see Appendix E).

Subsequently, on August 17, 2023 under NDA 217684 the Applicant submitted label and labeling employing the labeling mitigation strategies outlined in their risk analysis, including several alerts and warning statements intended to inform healthcare providers and caregivers that Vigafyde is a more concentrated solution than other vigabatrin products to address the potential for wrong dose medication errors due to confusion. Of note, the Applicant submitted updated labels and labeling on March 14, 2024 as part of their shared REMS proposal.

Our review of the labels and labeling submitted on March 14, 2024, determined that although the Applicant has employed several labeling mitigation strategies to reduce the risk of wrong dose medication errors, additional labeling mitigation strategies should be implemented to further reduce this risk. In addition, the proposed alerts and warning statements can be improved for clarity and readability. Thus, we have included our recommendations below in **Section 5** (Table 2) for the Division and in **Section 6** (Table 3) for Pyros Pharmaceuticals, Incorporated.

Evaluation of the Packaging

(b) (4) , in the August 17, 2023 submission under NDA 217684, the Sponsor proposed to the supply the product without a co-packaged oral syringe or (b) (4) bottle adapter (i.e., dispensing pharmacy to provide the oral syringe and

[a] Vigabatrin Oral Solution (IND 157997) Advice letter February 28, 2023. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8064a290

(b) (4)). As such, this is not a combination product and therefore, Human Factors (HF) requirements do not apply.

Evaluation of Superiority Claim and Human Factors (HF) Data

We note the Applicant's intention to demonstrate clinical superiority of the proposed product using an HF study as one method to support the Applicant's request for Orphan Drug Exclusivity. The proposed HF study protocol to establish superiority was reviewed under separate cover on January 31, 2024 under IND 157997 (TTT Review # 2023-7164).

4 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), medication (MG), instructions for use (IFU), container label, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in **Section 5** (Table 2) for the Division and in **Section 6** (Table 3) for Pyros Pharmaceuticals, Incorporated.

5 RECOMMEDATIONS FOR DIVISION OF NEUROLOGY 2 (DN 2)

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	In the (b) (4) Dosage and Administration sections of the HPI the statement "VIGAFYDE is a concentrated formulation" can be improved to include more descriptive language.	Inclusion of the term (b) (4) may help differentiate the proposed vigabatrin oral solution from the vigabatrin powder formulation products.	Consider revising the statement from "VIGAFYDE is a concentrated formulation" to "VIGAFYDE is a (b) (4) concentrated formulation" in the (b) (4) Dosage and Administration sections of the HPI.
2.	The Dosage Forms and Strengths section of the HPI includes the statement (b) (4)	The Dosage Forms and Strength section does not appear to be the appropriate place to include this statement. (b) (4)	We recommend removing the (b) (4)

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
		(b) (4)	
Full Prescribing Information – Section 2 Dosage and Administration			
1.	In section 2.1 Important Dosing and Administration Instructions the statement "VIGAFYDE is a concentrated (b) (4)" can be improved to include more descriptive language.	Inclusion of the term (b) (4) may help differentiate the proposed vigabatrin oral solution from the vigabatrin powder formulation. Additionally, to be in consistent with our recommendation in the Dosage and Administration section of the HPI.	Consider revising the statement from "VIGAFYDE is a concentrated (b) (4)" to "VIGAFYDE is a (b) (4) concentrated (b) (4)" Additionally, refer to recommendation number one under the heading "Highlights of Prescribing Information."
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	Section 16.1 How Supplied the statements (b) (4) can be improved to include more descriptive language and to increase readability.	Inclusion of the term (b) (4) may help differentiate the proposed vigabatrin oral solution from the vigabatrin powder formulation.	Recommend revising the statement in section 16.1 How Supplied to read: "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 150 mL bottle. (NDC 80789-003-15). The oral syringe and bottle adapter are provided separately by the pharmacy." Refer to recommendation number two under the heading "Instructions for Use" below regarding replacing the term (b) (4) with "bottle adapter".
Full Prescribing Information – Section 17 Patient Counseling Information			
1.	The instructions in Section 17 Patient Counseling Information	Lack of clear counseling instructions directed to caregiver may result in	We recommend revising (b) (4)

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	regarding switching from powder for oral solution to oral solution can be improved for clarity. Additionally, the administration instructions on proper administration technique lacks clarity. Lastly, the discard statement (b) (4) can be improved for clarity.	preparation and administration errors.	(b) (4) To read: "Inform caregivers that VIGAFYDE is a (b) (4) formulation. Inform caregiver when patients switching from vigabatrin powder for oral solution that VIGAFYDE is more concentrated (100 mg/mL) compared to reconstituted solutions of vigabatrin for oral solution (50 mg/mL), and the volume of solution that should be given to their infant will be lower than previously prescribed." Additionally, we recommend revising the discard statement from (b) (4) to "Advise caregivers to discard the unused portion 90 days after first opening." See Appendix E for complete recommendations for Section 17 Patient Counseling Information for the Division's consideration.
Medication Guide			

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
1.	**General Comment**: We note that the Applicant removed the following information in the medication guide (MG) that was not applicable to the proposed patient population (i.e., infants 1 month to 2 years of age.): (b) (4) We also note the Division added the statement "VIGAFYDE is not approved for use in adolescents or adults" in Section 5 of the prescribing information. We defer to the Division to determine what information should be carved out and whether a similar statement "VIGAFYDE is not approved for use in adolescents or adults" should also be included in the MG.		
2.	The statement in number (b) (4) of the medication guide (MG) (b) (4) may not be accurate in the future if other vigabatrin products with different concentrations are approved. Additionally, (b) (4) is unclear.	Revising this statement may help prevent confusion if other products are approved with another concentration. Further, the "volume" of Vigafyde will be less, but not the dose in mg; therefore, specifying "volume" instead of (b) (4) may help prevent wrong dosing errors.	We recommended revising this statement to read "VIGAFYDE is more concentrated than other vigabatrin solutions prepared from powder: The volume of VIGAFYDE solution prescribed by your healthcare provider may be less than the volume prescribed for other vigabatrin solutions prepared from powder". We defer to the Division and Patient Labeling Team for input.
3.	The first sentence under the section **"What is VIGAFYDE?"** does not include the (b) (4) description for the solution.	Inclusion of the term (b) (4) may help differentiate the proposed vigabatrin oral solution from the vigabatrin powder formulation.	We recommend revising the beginning of the statement from "VIGAFYDE is a (b) (4) prescription medicine used (b) (4) to read:

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			(b) (4) VIGAFYDE is a prescription medicine (b) (4) used (b) (4)
4.	The first bullet point in the section **"How should my baby take VIGAFYDE?"** reads: (b) (4) This can be improved for accuracy (i.e., the dose in mg will not be different) and may not be accurate in the future if other vigabatrin products with different concentrations are approved.	Revising this statement help prevent confusion if other products are approved with another concentration as well as prevent wrong dosing errors.	We recommend revising the statement in the first bullet point to read: "VIGAFYDE (b) (4) oral solution. The volume of VIGAFYDE solution prescribed by your healthcare provider may be less than other vigabatrin solutions prepared from powder." We defer to the review team for final determination for the appropriate language.
5.	The Section "**How should I store VIGAFYDE?**" does not include the post-opening date (i.e., discard statement).	Incomplete storage information may result in improper storage of the drug product which may lead to deteriorated drug medications errors.	We recommend including a post-opening expiration statement such as "Throw away any opened bottle of VIGAFYDE in the household trash (or dispose of in accordance with local laws) 90 days after first opening, even if there is still medicine in the bottle." We defer to the patient labeling team for the

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			appropriate storage statement for language and format.
Instructions For Use (IFU)			
1.	GENERAL COMMENT: We provide our recommendations below for the Instructions for Use (IFU) labeling. We defer to the patient labeling team (PLT) for recommendations and additional edits for the IFU labeling.		
2.	The adapter device term (b) (4) is used throughout the IFU including the images, except in Step 11 where the term "bottle adapter" was used instead of (b) (4)	Inconsistent terms to describe the adapter device ((b) (4) vs. bottle adapter) may result in confusion. Additionally, "bottle adapter" is more commonly used to describe the adapter device. Therefore, the term "bottle adapter" may be more familiar to caregivers than the term (b) (4)	We recommend revising the adapter device term from (b) (4) to "bottle adapter" throughout the IFU labeling including the images for consistency and to decrease the risk of confusion.
3.	As currently presented the warning statement " (b) (4) may not be accurate if additional products are approved with another concentration. Also, the statement can be	To help prevent confusion if other products are approved with another concentration . Further, the "volume" of Vigafyde will be less, but not the dose in mg; therefore, specifying "volume" rather than " (b) (4) " may help prevent wrong dosing errors.	We recommend revising the warning statement as follows or something similar: (b) (4) If your baby is switching from vigabatrin prepared from powder to VIGAFYDE (b) (4) oral solution, your baby's healthcare provider may have prescribed a smaller volume of medicine than before."

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	improved for accuracy as "(b) (4) is unclear.		
4.	The (b) (4) statement under Important Notes states the contents using (b) (4) Additionally, the term child-resistant cap is used throughout the instructions whereas the image in Figure A labels the cap component for the bottle as (b) (4) rather than "child-resistant cap."	(b) (4) Inconsistent terminology used throughout the instructions for the cap component of the bottle (i.e., "Child-resistant cap" vs. (b) (4)) may cause confusion.	We recommend revising the (b) (4) to bulleted points as well as removing (b) (4) from the list as follows: "Each VIGAFYDE oral solution carton contains (see figure A): • One bottle of VIGAFYDE oral solution • One Medication Guide (not pictured) • One Instructions for Use (not pictured) Additionally, we recommend replacing the term (b) (4) in figure A with "Child-resistant cap" for accuracy and consistency.
5.	(b) (4) under Important Notes may cause confusion. Additionally, there is an image of an (b) (4) oral	(b) (4) Additionally, if the oral syringe provided by the specialty pharmacy is not (b) (4), this may cause confusion and could lead to	We recommend revising the "pharmacy will provide" statement" (b) (4) to sentence format or bulleted point as follows: "The pharmacy will provide an oral syringe with a bottle adapter." Or "The pharmacy will provide an:

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	syringe and adapter corresponding to this statement. However, the image of the (b) (4) oral syringe may not be representative of the syringe that will be provided by the specialty pharmacy.	wrong dose medication errors.	• Oral Syringe • Bottle Adapter Refer to recommendation number two above under the heading "Instructions for use" regarding replacing the term "(b) (4) with "bottle adapter." Additionally, we recommend removing the image of the (b) (4) syringe and adapter or replacing it with a generic syringe that does not contain the specific mL unit markings similar to what is depicted in Figure B.
6.	The oral syringe image presented in Figure B labels the different components of the oral syringe (i.e., Barrel, Tip, Dose markings, and Plunger). However, as currently presented the plunger stopper component of the oral syringe is not labeled in the syringe image in Figure B.	Identifying the plunger stopper component of the oral syringe will help caregivers in proper preparation and administration technique, specifically to aid in accurate measurement of the prescribed dose to minimizes wrong dose medication errors.	We recommend labeling the plunger stopper component of the oral syringe presented in Figure B. Refer to recommendation number two above under the heading "Instructions for use" regarding replacing the term "(b) (4) with "bottle adapter."
7.	The Heading directly above Step 1 (b) (4) can be improved to use active voice.	Improved for clarity and readability.	We recommend revising this heading to read "How to prepare the bottle for first time use of VIGAFYDE oral solution:"
8.	The statement in Step 4 (b) (4)	This section is already titled "How to prepare the	We recommend deleting the first sentence in Step 4.

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	[redacted] is redundant. [redacted] is already reference in the [redacted] sentence in Step 4 (i.e., Make sure that the [redacted] is fully inserted (see figure F)).	bottle for first time use of VIGAFYDE oral solution:"	[redacted] as this information is provided in the [redacted] sentence in Step 4.
9.	The instruction in Step 4 [redacted] can be improved for readability.	To increase clarity and readability.	We recommend revising the last sentence in Step 4 to read "Do not remove the adapter from the bottle after it is inserted."
10.	We note in step 5 the image in Figure G shows the child-resistant cap (CRC) back on the bottle. However, there are no accompanying instructions informing caregivers to place the child-resistance cap back on the bottle before recording the date of opening on the bottle's label. Additionally, the statement in Step 5 [redacted] may be unclear as the bottle will be opened every day.	If users do not put the cap on the bottle after inserting the bottle adapter, e some of the oral solution may spill if the user turns the bottle to record the date of opening on the bottle's label. Additionally, putting the cap on the bottle will help ensure the adapter is pushed all the way in the bottle. Unclear discard instructions may lead to confusion and administration of degraded drug product.	We recommend including the instruction "put the child-resistant cap back on the bottle by turning it clockwise". Additionally, we recommend revising the statement [redacted] in Step 5 as follows: "Step 5: Put the cap back on bottle by turning it clockwise (to the right). Record the date of opening on the bottle's label. "VIGAFYDE may be used for up to 90 days after first opening (see Figure G)."

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
11.	The Heading for Step 6 (b) (4) can be improved to use active voice.	To increase clarity and readability.	We recommend revising the heading of Step 6 to read "How to prepare a dose of VIGAFYDE oral solution:"
12.	In Step 7 the instruction (b) (4) lacks clarity and may cause confusion.	Unclear instructions may lead to administration and wrong dose medication errors.	We recommend revising the statement in Step 7 to read: "Push the plunger of the oral syringe all the way down towards the tip of the syringe to remove air in the oral syringe (see Figure H)."
13.	In Step 8 the instruction (b) (4) can be improved to provide more specific instructions.	More specific instructions may help prevent inadvertent spilling and loss of product.	We recommend revising this statement in Step 8 to read: "Place the VIGAFYDE bottle on a flat surface. While keeping the bottle in an upright position, insert the tip of the oral syringe into the opening of the bottle adapter and push down gently. (See Figure I)"
14.	In Step 9 the instructions explaining how to align the plunger with the graduation markings on the barrel of the oral syringe to measure the prescribed dose is not clear and is confusing. Additionally, we note there is not an enlarged image next to the inset in Figure J to show what part of the plunger stopper (e.g., top of the	Unclear instruction on how to measure the dose with the oral syringe may lead to wrong dose medication errors.	We recommend revising Step 9 as follows or something similar: "Step 9: "While holding the oral syringe firmly into the bottle, turn the bottle upside down. Slowly pull back the plunger of the oral syringe until the top of the plunger stopper *(or replace with what the Applicant is lining up with the markings on the oral syringe)* lines up with the mL marking on the barrel of the oral syringe that matches the number of mLs of medicine

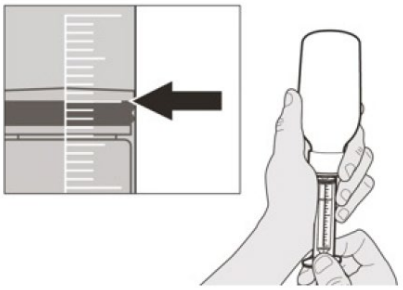
Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	plunger stopper) is being lined up with the graduation markings on the oral syringe to help guide caregivers in proper preparation and administration technique.		your baby's healthcare provider told you to give (see Figure J). After the correct dose is withdrawn, hold the plunger in place to keep the plunger from moving." Additionally, we recommend including an enlarged image that clearly shows what part of the plunger you are lining up with the oral syringe graduation markings to measure the prescribe dose. For example: 
15.	In Step 10 the instructions regarding checking for air bubbles lacks clarity and is confusing. Additionally, the accompanying images in Step 10 (Figure K) depicting how to identify the large air bubbles (for removal) and tiny air bubbles (that are normal) in the oral syringe look very similar.	Lack of clarity and readability may lead to confusion and medication dosing errors. As Figure K is currently presented, caregivers may be unable to differentiate between the large and tiny air bubbles.	We recommend adding a heading and revising the instructions in Step 10 as follows or something similar for increase caregiver comprehension: "Step 10: How to remove large air bubbles and measure to the prescribed dose: With the oral syringe attached to the bottle, check for air bubbles. Tiny air bubbles are normal. If large air bubbles are present (see Figure K), slowly push up on the plunger until the bubbles are removed. Then slowly pull back on the plunger

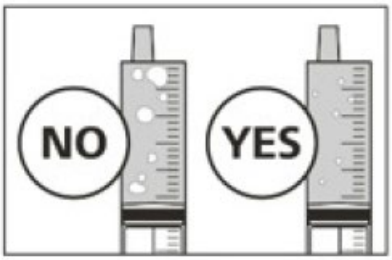
Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
			to measure the prescribed dose. The top of the plunger stopper *(or replace with what the Applicant is lining up with the markings on the oral syringe)* must line up with the mL markings on the oral syringe for the prescribed dose." Additionally, we recommend enlarging the image in Figure K to more clearly depict large air bubbles versus tiny air bubbles in the syringe. For example: 
16.	There is no heading before Step 12.	To increase readability.	We recommend adding a heading statement above Step 12 as follows: "How to give a dose of VIGAFYDE oral solution:"
17.	The instructions in step 13 (b) (4) is not grammatically correct and can be improved for readability.	Clearly presented instructions may increase readability.	We recommend revising the statements in Step 13 to read: "Leave the bottle adapter in place. Put the child-resistant cap back on the bottle by turning it clockwise (to the right). See Figure N."

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
18.	There is no heading before Step 14.	To increase readability.	We recommend adding a heading statement above Step 14 as follows: "How to clean the oral syringe after use:"
19.	The storage statement can be improved for clarity and to be presented in active voice.	Unclear storage information may lead to confusion and deteriorated drug medication errors.	We recommend revising the storage statement in the IFU as follows: "**How should I store VIGAFYDE?** Store [redacted] (b) (4) at room temperature between 68°F to 77°F (20°C to 25°C) [redacted] (b) (4) Throw away any opened bottle of VIGAFYDE [redacted] (b) (4) after 90 days of first opening, even if there is still medicine in the bottle. Keep VIGAFYDE and all medicines out of the reach of children."

6 RECOMMENDATIONS FOR PYROS PHARMACEUTICALS, INCORPORATED

Table 3. Identified Issues and Recommendations for Pyros Pharmaceuticals, Incorporated (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Container Label and Carton Labeling			
1.	The format for expiration date is not defined.	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date 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. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash be used to separate the portions of the expiration date.

Table 3. Identified Issues and Recommendations for Pyros Pharmaceuticals, Incorporated (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
2.	The warning statement (b) (4) presented on the principial display panel (PDP) of the container label, and PDP and side panel of the carton labeling can be improved to be more specific and accurate if in the future if other vigabatrin products with different concentrations are approved.	The text presented in the warning statement (b) (4) may be inaccurate and lead to confusion if additional products are approved with another concentration. This could lead to dosing errors.	We recommend revising the warning statement presented on PDP of the container label and the PDP and side panel of the carton labeling. Additionally, we recommend displaying the warning statement on the side panel of the carton labeling inside a red box with red font as it appears on the container label. For example, revise to: **ALERT: VIGAFYDE is a concentrated formulation.** Vigabatrin is available in different concentrations. Verify the dose and volume.
3.	The strength statement 100 mg/mL does not include the statement "concentrated formulation."	Including this statement may help further differentiate this product from other vigabatrin products and to decrease the risk of wrong product selection errors and wrong dose medications errors between the different vigabatrin concentrations (i.e., 100 mg/mL vs. 50 mg/mL after reconstitution).	We recommend including the statement "concentrated formualtion" directly underneath the strength statemnt. For example: **100 mg/mL** [Concentrated formulation]
4.	The statements "FOR ORAL USE ONLY" and (b) (4) appear with equal or more prominence than other critical information on	Clutter on the PDP reduces readability of critical information (e.g., established name, product strength and warning statements).	Ensure the statements "FOR ORAL USE ONLY" and (b) (4) do not appear more prominent that the other critical information (e.g., established name, strength

Table 3. Identified Issues and Recommendations for Pyros Pharmaceuticals, Incorporated (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	the principal display panel (PDP) of the carton labeling and container label.		statement and warning statements).
5.	The recommended dosage statement can be improved.	To ensure consistency with the prescribing information.	Revise the statement, (b) (4) to read "Dosage: See prescribing information."
6.	The discard statements (b) (4) can be combined to decrease redundancy and to increase readability of the important information.	Clear discard statements may help prevent administration of degraded drug products.	Revise and combine these statements to read "Discard unused portion 90 days after first opening."
7.	We note there are two different "affix label" statements on the carton labeling and container label as a visual indicator to indicate where to place the labels as follows: Carton: "Affix pharmacy label here" Container: (b) (4)	It is not clear if the "Affix Pharmacy Label" statement on the carton labeling and the (b) (4) statement on the container label serve different purposes.	Please clarify if there is a difference between (b) (4) and "pharmacy label". If they are intended for the same purpose, provide your rationale for including the (b) (4) statement on the container label and "Affix Pharmacy Label" statement on the carton labeling, given that the proposed product will be dispensed in the original container.
Container Label(s)			
1.	A medication guide (MG) will be available for this	The Medication Guide provides information that is	We recommend revising the statement (b) (4)

Table 3. Identified Issues and Recommendations for Pyros Pharmaceuticals, Incorporated (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	product in addition to the instructions for use (IFU). However, as currently presented the statement on the side panel of the container label (b) (4) does not state that the medication guide should be provided to each patient. Additionally, we note the adapter device is described as (b) (4) rather than the more common term "bottle adapter."	necessary to patients' safe and effective use of the product. Per 21 CFR 208.24(d), the label shall instruct the authorized dispenser to provide a Medication Guide to each patient and shall state how the Medication Guide is provided. Additionally, the bottle adapter is more commonly used to describe the adapter device. Therefore, the term "bottle adapter" may be more familiar to caregivers than the term "(b) (4)	(b) (4) to read: "Pharmacist: Dispense with enclosed medication guide and instructions for use." Additionally, ensure the adapter device term "bottle adaptor" is applied on all labels and labeling.
Carton Labeling			
1.	A medication guide (MG) will be available for this product in addition to the instructions for use (IFU). However, as currently presented in the statement on the principal display panel (PDP) (b) (4) does not state that the medication guide should be provided to each patient.	The Medication Guide provides information that is necessary to patients' safe and effective use of the product. Per 21 CFR 208.24(d), the label shall instruct the authorized dispenser to provide a Medication Guide to each patient and shall state how the Medication Guide is provided.	We recommend revising the statement on the PDP to read "Attention Pharmacist: Dispense the enclosed medication guide with each prescription." Additionally, we recommend adding the "instructions for use" on the "pack contains" list.

Table 3. Identified Issues and Recommendations for Pyros Pharmaceuticals, Incorporated (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
2.	We note the adapter device is described as "(b) (4) rather than the more common term "bottle adapter."	The bottle adapter is more commonly used to describe the adapter device. Therefore, the term "bottle adapter" may be more familiar to caregivers than the term "(b) (4)	Ensure the adapter device term "bottle adaptor" is applied on all labels and labeling.
3.	The statement on the side panel of the carton labeling (b) (4) can be improved to be more specific.	To improve clarity.	Consider revising this statement to read "Your healthcare provider will tell you how much VIGAFYDE solution to give."

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Vigafyde that Pyros Pharmaceuticals, Incorporated submitted on August 17, 2023, and the listed drug (LD) Sabril (NDA 022006)

Table 4. Relevant Product Information for Vigafyde and Listed Drug Sabril

Product Name	**Vigafyde**[b]	**Sabril**[c]
Initial Approval Date	N/A	August 21, 2009
Active Ingredient	vigabatrin	
Indication	Infantile Spasms – monotherapy in infants 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss.	• Refractory Complex Partial Seizures as adjunctive therapy in patients 2 years of age and older who have responded inadequately to several alternative treatments; Sabril is not indicated as a first line agent. • Infantile Spasms – monotherapy in infants 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss.
Route of Administration	Oral	
Dosage Form	Oral solution	Tablet and For oral solution
Strength	100 mg/mL	500 mg tablet 500 mg per packet for oral solution [Final concentration after reconstitution 50 mg/mL]

[b] Vigafyde (vigabatrin)[NDA 217684] proposed prescribing information submitted 2023 AUG 17 available from: \\CDSESUB1\EVSPROD\nda217684\0003\m1\us\114-labeling\draft\labeling\draft-labeling-text-tradename.pdf

[c] Sabril (vigabatrin) oral solution [NDA 022006 Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. October 2021. [cited 2024 MAR 15]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020427s025,022006s026lbl.pdf

Table 4. Relevant Product Information for Vigafyde and Listed Drug Sabril		
Product Name	**Vigafyde[b]**	**Sabril[c]**
Dose and Frequency	*For better viewing of dosing information see Section 2 Dosage and Administration of PI:* Dose and Frequency: The initial daily dosing is 50 mg/kg/day given in two divided doses (25 mg/kg twice daily); subsequent dosing can be titrated by 25 mg/kg/day to 50 mg/kg/day increments every 3 days, up to a maximum of 150 mg/kg/day given in two divided doses (75 mg/kg twice daily). (b) (4)	*For complete dosing information see Section 2 Dosage and Administration of PI:* <u>Refractory Complex Partial Seizures:</u> • Adults (17 years of age and older): Initiate at 1,000 mg/day (500 mg twice daily); increase total daily dose weekly in 500 mg/day increments, to the recommended dose of 3,000 mg/day (1,500 mg twice daily) • Pediatric (2 to 16 years of age): the recommended dose is based on body weight and administered as two divided doses. • The dosage may be increased in weekly intervals, depending on response • Dose patients weighing more than 60 kg according to adult recommendations. <u>Infantile Spasms</u>: Initiate at a daily dose of 50 mg/kg (25 mg/kg twice daily); increase total daily dose every 3 days in increments of 25 mg/kg/day to 50 mg/kg/day, up to a maximum daily dose of 150 mg/kg (75 mg/kg twice daily)
How Supplied	100 mg/mL oral solution is a clear, colorless to light yellow, peppermint-flavored oral solution in a 150 mL bottle. The oral syringe and (b) (4) are provided separately by the pharmacy.	500 mg tablets: bottles of 100 tablets 500 mg packets: packages of 50 (The oral syringes are provided separately by the pharmacy)

Table 4. Relevant Product Information for Vigafyde and Listed Drug Sabril		
Product Name	**Vigafyde[b]**	**Sabril[c]**
Storage	Store at room temperature (b) (4) (b) (4) or in a refrigerator	Store at 20°C to 25°C (68°F to 77°F). See USP controlled room temperature.
Container Closure	150 mL round bottle opaque HDPE with CR closure. Oral syringe and (b) (4) supplied by the specialty pharmacy.	Bottles Packets containing a white to off-white granular powder

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 15, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, Vigafyde and NDA 217684. Our search identified zero previous reviews.

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APPENDIX G. LABELS AND LABELING

G.1 List of Label and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error experiences with similar products, we reviewed the following Vigafyde label and labeling submitted by Pyros Pharmaceuticals, Inc. on March 14, 2024.

- Container label
- Carton labeling
- Prescribing Information, Medication Guide, and Instructions for Use (image not shown), available from: \\CDSESUB1\EVSPROD\nda217684\0006\m1\us\114-labeling\draft\labeling\draft-labeling-text-vigafyde.docx
- Annotated Prescribing Information, Medication Guide, and Instructions for Use (image not shown) available from: \\CDSESUB1\EVSPROD\nda217684\0006\m1\us\114-labeling\draft\labeling\draft-labeling-text-vigafyde.docx
- Red Line Prescribing Information, Medication Guide, and Instructions for Use (image not shown) available from: \\CDSESUB1\EVSPROD\nda217684\0006\m1\us\114-labeling\draft\annotated\redline-insert-label-text.pdf

G.2 Label and Labeling Images

Container label

(b) (4)

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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