CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217684Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 217684
Supplement #:	
Drug Name:	Vigabatrin oral solution 100 mg/ml (150 ml/bottle)
Indication(s):	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
Applicant:	Pyros pharmaceuticals
Date(s):	04/16/2024
Biometrics Division:	Division VI
Statistical Reviewer:	Chang Chen, Ph.D.
Concurring Reviewers:	Meiyu Shen, Ph.D.
Medical Division:	RPM, DN2
Project Manager:	Josephine Little, PharmD

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1 EXECUTIVE SUMMARY

On April 16th, 2024, Dr. Josephine Little at the Center for Drug and Research (CDER) requested CMC statistics team in the Office of Biostatistics (OB) at the Center for Drug and Research (CDER) to evaluate the Applicant's submission regarding the proposed shelf life of 24 months at long-term conditions given the stability data under long term conditions (25 °C), accelerated conditions (40 °C) and intermediate conditions (30 °C).

The Applicant proposed a shelf-life of 24 months for products stored at room temperature conditions. The Applicant has performed a stability study under Accelerated (40 ± 2 °C / 75 ±5% RH), Intermediate (30 ± 2 °C / 65 ±5% RH) and Long Term (25 ± 2 °C / 60 ±5% RH) conditions on the validation batches. The Applicant concluded that the quality of Vigabatrin oral solution 100 mg/ml (150 ml/bottle) remains stable under the influence of a variety of environmental factors such as temperature and humidity. The sponsor also stated that the drug product met its specification requirements at the proposed long-term, intermediate, and accelerated storage conditions.

After we evaluated their statistical analysis and results, the conclusion of our independent statistical analysis is summarized below:

- Under Long term conditions, the upper 95% confidence limit obtained from the provided stability data is within the current specification at 24-month. The Applicant's proposed 24-month shelf-life is acceptable for products stored at room temperature conditions.

2 INTRODUCTION AND BACKGROUND

On April 16th, 2024, Dr. Josephine Little at the Center for Drug and Research (CDER) requested CMC statistics team in the Office of Biostatistics (OB) at the Center for Drug and Research (CDER) to evaluate the Applicant's submission regarding the proposed shelf life of 24 months at long-term conditions given the stability data under long term conditions (25C), accelerated conditions (40C) and intermediate conditions (30C), which are summarized in the table below:

Table 1. Conditions of stability study, duration & type of Study

Temperature/Humidity Condition	Time / Duration of Study	Type of Study
☑ 40 ± 2 °C / 75 ±5% RH	6 months	Accelerated
☑ 30± 2 °C / 65± 5 % RH	12 months	Intermediate
☑ 25 ± 2 °C / 60 ± 5 % RH	24 months[1]	Long Term

The purpose of this stability study is to provide evidence on how the quality of Vigabatrin oral solution 100 mg/ml (150 ml/bottle) varies with time under the influence of a variety of environmental factors such as temperature and humidity and to establish a shelf life for the drug product and the recommended storage conditions.

3 STATISTICAL COMMENTS ON STABILITY DATA

The Applicant provided the following Stability results of Vigabatrin related compound A (RC-A) for all registration batches (Batch No. VAL/22/0003, VAL/22/0004, and VAL/22/0005) when stored for up to 6 months at Accelerated condition (**Table 2.**) and when stored up to 12 months at Intermediate condition (**Table 3.**) (**Received on 08/17/2023**):

Table 2. Vigabatrin oral solution 100 mg/ml (150 ml/bottle) (Condition: 40 ± 2 °C / 75 ±5% RH)

Organic Impurities (By HPLC)	Batch No.	Initial	1-month	3-month	6-month
Vigabatrin RC-A (%)	VAL/22/0003	BLOQ*	(b) (4)		
	VAL/22/0004	BLOQ*			
	VAL/22/0005	BLOQ*			

* BLOQ- Below limit of quantification.

Table 3. Vigabatrin oral solution 100 mg/ml (150 ml/bottle) (Condition: 30 ± 2 °C / 65 ±5% RH)

Organic Impurities (By HPLC)	Batch No.	Initial	3-month	6-month	9-month	12-month
Vigabatrin RC-A (%)	VAL/22/0003	BLOQ*	(b) (4)			
	VAL/22/0004	BLOQ*				
	VAL/22/0005	BLOQ*				

* BLOQ- Below limit of quantification.

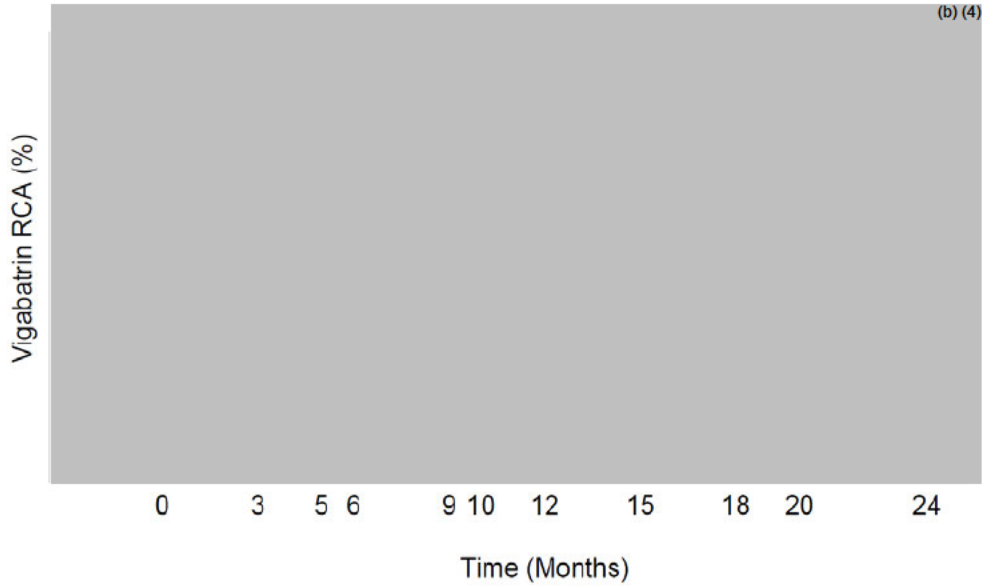

Figure 1. Regression Plot for RC-A under Intermediate condition (projection to 24-month).

Reviewer's Comments: When the specification of Vigabatrin related compound A is set at NMT (b) (4) *significant change* is observed during 6 months of storage under conditions of accelerated testing at 40 ± 2 °C / 75 ±5% RH, where *significant change* at 40°C /75% RH is defined as failure to meet the specifications [ICH Q1A]. However, according to **Table 3** and **Figure 1**, significant change does not occur during 12 months of storage under intermediate conditions (30 ± 2 °C / 65 ±5% RH). The statistical analysis of stability data for Long-term conditions and the evaluation of shelf life under Long-term conditions are discussed in the next section.

4. FDA CMC INDEPENDENT DATA ANALYSIS

The Applicant provided Stability results for all registration batches (Batch No. VAL/22/0003, VAL/22/0004, and VAL/22/0005) when stored for up to 24 months at Long-term condition at 25 ± 2 °C / 60 ±5% RH (**Received on 04/22/2024**). To evaluate the shelf life based on the stability data, an ANCOVA model was fitted to the stability data of Long-term condition (24-month) and Intermediate condition (12-month). An F-test was conducted to test whether batch specific slope and intercept can be pooled based on ICH guidance. The pooling test indicates that all the intercepts and slopes from each condition (Long-term condition and Intermediate condition) can be pooled following the ICH guidance, where α=0.25 is used to determine the significance.

A linear regression model with common intercept and common slope was fitted to the stability data of Long-term condition and Intermediate condition. The 95% confidence limits were obtained for each condition, as presented in **Figure 1** from previous section and **Figure 2** below. For each figure, the Light Blue solid line represents the fitted Linear Regression Line; the Blue dashed line indicates the Upper and Lower confidence band generated from the regression model; the Red dashed line denotes the current specification of Vigabatrin related compound A.

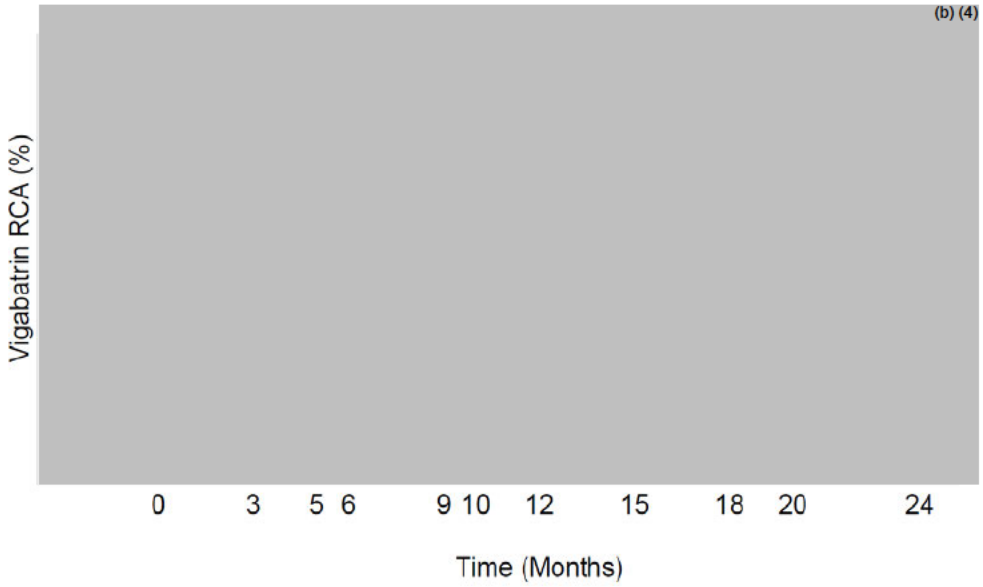

Figure 2. Regression Plot for Vigabatrin RC-A under Long-term conditions.

From **Figure 2**, both the upper and lower 95% confidence limits are within the specification at 24-month (NMT (b) (4) such statistical results support the 24-month shelf life for products stored at room temperature conditions, as proposed by the Applicant.

5. SUMMARY AND RECOMMENDATIONS

Under Long-term conditions, the upper 95% confidence limit obtained from the provided stability data is within the current specification at 24-month. The Applicant's proposed 24-month shelf-life is acceptable for products stored at room temperature conditions.

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/s/

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