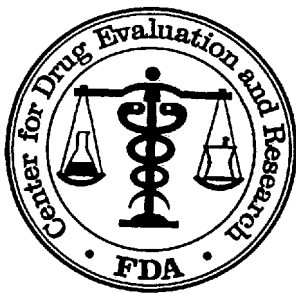


**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208686Orig1s000**

**STATISTICAL REVIEW(S)**



US 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

### Biometrics Division: VI

<b>NDA No.:</b>	208686
<b>DATE RECEIVED BY OB:</b>	June 20 <sup>th</sup> , 2016
<b>DRUG NAME:</b>	Epaned
<b>INDICATION:</b>	Hypertension, symptomatic heart failure treatment and asymptomatic left ventricular dysfunction
<b>SPONSOR:</b>	Silvergate Pharmaceuticals, Inc.
<b>REVIEW FINISHED DATE:</b>	June 30th , 2016
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## I. EXECUTIVE SUMMARY

The sponsor proposed shelf life of (b) (4) months is not appropriate (b) (4).  
 (b) (4). For the stability primary data, a significant change at the accelerated condition was observed at six months for enalapril (b) (4) enalaprilat, and total related substances (other than (b) (4)).

Based on the reviewer's independent analysis, the long term stability data support a shelf life of 22 months which is estimated by the shortest time at which the 95% confidence limits of the mean value intercept with the acceptance criteria for each attribute separately.

Please note that, the shelf life estimation is performed under the assumption that the time trend (b) (4) remains the same. The Sponsor's analysis is summarized in Section III. The detailed analyses are provided in Section IV.

**Table 1: Estimated Shelf Life (Months) for HPLC assay, (b) (4) and pH based on Long Term Stability Data of Assay using Pooled Data**

Test	Last Obs. Time Point	Acceptance Criterion	Estimated Shelf Life*
(b) (4)			

\*: shelf life is estimated by the shortest time at which the 95% confidence limits of the mean value intercept with the acceptance criteria using the pooled data.

## II. INTRODUCTION

On June 20<sup>th</sup>, 2016, Office of New Drug Products (ONDP) requested the CMC statistics team in Office of Biostatistics to provide statistical assessment for NDA 208686, on Silvergate Pharmaceuticals, Inc., to verify the shelf life prediction based on HPLC assay, (b) (4) (b) (4), enalapril (b) (4), enalaprilat, total related substances (other than (b) (4)), (b) (4) and pH under long term conditions. The applicant has provided 12 months Primary Data from the primary batches HCP, HCR, and HCS, and 12 months Supporting Data and is requesting a (b) (4) month when stored refrigerated, including 60 days at room temperature after it is dispense to the patient. The sponsor's stability data under the long-term storage conditions is provided in table2. Based on the above data, FDA statistics reviewer conducted independent stability analyses to estimate the shelf life for the drug substance.

#### IV. FDA Statistical Reviewer's Analyses

Due to the deficiency of Sponsor's analysis as pointed out earlier, we performed independent statistical analysis on the long-term stability data of HPLC Assay, (b) (4) and pH. The shelf life is estimated by the shortest time at which the two-sided 95% confidence limits of the mean value intercept with the acceptance criteria of attributes.

##### *Shelf life estimation using pooled data*

We conducted the poolability test based on the approach outlined in ICH Q1E guidance. The results are shown in 5a, 5b, 5c, below.

**Table 5a: Poolability Testing Results for Stability Data of HPLC assay under the Long-term Storage Conditions**

Source	DF	Type I SS	Mean Square	F Value	Pr > F
batch	2	(b) (4)			
time	1				
time*batch	2				

**Table 5b: Poolability Testing Results for Stability Data of (b) (4) under the Long-term Storage Conditions**

Source	DF	Type I SS	Mean Square	F Value	Pr > F
batch	2	(b) (4)			
time	1				
time*batch	2				

**Table 5c: Poolability Testing Results for Stability Data of pH under the Long-term Storage Conditions**

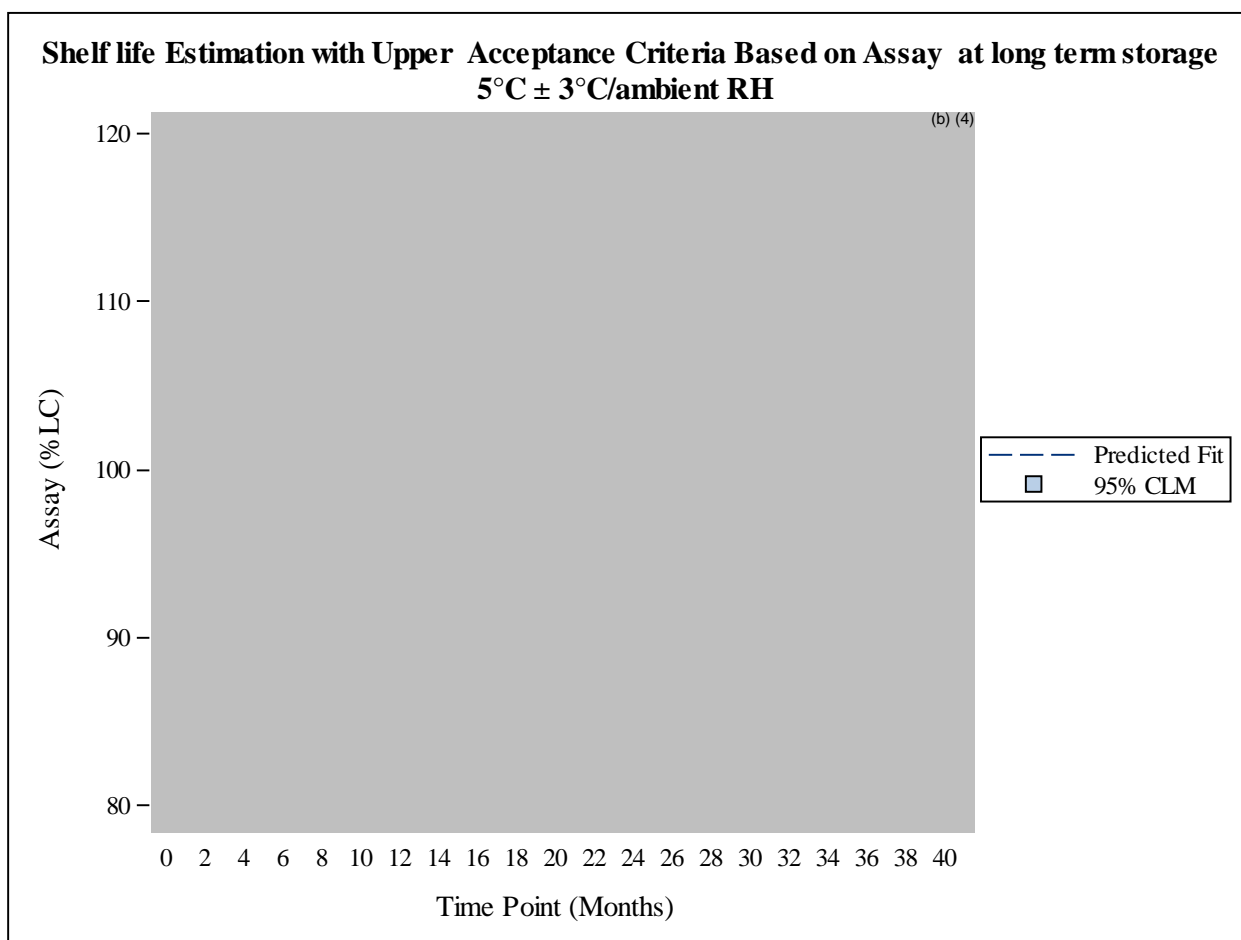
Source	DF	Type I SS	Mean Square	F Value	Pr > F
batch	2	(b) (4)			
time	1				
time*batch	2				

In Table 5a, 5b, and 5c, the p-values of batch and the interaction between time and batch of HPLC Assay, (b) (4), and pH are (b) (4), (b) (4), respectively. They are all larger than the (b) (4). Thus, based on ICH Q1E guidance, the shelf life can be determined by the pooled data of all three batches HCP, HCR, HCS for any of the attributes.

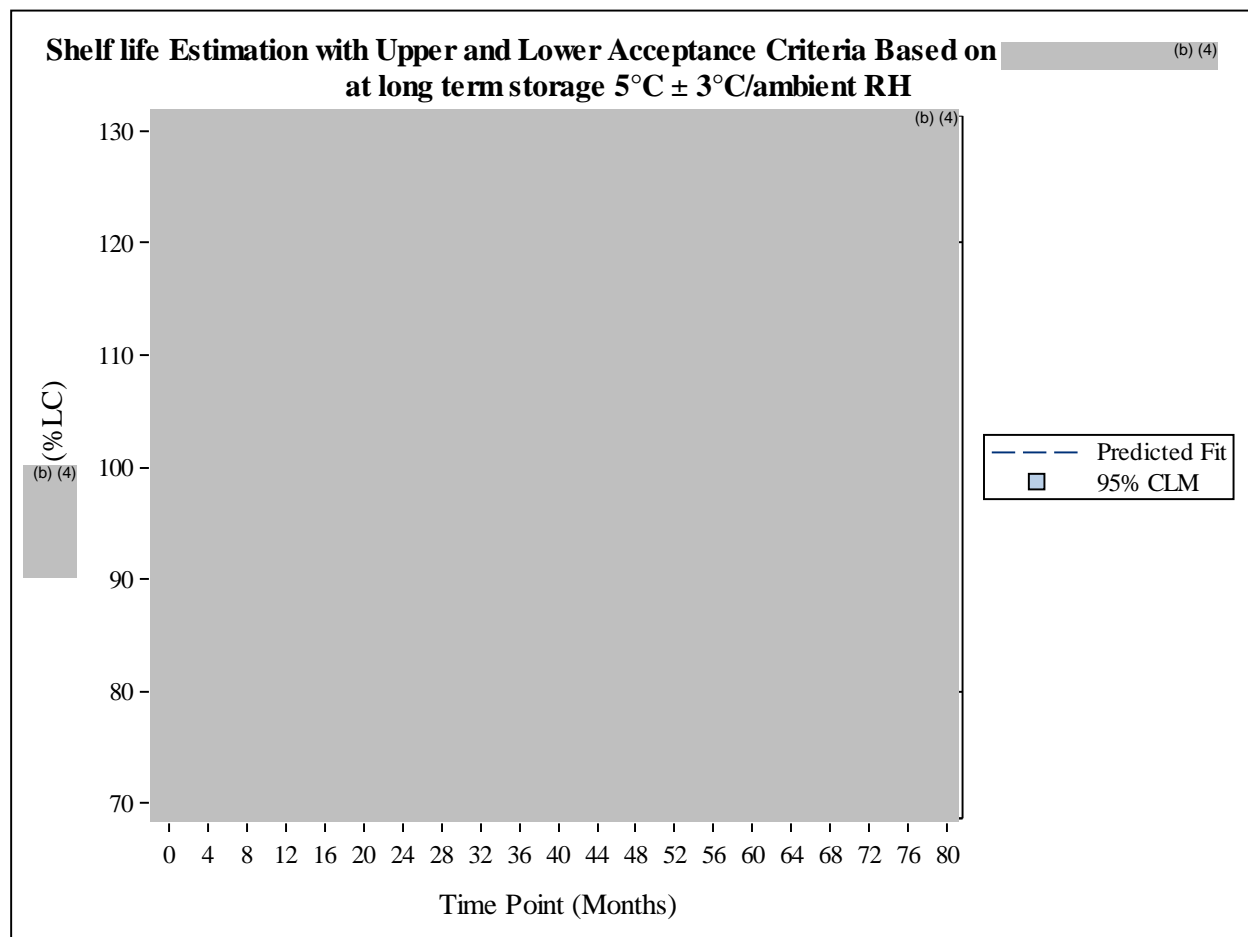
The stability analysis results from the pooled data of batches HCP, HCR, HCS for the attributes are summarized in Table 6. The predicted mean values, 95% confidence limits of mean, and the estimated shelf life are summarized in Figure 1a, 1b, 1c, and Table 7

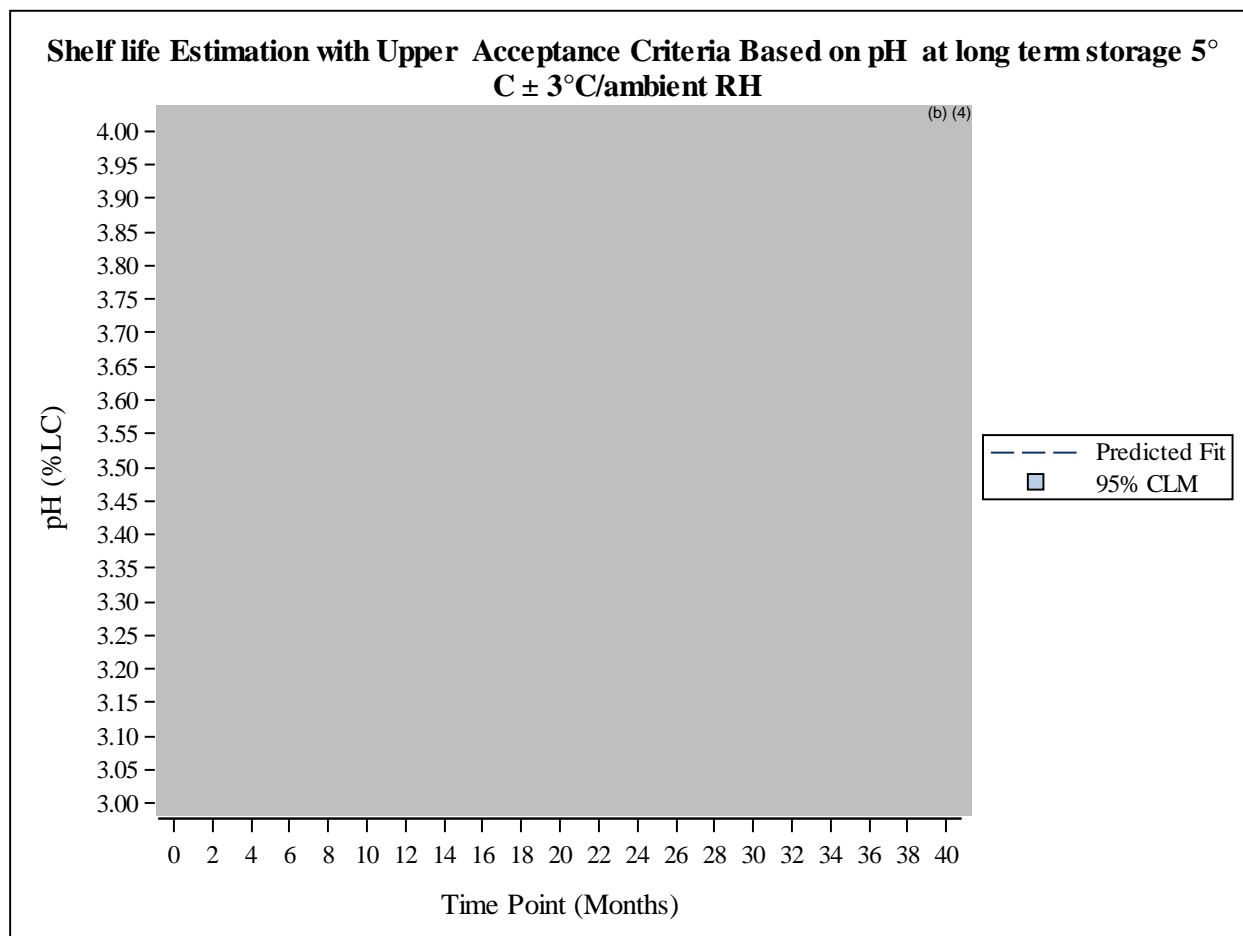
**Table 6: Stability regression model estimation under the Long-term Storage Conditions using pooled data**

Attributes	Label	DF	Parameter Estimate	Standard Error	t Value	Pr >  t
<b>HPLC Assay</b>	Intercept	<b>1</b>				(b) (4)
	time	<b>1</b>				
(b) (4)	Intercept	<b>1</b>				
	time	<b>1</b>				
<b>pH</b>	Intercept	<b>1</b>				
	time	<b>1</b>				

**Fig 1a: Stability Plot of HPLC assay under the Long-term Conditions of the pooled data**

**Fig1b: Stability Plot of (b) (4) under the Long-term Conditions of the pooled data**



**Fig1c: Stability Plot of pH under the Long-term Conditions of the pooled data**

In Figure 1c, the predicted mean values obtained by linear regression are shown in dashed line and the corresponding two-sided 95% confidence limits of the mean values are shown in shaded area. The specified control limits are 3.1 and 3.5. As Figure 1c and Table 7 show, the lower and upper 95% confidence limits corresponding to pH attribute are not within the acceptance criteria (AC) of (b) (4) months. Although the confidence limits intercept with the AC at 21 months, thus, the stability analysis supports a shelf life of 22 months using the pooled data.



**Table 7: Stability Analysis Results of attributes at 30 Months (LCL = Lower Confidence Limit of Mean, UCL = Upper Confidence Limit of Mean, Est. = Estimated)**

Attributes & Batch	Acceptance Criterion	At 30 Months			Est. Shelf Life
		Prediction	95% LCL	95% UCL	
HPLC assay HCP, HCR, HCS					(b) (4)
(b) (4) HCP, HCR, HCS					
pH HCP, HCR, HCS					

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