CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209988Orig1s000

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

NDA NO.:	209988
DATE RECEIVED BY OB:	March 12, 2018
DRUG NAME:	Furosemide Infusor
SPONSOR:	scPharmaceuticals Inc.
INDICATION:	(b) (4)
DOSAGE FORM:	Drug-device combination
STRENGTHS:	80 mg/10 mL
REVIEW FINISHED DATE:	March 22, 2018
CMC STATISTICAL REVIEWER:	Zhuang Miao, Ph.D
CMC REVIEWER:	Chelliah, Mariappan, Ph.D

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I. EXECUTIVE SUMMARY

The purpose of this review is to determine if the proposed shelf life extension to 36 months is supported based on the long term stability data. The reviewer concludes that the sponsor's proposed shelf life extension to 36 months is supported by the long term stability data. At the long term condition of 25 °C/60%RH, "if the long-term and accelerated data show little change over time and little variability", the proposed retest period or shelf life can be up to two times as long as, but should not be more than 12 months beyond the shortest last observation time based on ICH Q1E guidance.

Our estimations on the shelf life for each attribute are summarized in Table 1.

Table 1: FDA Statistics Reviewer's Estimated Shelf Life using Long-term Stability Data

Attribute (Acceptance Criteria)	Batch	Last Observed Month	Statistical Method	Predicted Value, %LC (95% Confidence interval) at 36 months	Is 36 months shelf life supported?
Assay, Inverted (b) (4)	005M14	24	Different Intercept Different Slope	7.84(7.97, 8.09)	Yes
	006E14	24		7.87(7.76, 7.98)	
	008A15	24		8.08(7.85, 8.3)	
	018H14	30		7.82(7.75, 7.90)	
Assay, Upright (b) (4)	005M14	24	Different Intercept Common Slope	7.95(7.87, 8.03)	Yes
	006E14	24		7.91(7.82, 7.99)	
	008A15	24		7.86(7.78, 7.95)	
	018H14	30		7.91(7.83, 7.98)	

Based on FDA statistics reviewer's independent analysis on the long-term 25 °C/60%RH stability data of Assay (Upright) and Assay (Inverted), our conclusions are summarized below:

- A shelf life extension to 36 months is supported by the current long term stability data from Assay (Upright) and Assay (Inverted).

Please note that, the shelf life estimation is performed under the assumption that the time trend beyond 24 months remains the same. The detailed analyses are provided in Section IV.

II. PURPOSE OF THE REVIEW

On March 12, 2017, Office of Product Quality requested the CMC statistics team in Office of Biostatistics to evaluate the shelf life estimation for NDA209988. The sponsor proposed a shelf life extension to 36 months. The OLDP reviewer requested the OB reviewer to conduct the analysis in order to determine if the proposed shelf life for the drug is supported.

III. FDA STATISTICAL REVIEWER'S ANALYSES

The FDA statistical reviewer performed independent statistical analysis on the long-term stability data from all primary stability batches. The FDA chemist Dr. Chelliah, Mariappan requested the CMC statistical reviewer to perform the stability analysis on the assay value. 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 each attribute.

III.1 Stability Analysis for Assay

III.1.1 Stability Analysis for Assay, Inverted

For Assay (Inverted), we performed different intercept different slope on the long term stability data. The AC for assay is (b) (4) mg/mL. The summaries of the results and the stability plot are in the Table 2, Table 3 and Figure 1, respectively.

As shown in Table 2, the P-values of batch and the interaction between time and batch are 0.065 and 0.007, respectively. The P-value for factor Batch is smaller than the significant level 0.25 and the P-value for Batch*Time is smaller than the significant level 0.25. Thus, based on ICH Q1E guidance, the shelf life will be determined by a different -slope- different -intercept model.

Table 2: Poolability Testing Results for Stability Data of Assay (Inverted)

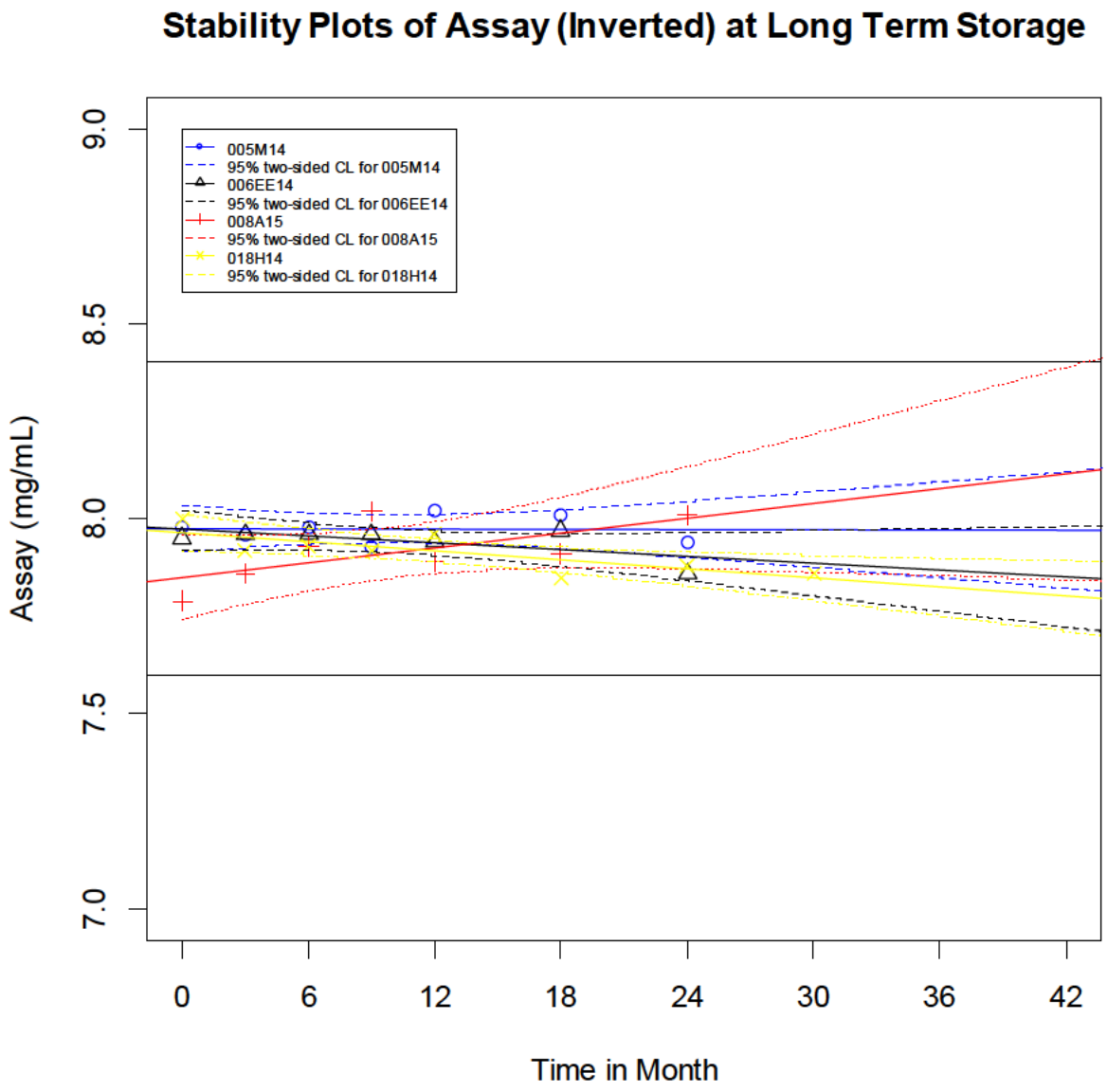
Varible	P-value	Significant Level
Batch	0.065	0.25
Batch*Time	0.007	0.25

In Figure 1, the predicted mean values obtained by linear regression are shown in solid lines and the corresponding 95% two-sided confidence limits of the mean values are shown in dashed lines. The specified control limits are (b) (4) mg/mL. The 95% confidence limit intercept with the AC at >36 months. The proposed retest period or shelf life can be up to two times as long as, but should not be more than 12 months beyond the shortest last observation time based on ICH Q1E guidance. The estimated shelf life for each batch is shown in Table 3.

Table 3: Stability Regression Model Estimation using the Long Term Stability Data of Assay(Inverted)

Batch	Last Observed month	Estimated Intercept (Standard Error)	Estimated Slope (Standard Error)	Predicted Value, %LC (95% Confidence interval) at 36 months	Acceptance Criteria	Is 36 months shelf life supported?
005M14	24	7.97(0.02)	-0.0009(0.0002)	7.84(7.97, 8.09)	(b) (4)	YES
006E14	24	7.97(0.02)	-0.003(0.002)	7.87(7.76, 7.98)		
008A15	24	7.85(0.04)	0.006(0.003)	8.08(7.85, 8.3)		
018H14	30	7.96(0.02)	-0.004(0.001)	7.82(7.75, 7.90)		

Figure 1: Stability Plot for Assay (Inverted), at Long Term Condition



III.1.2 Stability Analysis for Assay, Upright

For Assay (Upright), we performed a common-slope-different-intercept analysis on the long term stability data. The AC for assay i (b) (4) mg/mL. The summary of the results and the stability plot are in Table 5, Table 6 and Figure 2.

As shown in Table 5, the P-values of batch and the interaction between time and batch are 0.09 and 0.48, respectively. The P-value for factor Batch is smaller than the significant level 0.25 and the P-value for Batch*Time is larger than the significant level 0.25. Thus, based on ICH Q1E guidance, the shelf life will be determined by a common-slope-different-intercept model.

Table 4: Poolability Testing Results for Stability Data of Assay (Upright)

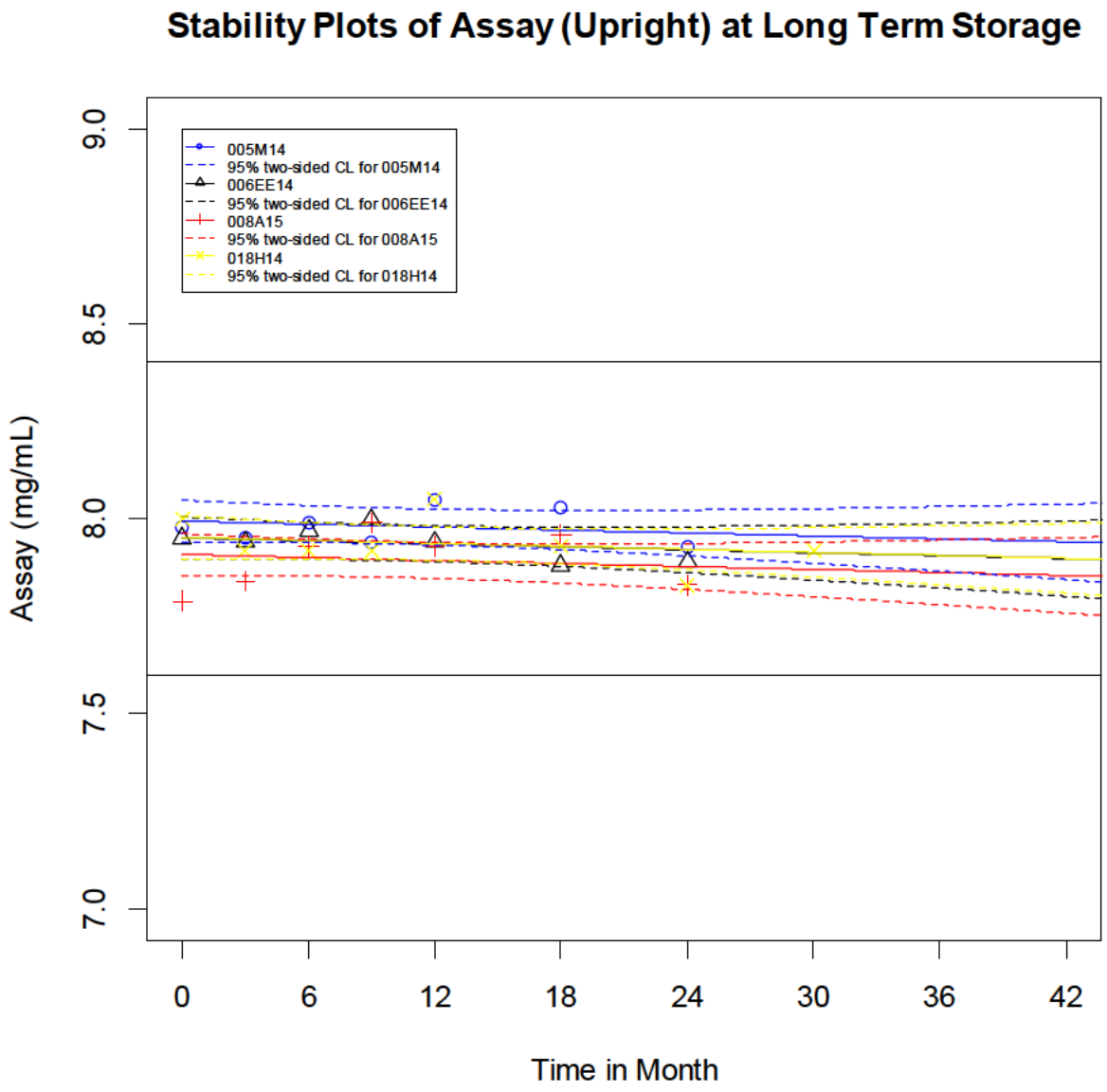
Varible	P-value	Significant Level
Batch	0.09	0.25
Batch*Time	0.48	0.25

In Figure 2, the predicted mean values obtained by linear regression are shown in solid lines and the corresponding 95% two-sided confidence limits of the mean values are shown in dashed lines. The specified control limits are (b) (4) mg/mL. The 95% confidence limit intercept with the AC at >36 months. The proposed retest period or shelf life can be up to two times as long as, but should not be more than 12 months beyond the shortest last observation time based on ICH Q1E guidance. The estimated shelf life for each batch is shown in Table 6.

Table 5: Stability Regression Model Estimation using the Long Term Stability Data Assay (Upright)

Batch	Last Observed month	Estimated Intercept (Standard Error)	Estimated Slope (Standard Error)	Predicted Value, %LC (95% Confidence interval) at 36 months	Acceptance Criteria	Is 36 months shelf life supported?
005M14	24	7.951(0.03)	-0.001(0.001)	7.95(7.87, 8.03)	(b) (4)	YES
006E14	24	7.952(0.03)		7.91(7.82, 7.99)		
008A15	24	7.91(0.03)		7.86(7.78, 7.95)		
018H14	30	7.952(0.03)		7.91(7.83, 7.98)		

Figure 2: Stability Plot for Assay (Upright), at Long Term Condition



IV. CONCLUSIONS AND RECOMMENDATIONS

Based on FDA statistics reviewer's independent analysis on the long-term 25 °C/60%RH stability data of Assay (Upright) and Assay (Inverted), our conclusions are summarized below:

- A shelf life extension to 36 months is supported by the current long term stability data from Assay (Upright) and Assay (Inverted).

Table 6: FDA Statistics Reviewer's Estimated Shelf Life using Long-term Stability Data

Attribute (Acceptance Criteria)	Batch	Last Observed Month	Statistical Method	Predicted Value, %LC (95% Confidence interval) at 36 months	Is 36 months shelf life supported?
Assay, Inverted (b) (4)	005M14	24	Different Intercept Different Slope	7.84(7.97, 8.09)	**Yes**
	006E14	24		7.87(7.76, 7.98)	
	008A15	24		8.08(7.85, 8.3)	
	018H14	30		7.82(7.75, 7.90)	
Assay, Upright (b) (4)	005M14	24	Different Intercept Common Slope	7.95(7.87, 8.03)	**Yes**
	006E14	24		7.91(7.82, 7.99)	
	008A15	24		7.86(7.78, 7.95)	
	018H14	30		7.91(7.83, 7.98)	

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/s/

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03/23/2018

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