CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

NDA NO.:	209-359
SERIAL NO.:	S000
DATE RECEIVED BY THE CENTER:	May 25, 2017
DRUG NAME:	Epinephrine
DOSAGE FORM:	Injection
INDICATION:	Agents Used in Hypotension and Shock
SPONSOR:	Hospira Inc
DOCUMENTS REVIEWED:	May 25, 2017
REVIEW FINISHED	September 24, 2017
NAME OF STATISTICAL REVIEWER:	Meiyu Shen, Ph.D.
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1 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

1.1 Purpose of this review

On June 21, 2017, Office of New Drug Products (ONDP) requests CMC statistics team in the Office of Biostatistics (OB) to evaluate if the sponsor's proposed shelf life of 15 months is acceptable.

1.2 Introduction and Background

Hospira, a Pfizer company, proposed the 15 month shelf life based on the 6-month long term (25°C/40% RH) stability data of epinephrine assay, d-epinephrine (d-epi) and epinephrine sulfonic acid (ESA) impurities for Epinephrine Injection USP Abboject Syringe from an exhibit batch (b) (4) Lot 66-454-SB, and two other batches manufactured (b) (4) at the manufacturing site at the Rocky Mount plant and the up to 24-month long term stability data of epinephrine assay, d-epinephrine (d-epi) and epinephrine sulfonic acid (ESA) impurities from 5 batches (b) (4).

The sponsor updated their data to 12 months on September 22, 2017. The available data from three batches (b) (4) and 5 batches (b) (4) is listed in Table 1.

Table 1 Stability Data

Product	Batch	Batch number	Data available	pH
Abboject (b) (4)	Exhibit Batch (Made at the Rocky Mount Plant)	66-454-SB 3.0	12 months	3
	Additional Batches (Made at the Rocky Mount Plant)	66-453-SB	12 months	3
		66-512-SB	12 months	3
Abboject (b) (4)	Exhibit Batch (Made at the Rocky Mount Plant)	48-332-SB	up to 24-month	3.1
		48-333-SB		3.1
		48-334-SB		3.1
	Lab Batches (Made at the Lake Forest R&D facility)	ELN-347		3.1
		ELN-345		2.8

1.3 Data Analyzed and Sources

The data of epinephrine assay, d-epinephrine (d-epi) and epinephrine sulfonic acid (ESA) impurities were submitted under the long term stability condition in electronic format on June 25, 2017 and updated on September 22, 2017. The data are located in the DARTTS.

1.4 Sponsor's Analysis, Results and Conclusions

The sponsor combined the data from batches with (b) (4) and batches (b) (4) and developed a linear regression model for predicting the values of epinephrine assay, d-epinephrine (d-epi) and epinephrine sulfonic acid (ESA) impurities at 15 months for batches (b) (4) since up to 12 month long term stability data from batches (b) (4) was used in the model. In the sponsor's ANCOVA model, pH and batches were independent variables.

Table 2 lists the following specifications for epinephrine assay, d-epinephrine (d-epi) and epinephrine sulfonic acid (ESA) impurities.

Table 2 The sponsor's proposed specification and actually used specification

Parameter	Specification limits
Epinephrine Assay	(b) (4) % LC
d-epinephrine (d-epi)	(b) (4) % LC
epinephrine sulfonic acid (ESA)	(b) (4) %LC

Based on the 95% upper prediction interval at 15 months calculated from the ANCOVA model using he combined data, the sponsor concluded that the shelf life of 15 months is supported by the combined data.

Statistical reviewer's comments: The sponsor's statistical analyses used the combined data from batches with (b) (4) *and batches with* (b) (4) *is not acceptable since the stability trends of the parameters of interest are not perfect linear with respect to time. Given the product is developed as a product with* (b) (4) *the data from* (b) (4) *is not directly relevant. The statistical reviewer performed independent statistical analysis of the long-term stability data from 3 batches* (b) (4).

1.5 Reviewers' Analysis, Results and Conclusions

1. Data

The statistical reviewer determines the shelf life for the product (b) (4) based on the up to 12-month long term stability data of epinephrine assay, d-epinephrine (d-epi) and epinephrine sulfonic acid (ESA) impurities for Epinephrine Injection USP Abboject Syringe from an exhibit batch (b) (4), Lot 66-454-SB, and two other batches manufactured (b) (4) at the manufacturing site at the Rocky Mount plant.

Table 3 Nine month long term stability data from batches (b) (4)

BATCH	PH	TIME, MONTH	EPINEPHRINE ASSAY, % LC	D-EPINEPHRINE (D-EPI), % LC	EPINEPHRINE SULFONIC ACID (ESA), % LC
66-454-SB	3	0	98.6	0.5	0.3
66-454-SB	3	3	98	1.5	1.6
66-454-SB	3	6	95.6	2.4	2.5
66-454-SB	3	9	95.3	3.3	3.4
66-454-SB	3	12	95.1	4.2	4.3
66-454-SB	3	12	95.4	4.4	4.1
66-453-SB	3	0	98.6	0	0.3
66-453-SB	3	3	97.7	1.4	1.6
66-453-SB	3	6	95	2.3	2.6
66-453-SB	3	9	95.3	3.1	3.6
66-453-SB	3	12	94.4	4.0	4.3
66-453-SB	3	12	95.2	4.1	4.1
66-512-SB	3	0	98.2	0	0
66-512-SB	3	3	98.3	1.3	1.3
66-512-SB	3	6	97.5	2.1	2.5
66-512-SB	3	9	94.8	3	3.4
66-512-SB	3	12	95.9	4.0	3.9
66-512-SB	3	12	95.1	4.1	3.8

2. Statistical analyses

The long term stability data for assay and impurities is modeled by the following linear (ANCOVA) model: $y_{ij} = \beta_0 + \beta_1 Time_j + \beta_2 Batch_i + \beta_{12} Time_j * Batch_i + \varepsilon_{ij}$, where y_{ij} represents the observation obtained for the

ith batch at the jth time, and ε_{ij}, the error term, is a normal variable with the mean of zero and variance of σ^2. The model can be reduced based on the pooling test recommended by the ICH Q1E guidance. The shelf life is estimated by the shortest time at which the two-sided 95% or one-sided 95% confidence limits of the mean value from the ANCOVA model intercepts with the acceptance criteria of each attribute.

1) Epinephrine Assay

The time*batch term is removed from the ANCOVA model since the p-value for time*batch term is 0.9480, greater than 0.25. We can pool the slopes across three batches. Furthermore the p-value for batch factor is 0.3901, greater than 0.25, and so the batch factor is removed from the ANCOVA model. The final model is $\hat{y}_{ij} = 98.703 - 0.3989 Time_j$. Here $\hat{y}_{ij}$ is the observed value for Epinephrine Assay for the ith batch at the jth time.

Figure 1 shows the relationship between Epinephrine Assay and time for all 3 batches (b) (4) From Figure 1, it is easily seen that the shelf life of 15 months is supported since 95% lower confidence bound is 93.43% LC, which is greater than the lower specification limit, 90% LC.

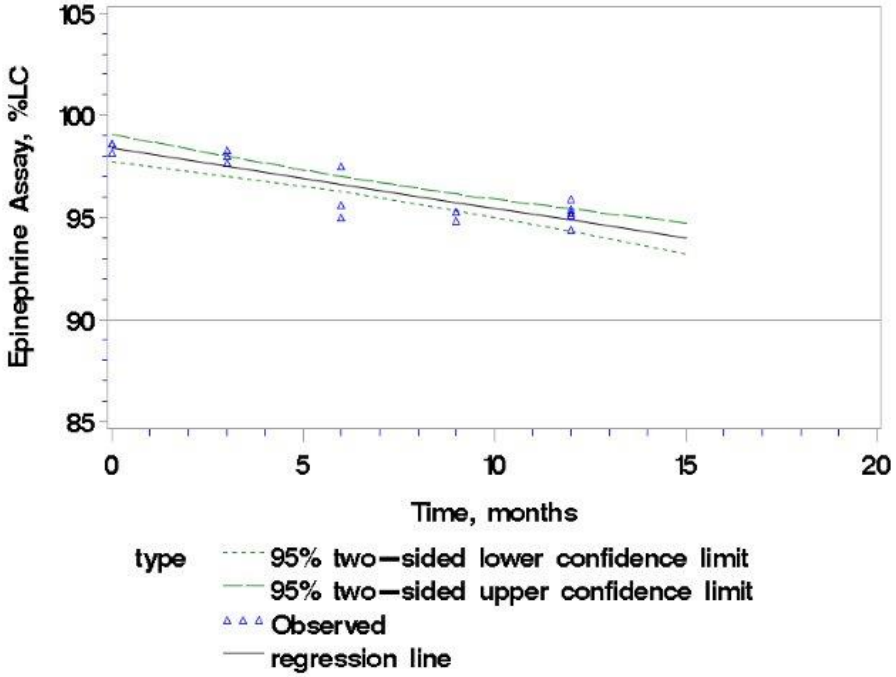


Figure 1 Stability trend over time for Epinephrine Assay under long term condition

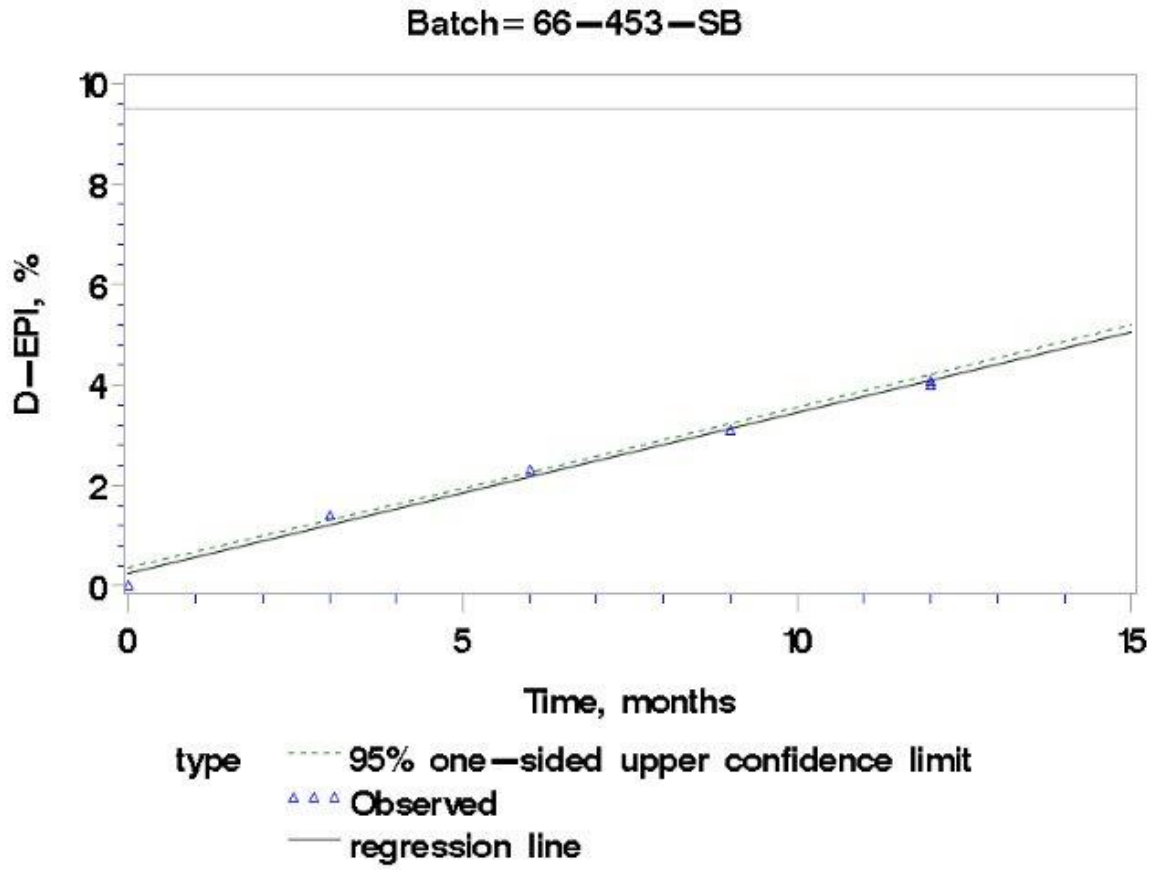
2) D-EPINEPHRINE (D-EPI)

The time*batch term is removed from the ANCOVA model since the p-value for time*batch term is 0.7556, greater than 0.25. We can pool the slopes across three batches. However, the batch factor can't be removed from the ANCOVA model since the p-value for batch factor is 0.0025, smaller than 0.25. The final model is $y_{ij} = \beta_0 + \beta_1 Time_j + \beta_2 Batch_i + \varepsilon_{ij}$. Here y_{ij} is the observed value for D-Epinephrine for the ith batch at the jth time. The estimates of parameter are listed in Table 4. Figure 2 shows the relationship between D-Epinephrine and time for all 3 batches (b) (4)

From Figure 2, it is easily seen that the shelf life of 15 months is supported since 95% upper confidence bounds for three batches are all smaller than the upper specification limit, 9.5% LC.

Table 4 Estimates of parameters and standard errors for D-EPI

Parameter	Estimate	Standard Error
Intercept	0.1669	0.0690
time	0.3214	0.0066
Batch 66-453-SB	0.0667	0.0724
Batch 66-454-SB	0.3000	0.0724
Batch 66-512-SB	0.0000	



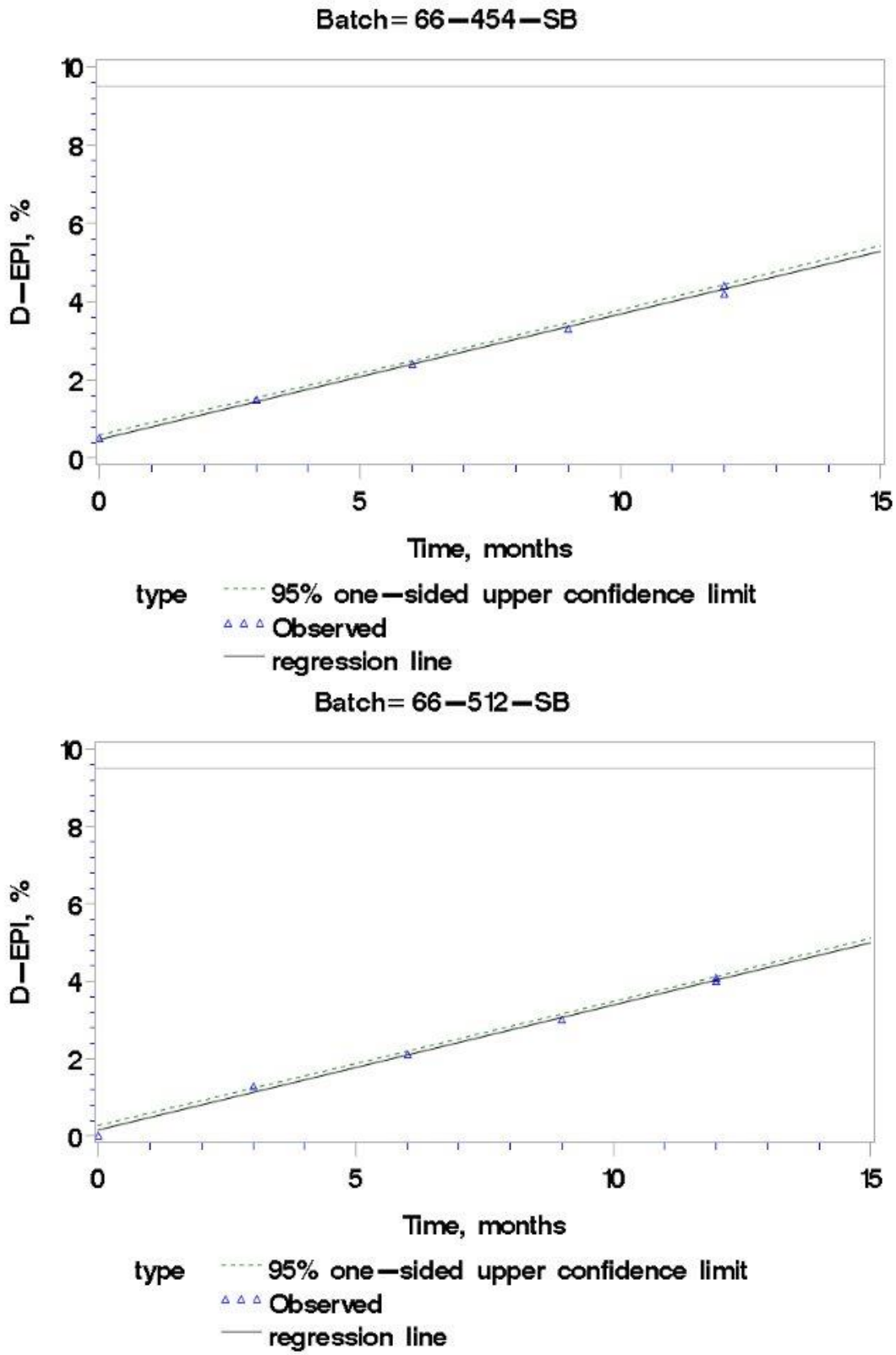


Figure 2 Stability trend over time for D-Epinephrine under long term condition

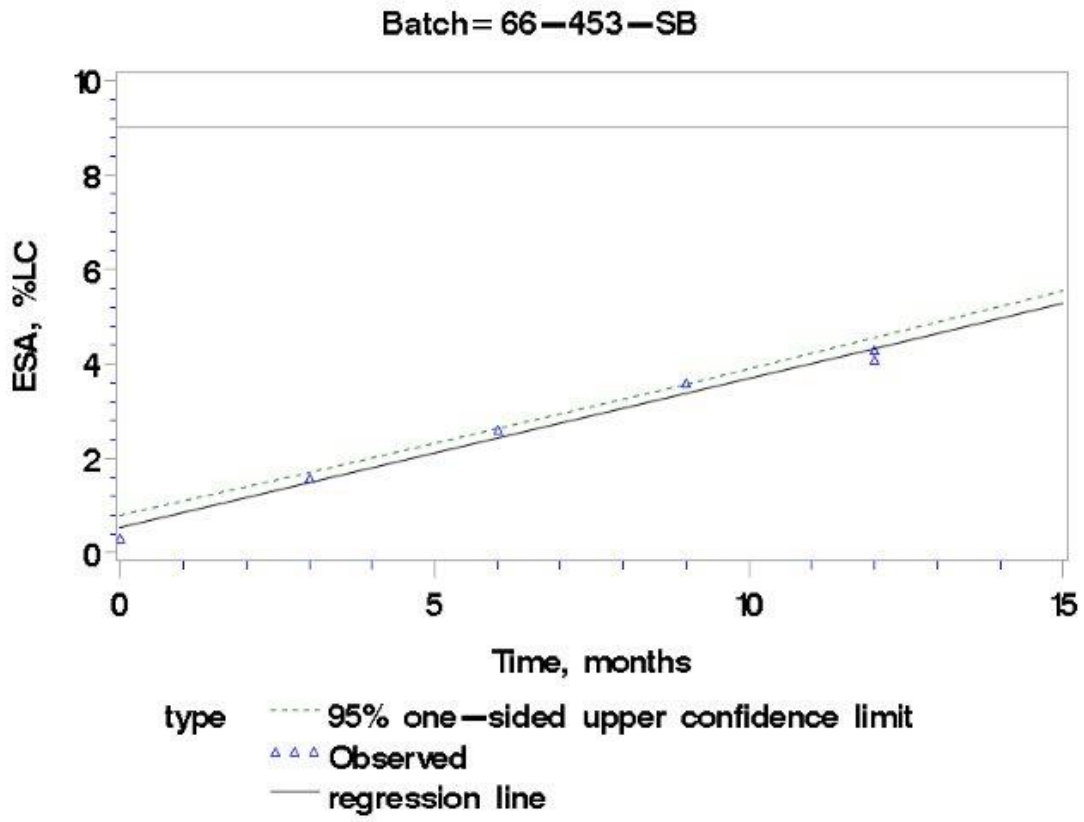
3). EPINEPHRINE SULFONIC ACID (ESA)

The time*batch term is removed from the ANCOVA model since the p-value for time*batch term is 0.9907, greater than 0.25. We can pool the slopes across three batches. However, the batch factor can't be removed from the ANCOVA model since the p-value for batch factor is 0.1193, smaller than 0.25. The final model is $y_{ij} = \beta_0 + \beta_1 Time_j + \beta_2 Batch_i + \varepsilon_{ij}$. Here y_{ij} is the observed value for ESA for the ith batch at the jth time. The estimates of parameter are listed in Table 5. Figure 3 shows the relationship between ESA and time for all 3 batches (b) (4)

From Figure 3, it is easily seen that the shelf life of 15 months is supported since 95% upper confidence bounds for three batches are all smaller than the upper specification limit, 9.0% LC.

Table 5 Estimates of parameters and standard errors for ESA

Parameter	Estimate	Standard Error
Intercept	0.2764	0.1212
time	0.3153	0.0116
Batch 66-453-SB	0.2667	0.1272
Batch 66-454-SB	0.2167	0.1272
Batch 66-512-SB	0.0000	.



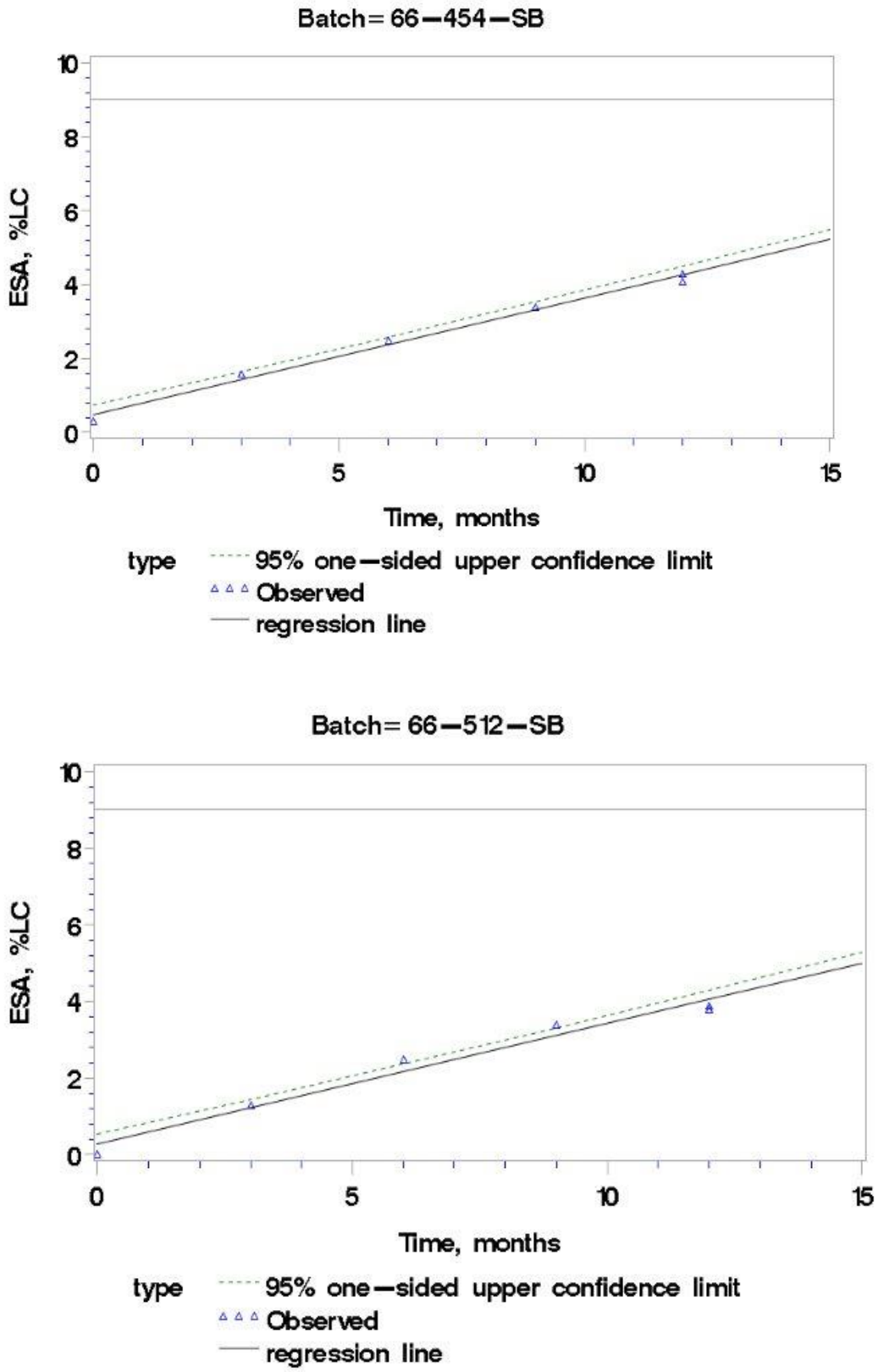


Figure 3 Stability trend over time for ESA under long term condition

1.6 Conclusions and Recommendation

Based on these analyses and evaluations of the 12-month long term stability data from 3 batches (b) (4) the product is expected to remain within specifications through 15 months (see Figures 1-3).

However, the statistical reviewer must point out that all three batches are manufactured at same condition of pH (b) (4) This would limit the flexibility of generalizing statistical analyses to other pH conditions. The review Chemist, Dr. Mariappan Chelliah, acknowledged this limitation and pointed out that the statistical analysis should be still valid since the target pH during formulation should be controlled at the range of (b) (4) although the specification of pH during shelf-life was 2.3-3.5.

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/s/

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09/25/2017

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