

GUANIDINE THIOCYANATE
REAL-TIME STABILITY REPORT:
GT3200-033-1016

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1 OVERVIEW:

The purpose of this report is to analyze the data obtained from the Real-Time Stability of Guanidine Thiocyanate manufactured at BioSpectra's Bangor, PA facility. Samples were placed on the Stability Testing Program in June 2017, to fulfil the requirements of adding one GMP manufactured batch per year. The long-term Real-Time Stability Program consists of testing every three months for the first year, every six months for the second year and annually for each subsequent year, notated as T_n , where n represents the number of months on stability. Analysis has been conducted for a total of thirty-six months in order to assure that the manufactured material remains stable under the specified conditions and for the specified interval of time. The analysis of the compiled data may be used to re-evaluate the retest period for future lots of manufactured material.

This Real-Time Stability analysis assesses the stability of one lot of Guanidine Thiocyanate that completed three years of long-term stability in June 2020. The study included the following analyses: Absorbance (1.7M), Assay (Dried), Identification (IR), pH (5% Solution), and Melting Range. Appearance and Color was added to the study in September 2019, between T_{24} and T_{36} . Results from all analyses are summarized in Table 2 and Shelf-Life Plot determinations have been created for quantitative analyses. Shelf-Life Plots determine the point in time at which the slope would exceed the acceptance criteria. As long as the slope has a statistically significant difference from zero using a 95% confidence limit, an estimated time in months can be established at which the acceptance criteria will no longer be met, i.e. the Predicted Shelf Life. This allows BioSpectra to ensure that the product will be stable over the time period in which it is part of the Stability Testing Program.

2 REFERENCES:

- 2.1 Current USP
- 2.2 ICH Q1
- 2.3 [Stability Testing Program](#)
- 2.4 [Stability Inventory](#)

3 SAMPLE DESIGNATION:

Samples placed on the Stability Testing Program consisted of one lot of Guanidine Thiocyanate. Stability samples from this batch were put into three different packaging configurations. These samples were packaged in accordance with the Stability Inventory SOP. Reference Table 1, below, for packaging configurations and descriptions. The type of packaging utilized in this stability study was based on BioSpectra packaging offered to the customer.

TABLE 1: PACKAGING DETAILS

Packaging Configuration	Packaging Description
Poly/Poly (P/P)	Samples are packaged into small poly bags and sealed with a ziptie. All individual samples are then placed into a poly pail.
2Poly/Fiber (2P/F)	Samples are packaged into small poly bags and sealed with a ziptie. All individual samples are then placed into a larger poly bag, sealed with a ziptie, and then are placed into a fiber drum.

Labline	Samples are packaged individually into separate lab screw-top bottles and are sealed with tamper evident seals.
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4 STORAGE:

At the start of this stability study, Guanidine Thiocyanate stability samples were being stored in the Zone M Warehouse. Due to the inability to control the temperature of the warehouse during the summer months, the stability samples were relocated to the long-term stability chamber.

From June 31, 2017 through September 25, 2019, the samples were stored in the Zone M Warehouse. The temperature was monitored continuously using MadgeTech data loggers. The maximum temperature of the warehouse during the stability study was 33.67°C and the minimum temperature of the warehouse was 12.17°C.

On September 25, 2019, all stability samples were moved from the Zone M Warehouse to the long-term stability chamber. The samples were stored in this location until the end of the 36-month stability study on June 28, 2020. The temperature was monitored continuously using MadgeTech data loggers, with an allowable temperature range of 23°C – 27°C. The minimum temperature reached during this time was 23.97°C and the maximum temperature reached was 27.72°C. The maximum temperature was out of specification for less than one hour and the humidity remained within specification during this time. No discrepancy was issued for this excursion.

5 INVESTIGATIONS:

- 5.1 BDI18-20: The temperature Alarm Notifications were not received by BioSpectra due to the way the alarms rules were established. The temperature in the Zone M Warehouse was reported as less than 15°C on multiple dates ranging from 12/28/17 to 3/4/18. The average temperature was reported as 18.87°C and the minimum temperature was reported as 12.20°C. T₆ and T₉ samples were pulled and tested during this timeframe, and all results met specification.
- 5.2 BLI17-36: The GT3200-033-1016 T₀ sample was analyzed for Loss on Drying and obtained an Out of Specification Result of 0.7297%. The re-tests met the required specification and the initial failure was attributed to improper sample transfer and potentially a lack of homogeneity during the original preparation.
- 5.3 BLI20-16: GT3200-033-1016 T₃₆ samples failed for Appearance and Color for the P/P and Labline packaging configurations. The official result reported for each packaging is Yellow/Crystals.

6 LOT EVALUATION:

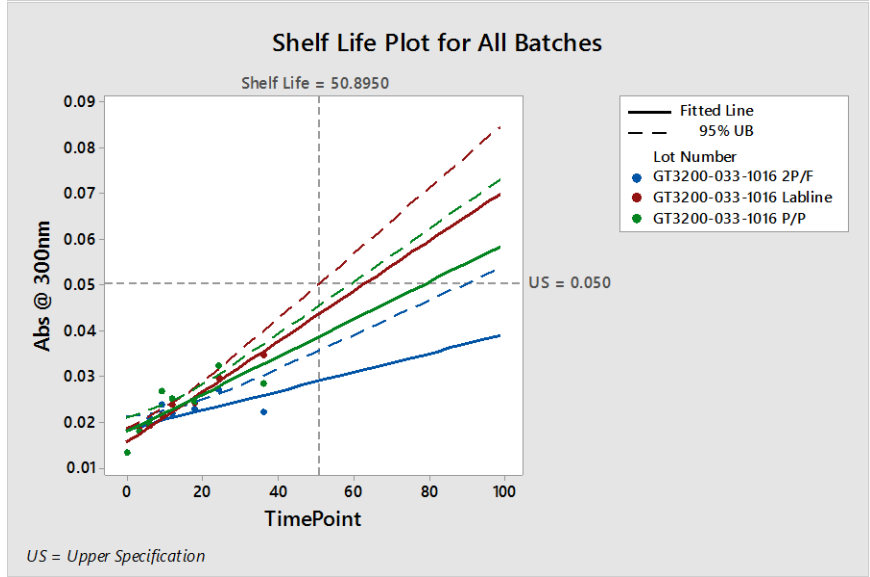
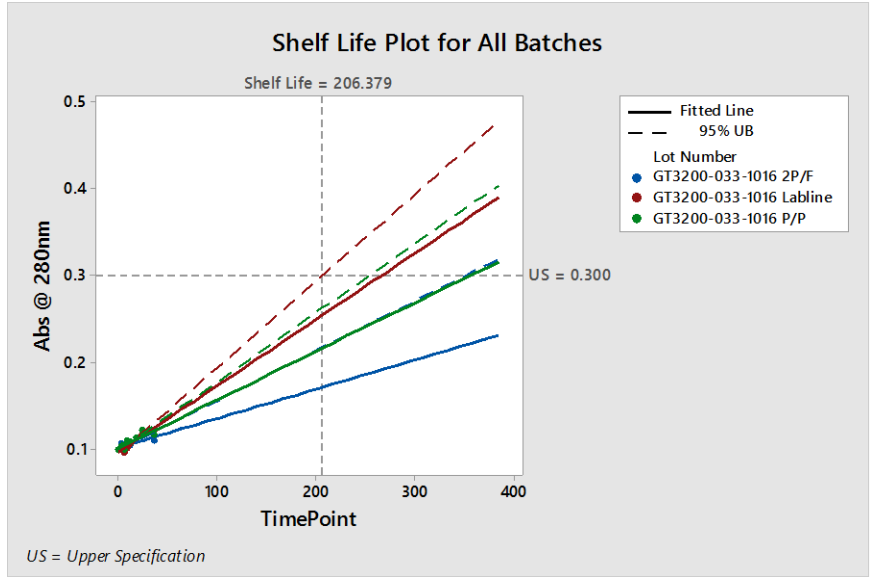
TABLE 2: RESULTS OF LONG-TERM STABILITY ANALYSES

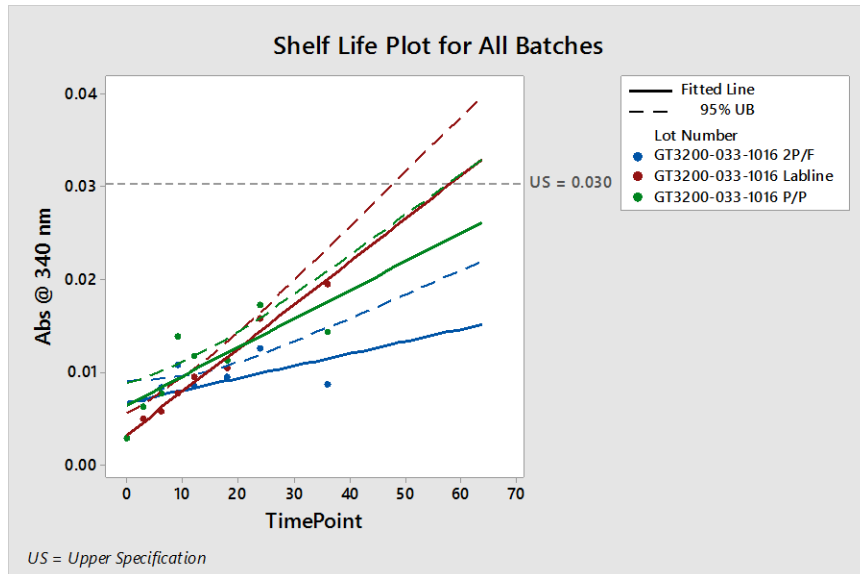
Guanidine Thiocyanate Stability Data										
Lot Number	Analysis	Specification	T ₀	T ₃	T ₆	T ₉	T ₁₂	T ₁₈	T ₂₄	T ₃₆
GT3200-033-1016 P/P	Absorbance (1.7M) @ 280nm	0.300 a.u. max	0.0995	0.1049	0.0991	0.1098	0.1084	0.1133	0.1216	0.1165

Guanidine Thiocyanate Stability Data

Lot Number	Analysis	Specification	T₀	T₃	T₆	T₉	T₁₂	T₁₈	T₂₄	T₃₆	
	Absorbance (1.7M) @ 300nm	0.050 a.u. max	0.0133	0.0180	0.0197	0.0269	0.0250	0.0245	0.0323	0.0284	
	Absorbance (1.7M) @ 340nm	0.030 a.u. max	0.0029	0.0063	0.0077	0.0139	0.0118	0.0113	0.0172	0.0143	
	Appearance and Color	White/ Crystals	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Yellow/ Crystals
	Assay, Dried	99.5% - 100.5%	99.71%	99.94%	100.23%	100.35%	99.67%	99.86%	99.99%	99.90%	
	Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	
	pH (5% Solution)	4.0 – 7.0	5.581	5.51	5.63	5.49	6.29	5.44	5.55	5.60	
	Melting Range	115 – 121°C	119.6 – 120.8°C	119.4 – 120.0°C	119.7- 120.6°C	119.3 – 120.6°C	119.4 – 120.9°C	119.7 – 120.5°C	119.3 – 120.2°C	119.1 – 120.4°C	
	Loss on Drying	0.5% max	0.4820%	0.2397%	0.1526%	0.1130%	0.0428%	0.1022%	0.0876%	0.0299%	
GT3200-033-1016 Labline	Absorbance (1.7M) @ 280nm	0.300 a.u. max	0.0995	0.1029	0.0962	0.1013	0.1060	0.1129	0.1208	0.1223	
	Absorbance (1.7M) @ 300nm	0.050 a.u. max	0.0133	0.0187	0.0191	0.0214	0.0238	0.0243	0.0298	0.0348	
	Absorbance (1.7M) @ 340nm	0.030 a.u. max	0.0029	0.0050	0.0058	0.0077	0.0095	0.0104	0.0158	0.0195	
	Appearance and Color	White/ Crystals	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Yellow/ Crystals
	Assay, Dried	99.5% - 100.5%	99.71%	99.94%	100.01%	100.18%	99.60%	100.01%	99.99%	99.96%	
	Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	
	pH (5% Solution)	4.0 – 7.0	5.581	5.51	5.60	5.40	5.45	5.43	5.49	5.57	
	Melting Range	115 – 121°C	119.6 – 120.8°C	119.6 – 120.4°C	119.9 – 120.8°C	119.5 – 120.8°C	119.6 – 120.9°C	119.8 – 120.9°C	119.3 – 120.3°C	119.1 – 120.6°C	
Loss on Drying	0.5% max	0.4820%	0.3282%	0.4039%	0.2068%	0.0732%	<0.0097%	0.0221%	0.0233%		
GT3200-033-1016 2P/F	Absorbance (1.7M) @ 280nm	0.300 a.u. max	0.0995	0.1065	0.1003	0.1070	0.1044	0.1105	0.1174	0.1094	
	Absorbance (1.7M) @ 300nm	0.050 a.u. max	0.0133	0.0189	0.0209	0.0237	0.0219	0.0227	0.0271	0.0221	
	Absorbance (1.7M) @ 340nm	0.030 a.u. max	0.0029	0.0071	0.0084	0.0108	0.0085	0.0094	0.0126	0.0087	
	Appearance and Color	White/ Crystals	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	White/ Crystals
	Assay, Dried	99.5% - 100.5%	99.71%	99.99%	99.99%	100.29%	99.71%	99.84%	100.01%	100.10%	
	Identification (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	
	pH (5% Solution)	4.0 – 7.0	5.581	5.53	5.53	5.47	5.49	5.44	5.50	5.62	
	Melting Range	115 – 121°C	119.6 – 120.8°C	119.0 – 120.6°C	119.7 – 121.0°C	119.6 – 120.5°C	119.5 – 120.8°C	119.8 – 120.9°C	119.4 – 120.2°C	119.2 – 120.4°C	
	Loss on Drying	0.5% max	0.4820%	0.0629%	0.0363%	0.0398%	0.0191%	0.0372%	0.0342%	0.0200%	

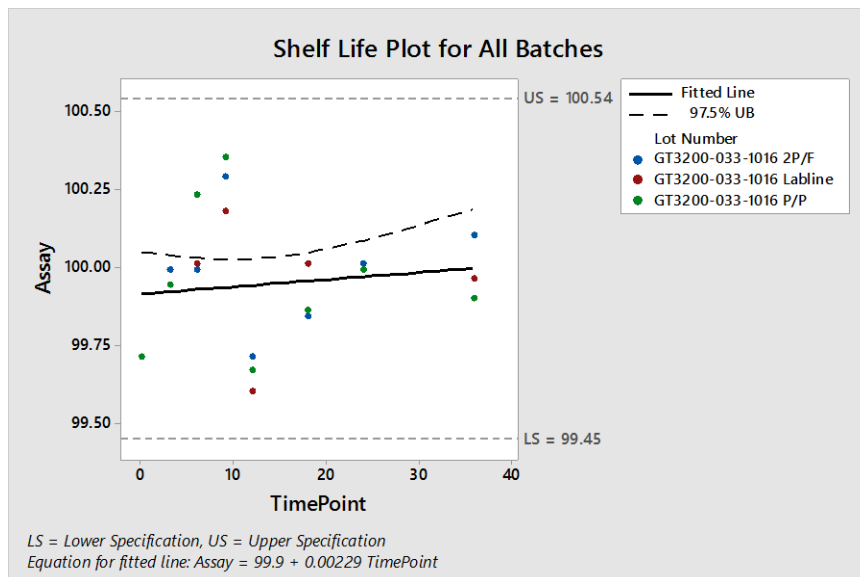
GRAPHS 1-3: ABSORBANCE SHELF LIFE PLOTS





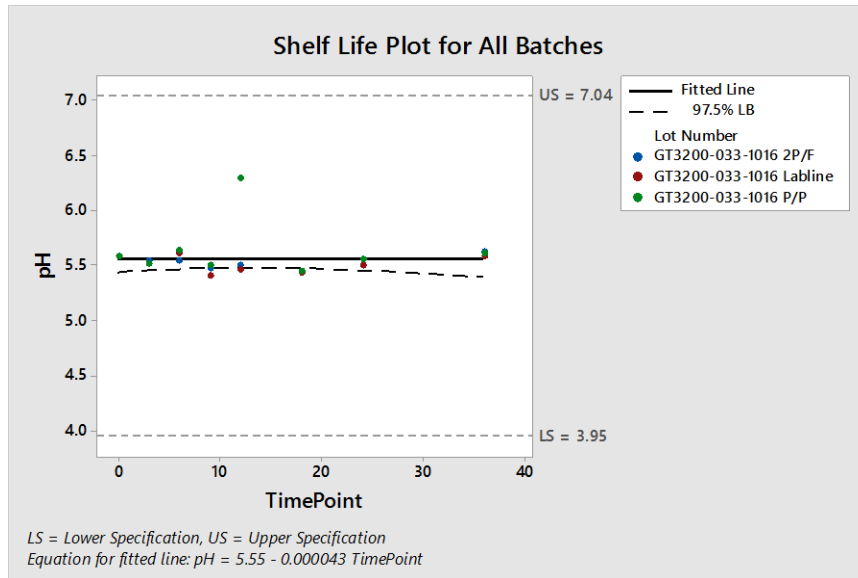
The predicted shelf life for Absorbance (1.7M at 280, 300, and 340nm) was determined to be 40.098 months. This is well beyond the thirty-six-month stability study, and shows no indication of issue to the product or the current twenty-four-month shelf-life for this material.

GRAPH 4: SHELF LIFE PLOT FOR ASSAY



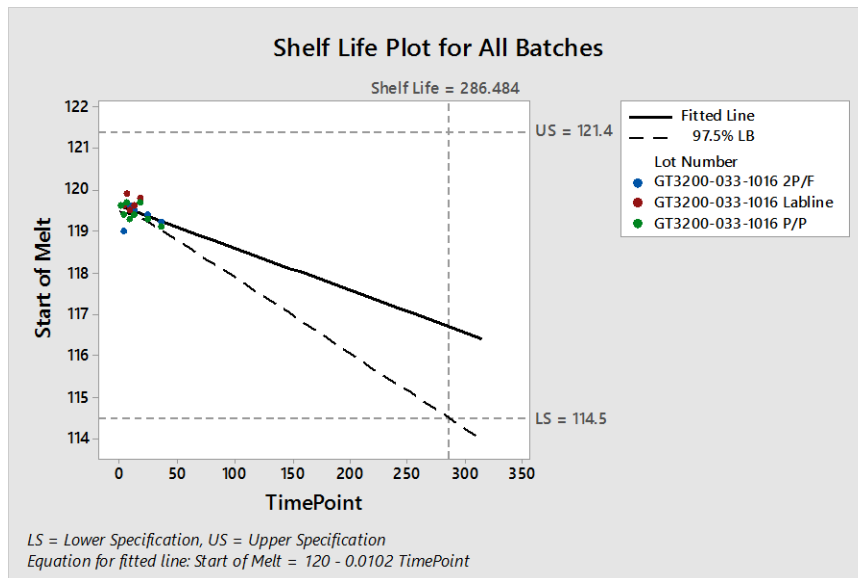
No shelf life is able to be determined for Assay, as the mean response slope is not significantly different from zero. There is no impact to the product or the current twenty-four-month expiration of this material.

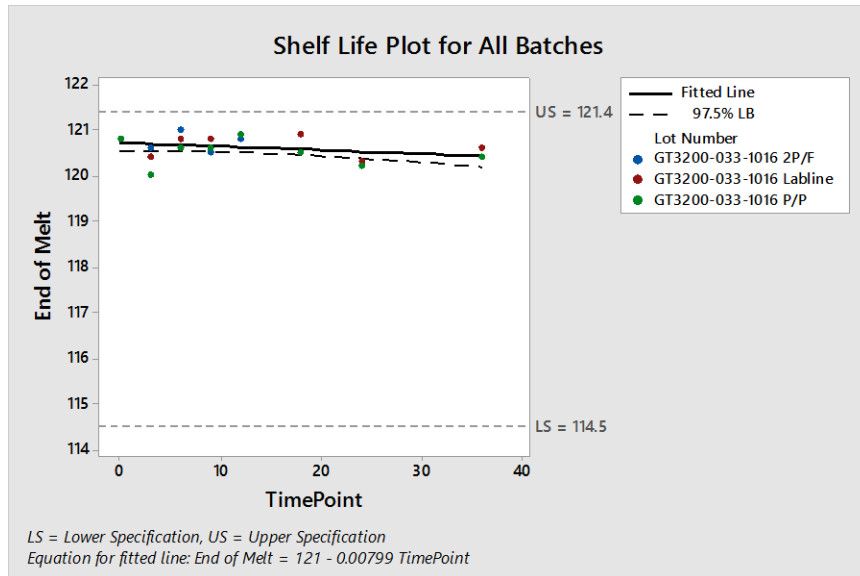
GRAPH 5: SHELF LIFE PLOT FOR pH



No shelf life is able to be determined for pH, as the mean response slope is not significantly different from zero. There is no impact to the product or the current twenty-four-month expiration of this material.

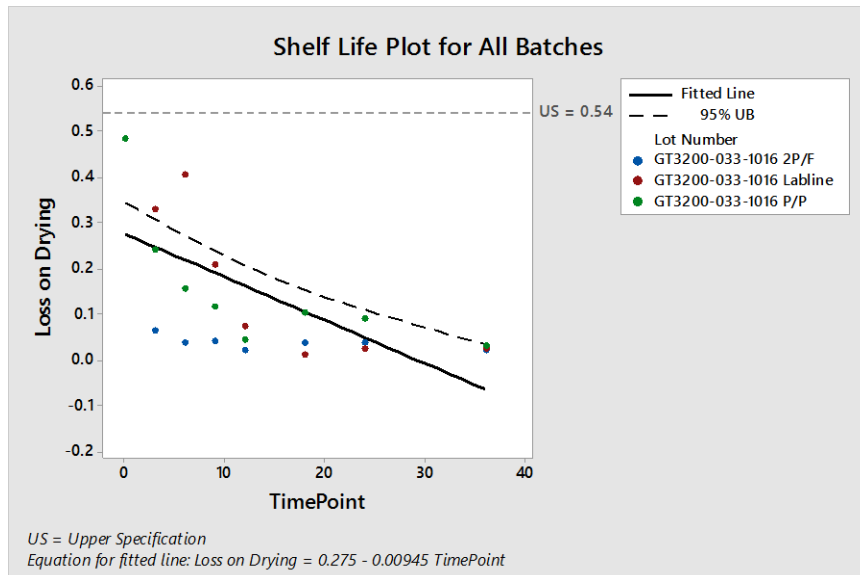
GRAPHS 6 – 7: SHELF LIFE PLOT FOR MELTING RANGE





The predicted shelf life for Melting Range (Start of Melt and End of Melt) was determined to be 286.484 months. This is well beyond the thirty-six-month stability study, and shows no indication of issue to the product or the current twenty-four-month shelf-life for this material.

GRAPH 8: SHELF LIFE PLOT FOR LOSS ON DRYING



No shelf life is able to be determined for Loss on Drying, as the mean response slope is not significantly different from zero. There is no impact to the product or the current twenty-four-month expiration of this material.

7 CONCLUSION:

All data met the specifications set forth in the Stability Testing Program, with the exception of the newly added Appearance and Color analysis for the P/P and Labline packagings. It has been determined that Guanidine Thiocyanate is a light-sensitive material and will degrade to a yellow-colored crystal when not stored in light-proof packaging. The change in color has not shown any effect on quantitative analyses. A retest date of 24 months will be applied to all Guanidine Thiocyanate sold in P/P and Labline packaging configurations.

In accordance with ICH Q1E 2.4.2.1, the retest date may be proposed for up to $2x$, where x is the period covered by long-term stability data, but should be no more than 12 months beyond. The data obtained during this stability study indicates that the material packaged in 2P/F packaging is stable for 36 months, and the material packaged in P/P and Labline packaging is stable for 24 months. All future lots of Guanidine Thiocyanate will continue to be assessed for Appearance and Color and the re-test date for Labline and P/P packagings may be reevaluated.

8 STATEMENT OF COMMITMENT:

8.1 BioSpectra is responsible for the following regarding Stability Data in this Report:

8.1.1 In the event that any stability analysis produces results found to be out of specification, the batch produced immediately before and after will be tested in full and analyzed in comparison with the batch in question.

8.1.1.1 This will serve to provide information to effectively ensure that the root cause of the investigation has not impacted the batch manufactured before or after the batch in question.

8.1.2 If a stability analysis is found to be out of specification, the batch will be withdrawn from the market through communication with the Applicant and any additional customer. Additionally, an investigation will be conducted to determine the possible withdrawal of the batches produced before and after the batch in question.

8.1.3 In the event that any out of specification results are confirmed, all authorized users of the material will be notified.

GUANIDINE THIOCYANATE 2017
LONG TERM STABILITY
REPORT

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1. OVERVIEW:

The purpose of this Report is to analyze and conclude on the data obtained from the Long Term Stability Study of Guanidine Thiocyanate. Testing intervals are designated by T_n , where n = the number of months on stability. Testing is performed every three months for the first year, every six months for the second year, and annually for each subsequent year in order to maintain that the manufactured product remains stable under the specified conditions and for the specified interval of time. The analysis of the compiled data may also aid in a re-evaluation of the retest date for the finished good product.

The data was analyzed utilizing a Shelf-Life Plot, which determines the point in time at which the slope would exceed the acceptance criteria. As long as the slope has a statistically significant difference from zero using a 95% confidence limit, an estimated time in months can be established at which the acceptance criteria will no longer be met, i.e. the Shelf Life. This allows BioSpectra to ensure that the product is stable over the time period in which it is part of the Stability Program. All quantitative data was analyzed using these methods. The data can be found in the Guanidine Thiocyanate Long Term Stability Program binders.

This Long Term Stability analysis will assess the stability of 3 validation lots of Guanidine Thiocyanate that were placed on stability in 2014, with the stability studies concluding in 2017.

2. DEFINITIONS:

CL: Control Limit, the average

UCL: Upper control limit, 3 sigma above the CL

LCL: Lower control limit, 3 sigma below the CL

OOT: Out Of Trend, this means that the material still meets control limits but was not in trend with the rest of the material.

OOS: Out of Specification, for the purpose of this stability analysis, OOS will mean that there is a point(s) that fall outside of the UCL or LCL.

3. SAMPLE DESIGNATION:

Samples initially placed on the Stability Program consisted of all process validation batches and one lot per year. Stability samples from each of these batches were packaged as Poly/Poly (P/P) in accordance with the Sampling Matrix SOP.

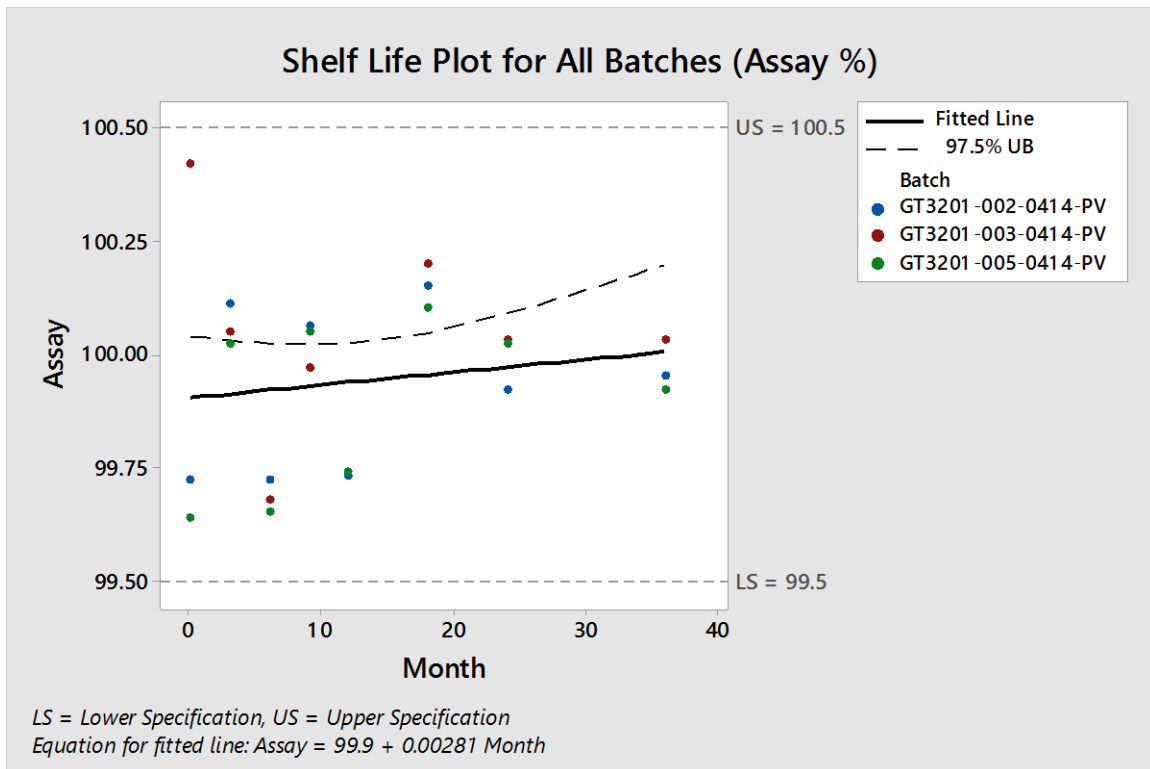
4. STORAGE:

Although there are currently no storage conditions for Guanidine Thiocyanate, storage conditions have been continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature (15-30°C) and humidity (monitor).

5. LOT ANALYSIS:

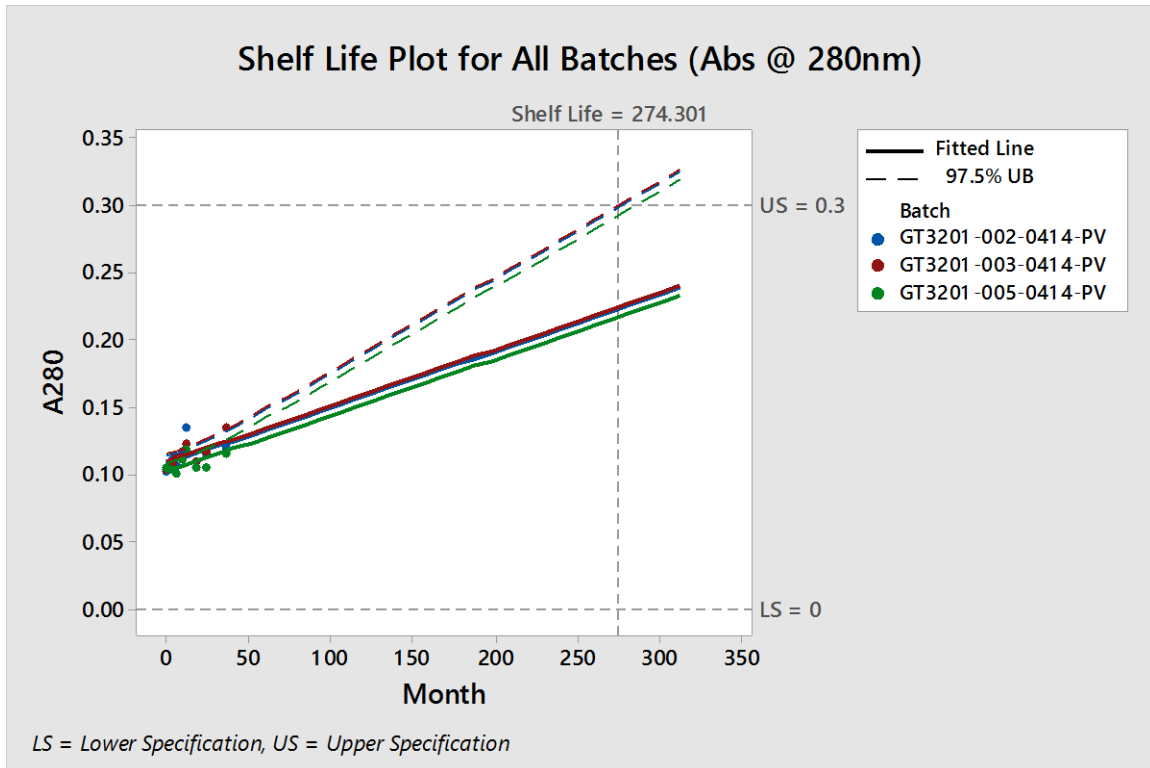
The following graphs will evaluate the three validation batches of Guanidine Thiocyanate placed on stability in 2014: GT3201-002-0414-PV, GT3201-003-0414-PV, and GT3201-005-0414-PV. All batches were analyzed for Assay, Absorbance @ 280nm, 300nm, 340nm, Identification (IR), Loss on Drying, pH and Melting Range at each of the eight time points. Only quantitative data will be analyzed by the Shelf Life Plot. All batches passed analysis for Identification (IR) at all eight time points.

GRAPH 1. ASSAY (%)



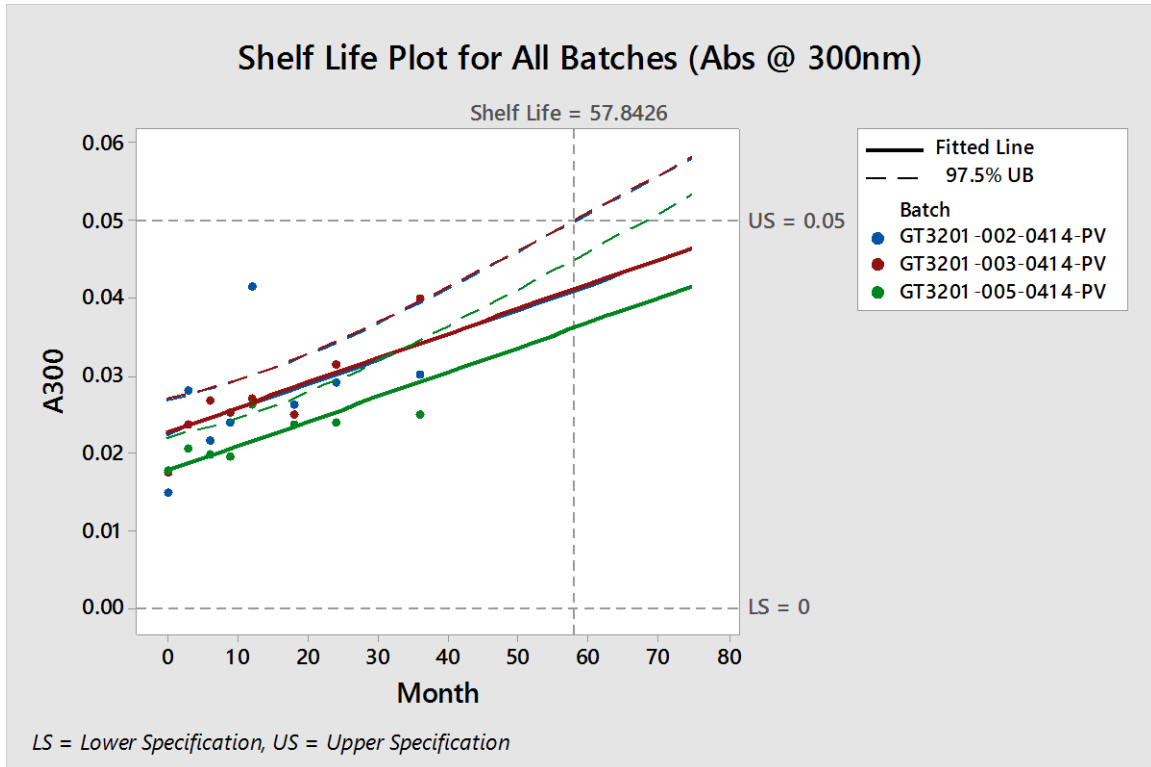
Results for assay showed no predictable shelf life as the mean response slope is not significantly different from zero. This is observed as there is negligible degradation of the product shown from these analyses in the 36 month analysis timeframe.

GRAPH 2. ABS @ 280NM



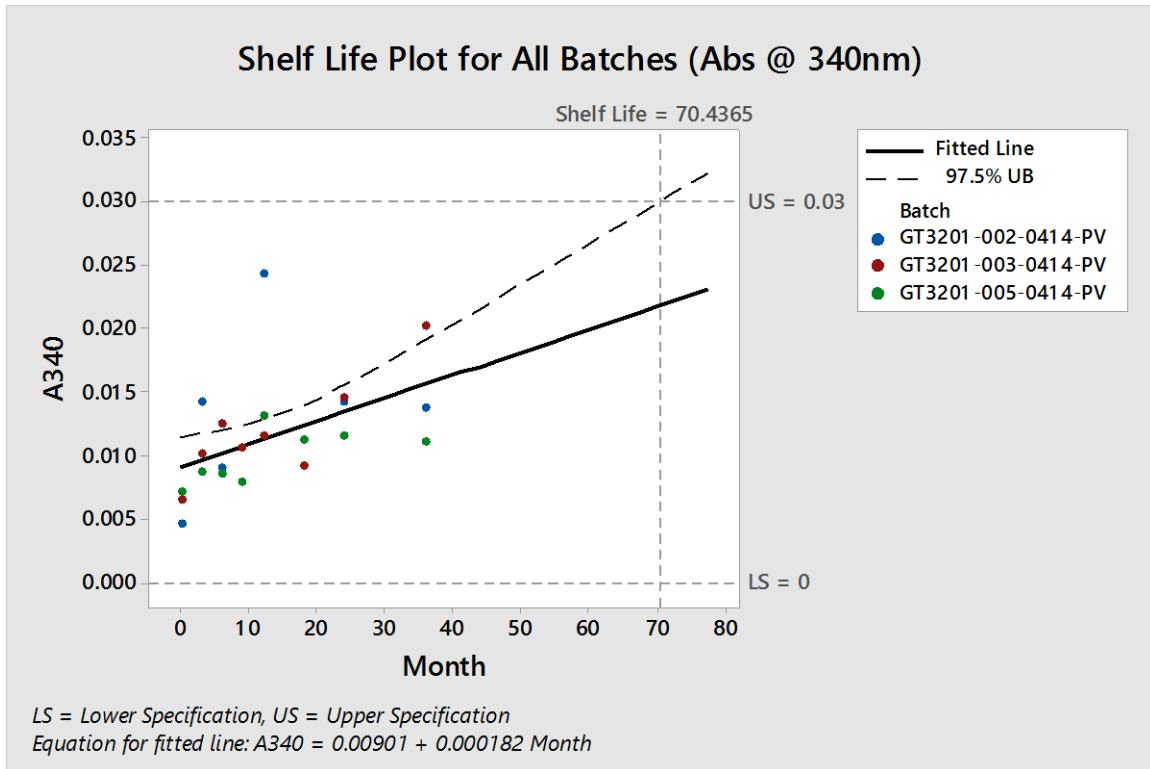
A Shelf life of 274.301 months was predicted based on data for absorbance at 280nm. The predicted shelf life exceeds the current 24 month retest date as well as the 36 month maximum expiration date assigned to this material.

GRAPH 3. ABS @ 300NM



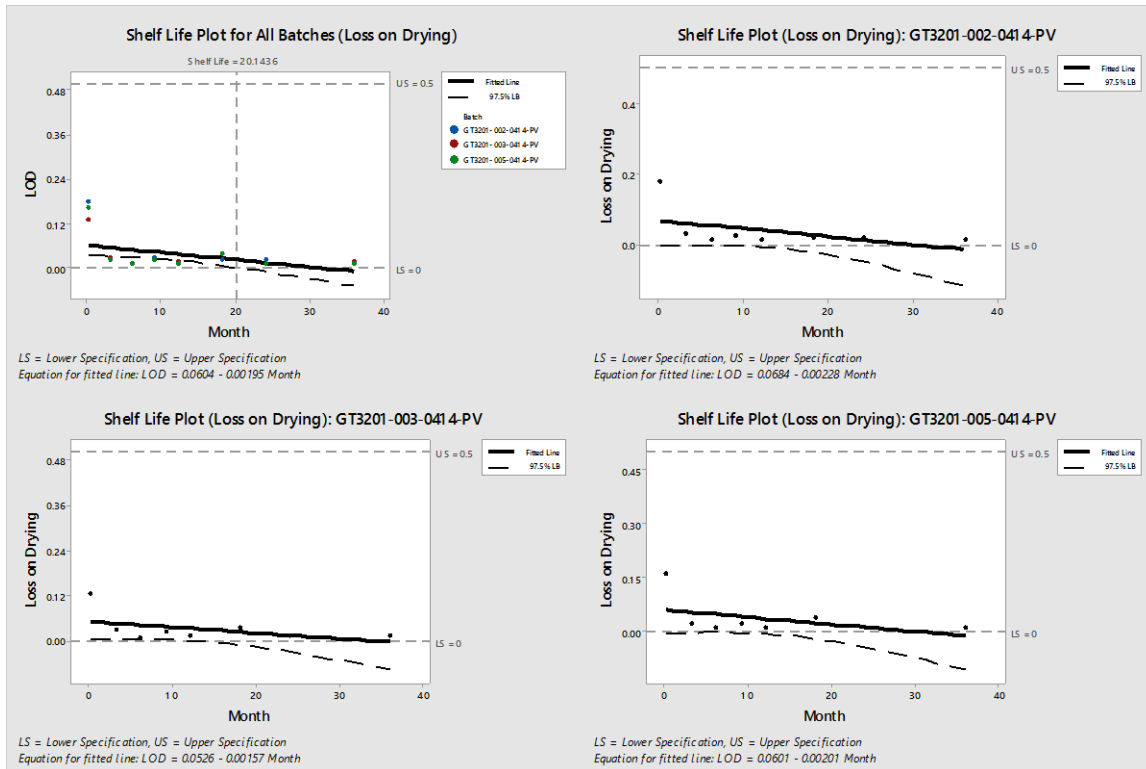
A Shelf life of 57.8426 months was predicted based on data for absorbance at 300nm. The predicted shelf life exceeds the current 24 month retest date as well as the 36 month maximum expiration date assigned to this material.

GRAPH 4. ABS @ 340NM



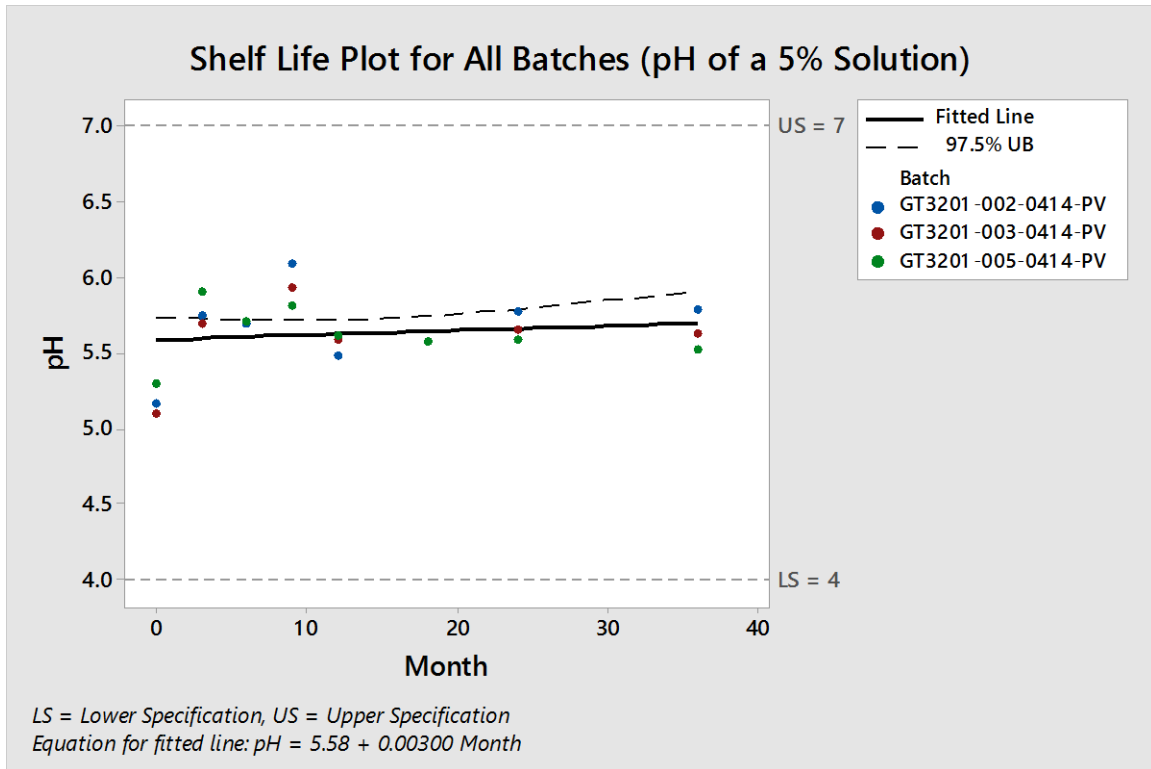
A Shelf life of 70.4365 months was predicted based on data for absorbance at 340nm. The predicted shelf life exceeds the current 24 month retest date as well as the 36 month maximum expiration date assigned to this material.

GRAPH 5. LOSS ON DRYING (%)



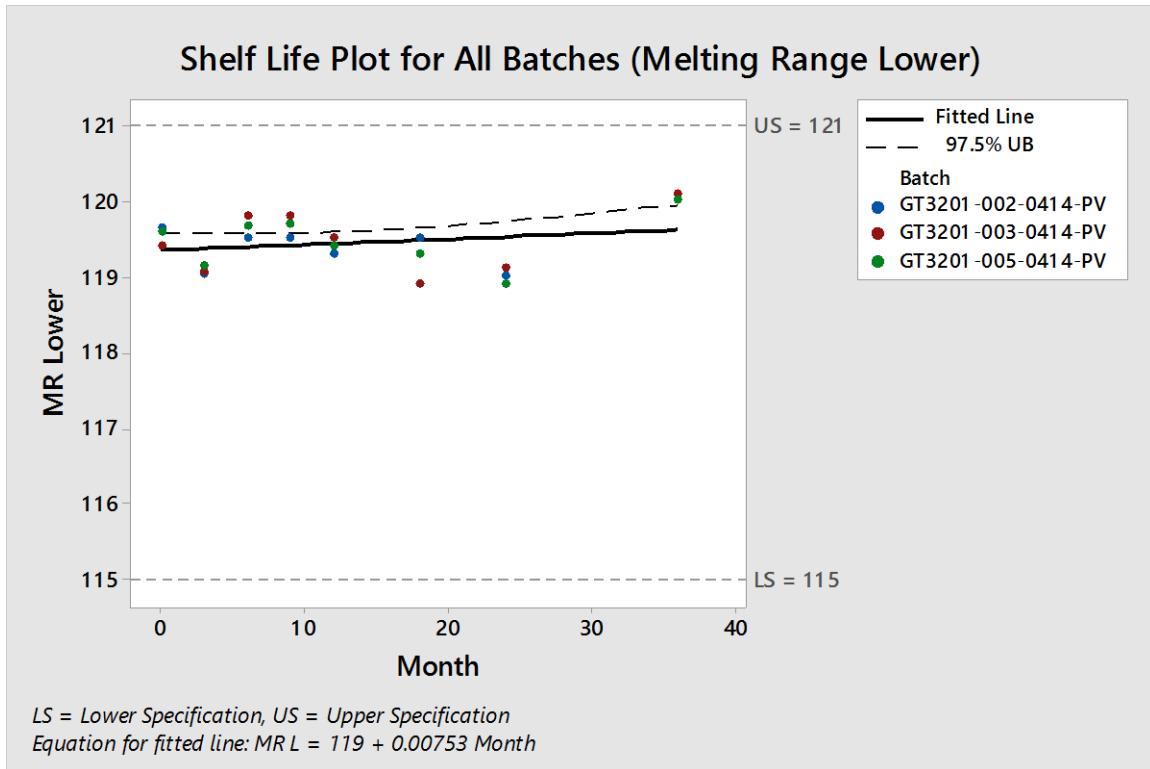
A Shelf life of 20.1436 months was predicted based on data for loss on drying. The predicted shelf life does not exceed the current 24 month retest date as well as the 36 month maximum expiration date assigned to this material. However this shelf life is only predicted when the data for all three lots are pooled together, due to a decrease in LOD %. The specification for LOD is 0.5% maximum therefore a shelf life predicted for a decrease in LOD% is not a concern. Shelf life graphs for all three lots when determined separately show no predictable shelf life as the mean response slope is not significantly different from zero. This is observed as there is negligible degradation of the product shown from these analyses in the 36 month analysis timeframe.

GRAPH 6. pH OF A 5% SOLUTION



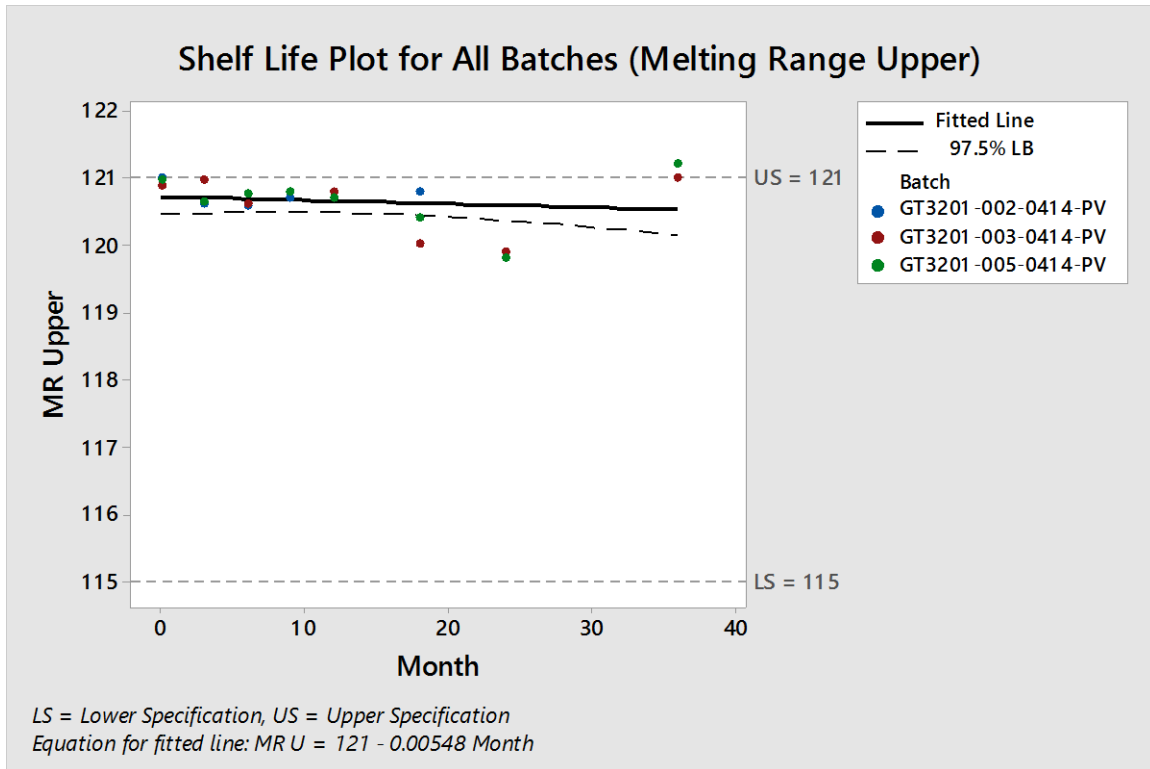
Results for pH showed no predictable shelf life as the mean response slope is not significantly different from zero. This is observed as there is negligible degradation of the product shown from these analyses in the 36 month analysis timeframe.

GRAPH 7. MELTING RANGE LOWER (°C)



Results for melting range at the lower point showed no predictable shelf life as the mean response slope is not significantly different from zero. This is observed as there is negligible degradation of the product shown from these analyses in the 36 month analysis timeframe.

GRAPH 8. MELTING RANGE UPPER (°C)



Results for melting range at the upper point showed no predictable shelf life as the mean response slope is not significantly different from zero. This is observed as there is negligible degradation of the product shown from these analyses in the 36 month analysis timeframe.

6. CONCLUSION:

Long Term Stability Data obtained for lots manufactured in 2014 indicate that the material is stable for a minimum of 36 months. A 2 year retest date remains for this material since all lots that have reached the 24 month data point have met specifications. Additional time after the two years may be given based on historical and current data up to one year after a retest has been conducted.

7. STATEMENT OF COMMITMENT:

BioSpectra is responsible for the following regarding Stability Data in this report:

- In the event that any stability analysis produces results found to be out of specification, the batch produced immediately before and after will be tested in full and analyzed in comparison with the batch in question.
 - This will serve to provide information to effectively ensure that the root cause of the investigation has not impacted the batch manufactured before or after the batch in question.
- If a stability analysis is found to be out of specification, the batch will be withdrawn from the market through communication with the Applicant and any additional customer. Additionally, an investigation will be conducted to determine the possible withdrawal of the batches produced before and after the batch in question.
- In the event that any out of specification results are confirmed, all authorized users of the material will be notified.