BIOSPECTRA
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GUANIDINE THIOCYANATE 2020 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 real-time 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.

This Real Time stability analysis will assess the stability of Guanidine Thiocyanate validation lot GT3200-084-0720-PV that completed thirty-six (36) months of real-time stability in August 2023. This study includes the following analyses: Absorbance (1.7M) at 280 nm, Absorbance (1.7M) at 300 nm, Absorbance (1.7M) at 340 nm, Assay (Dried), Appearance and Color, Identity (IR), Loss on Drying (LOD), Melting Range, and pH (5% solution). Results from all analyses are summarized in Table 2 through 3. 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 stability program is designed to analyze for the stability indicating analyses established for a product in accordance with the Stability Testing Program, BSI-SOP-0136. The specifications for the stability indicating analyses are established in accordance with the Stability Indication Protocol, BSI-SOP-0289, when a new product is manufactured. The study is used to trend the data to determine if there is any significant change over the course of the study to establish the shelf life of the product. This study will be used to establish shelf life for all product codes under the intermediate code of GTHI-3200 for Guanidine Thiocyanate. The following product codes are commercially available:

- GTHI-3220
- GTHI-4220
- GTHI-7201

2. REFERENCES:

2.1. BSI-SOP-0136, Stability Testing Program
2.2. BSI-SOP-0146, Stability Inventory
2.3. BSI-SOP-0289, Stability Indication Protocol
2.4. Current USP
2.5. ICH Q1

3. SAMPLE DESIGNATION:

3.1. Samples initially placed on the stability program consisted of one lot of Guanidine Thiocyanate. Stability samples from this lot were put into Poly/Poly and Labline packaging configurations. The samples were packaged in accordance with the Stability Inventory Procedure, BSI-SOP-0146. Reference table 1 for packaging configuration and description. The type of packaging utilized in this stability study was based on BioSpectra's packaging configurations offered to the customer.

TABLE 1: PACKAGING DETAILS

Packaging Configuration	Packaging Description
Poly/Poly (P/P)	Samples are individually placed into small polyethylene bags and are sealed with a zip tie. All individual bags are then placed into a poly pail and sealed.
Labline (HDPE Bottle)	Samples are packaged into a HDPE Lab Screw-Top Bottle. Bottles are sealed with a tamper evident lid.

4. STORAGE:

4.1. The Packaging and Storage requirements for Guanidine Thiocyanate are to be in tightly closed container, and stored in a dry, well-ventilated area away from incompatible substances. For this study, Guanidine Thiocyanate samples were stored in the Real Time Stability Chamber at the Bangor, PA facility for the time period of August 2020 to August 2023. Storage conditions have been continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature (25°C±2°C), mean kinetic temperature (monitor) and relative humidity (60%±5%). The maximum temperature recorded was 27.80°C, the minimum temperature was 22.63°C, the average temperature was 25.46°C, and the Average Mean Kinetic Temperature was 25.46°C. The maximum relative humidity recorded was 72.4%, the minimum relative humidity was 31.1%, and the average relative humidity was 61.4%. Maximum and minimum values that are outside limits for temperature and humidity are due to opening the door of the chamber as explained in Temperature and Humidity Monitoring Assessments for the chambers. Section 5 will include any excursions from these conditions that resulted in an investigation.

5. INVESTIGATIONS:

5.1. BDI22-61: This discrepancy investigation documents missing data points from the download of the MadgeTech temperature logger data between 1/28/22 and 2/9/22. After restarting the logger, the logger had begun functioning properly and had no lapses in data recording and acquisition. The root cause was determined to be a fault or malfunction of the data logger itself. There is no impact to the stability samples being stored in the chamber as the analog chart recorders showed no temperature deviations.

5.2. BDI22-138: This discrepancy investigation documents an out of specification humidity readings. The out of specification minimum recorded relative humidity result was 50.8% and lasted for over 4 hours. This was due to a valve that regulates the humidity being closed. There is no impact to the stability samples because the excursion was brief and lasted less than 5 hours.

5.3. BDI22-143: This discrepancy investigation documents the observed deviation in the Real Time Stability Chamber in November 2021 for missing data points. The root cause was identified as expired batteries in the MadgeTech temperature loggers. There is no impact to the stability samples being stored in the chamber as the analog chart recorders showed no temperature deviations outside of their respective specification ranges.

5.4. BDI22-275: This discrepancy investigation documents the Temperature and Humidity assessments for the month of July 2022 being completed in excess of a month after the data was downloaded. The root cause was determined to be time management, specifically failure to prioritize time sensitive job functions. There is no impact to the stability samples as all data recorded during this time was found to be within their respective specifications.

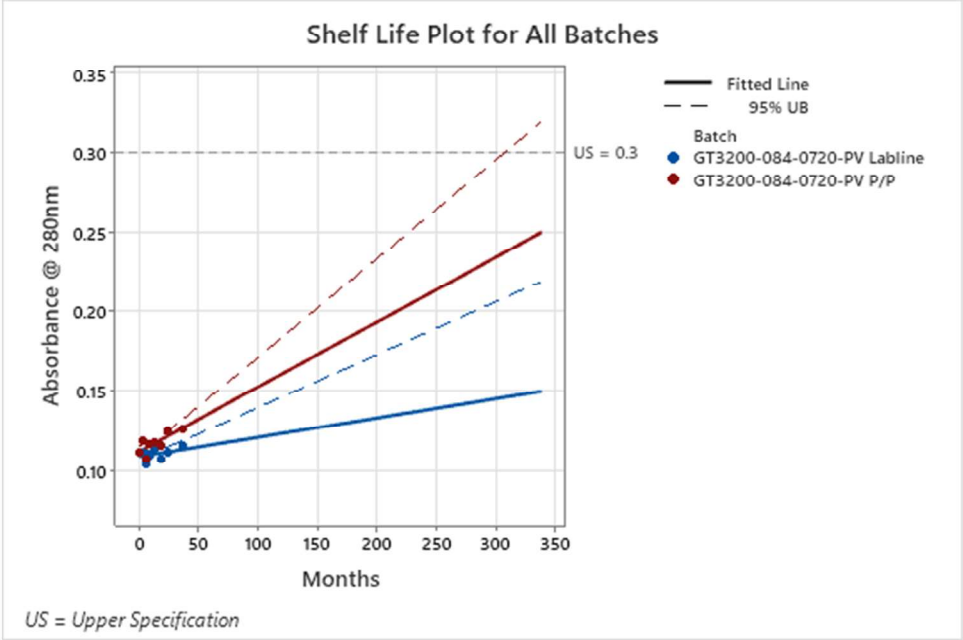
6. LOT EVALUATION:

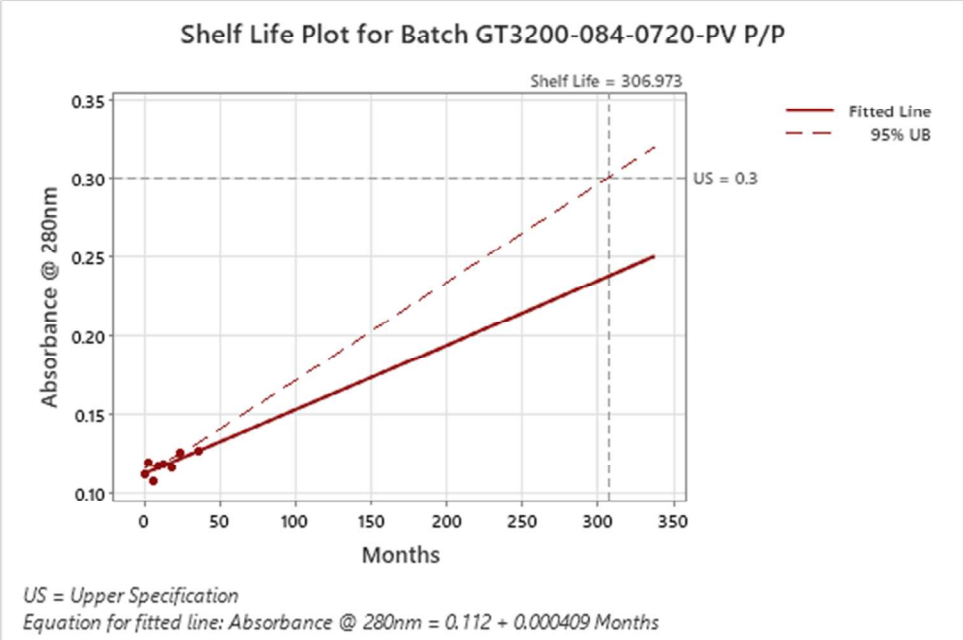
TABLE 2: RESULT OF REAL TIME STABILITY ANALYSES FOR GT3200-084-0720-PV P/P

Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}	T_{36}
Absorbance (1.7M)	≤0.300 a.u. @ 280 nm	0.1112 a.u.	0.1186 a.u.	0.1075 a.u.	0.1166 a.u.	0.1173 a.u.	0.1153 a.u.	0.1249 a.u.	0.1260 a.u.
	≤ 0.050 a.u. @ 300 nm	0.0185 a.u.	0.0236 a.u.	0.0193 a.u.	0.0234 a.u.	0.0232 a.u.	0.0219 a.u.	0.0303 a.u.	0.0297 a.u.
	≤ 0.030 a.u. @ 340 nm	0.0058 a.u.	0.0091 a.u.	0.0058 a.u.	0.0082 a.u.	0.0085 a.u.	0.0069 a.u.	0.0124 a.u.	0.0124 a.u.
Appearance and Color	White/Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystal	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals
Assay (Dried)	99.5-100.5%	99.82%	100.16%	100.12%	100.43%	99.91%	99.95%	99.96%	100.37%
Identity (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Loss on Drying (105°C)	≤ 0.5%	0.2184%	0.1475%	0.0750%	0.0598%	0.0866%	0.0527%	0.0560%	0.1056%
Melting Range	115 – 121°C	117.6 – 119.0°C	119.2 – 120.5°C	119.6 – 120.4°C	119.5 – 120.7°C	119.3 – 120.8°C	119.6 – 120.5°C	119.4 – 120.3°C	119.1 – 120.6°C
pH (5%)	4.0 – 7.0	5.48	5.51	5.60	5.59	5.69	5.42	5.64	5.60

TABLE 3: RESULT OF REAL TIME STABILITY ANALYSES FOR GT3200-084-0720-PV LABLINE

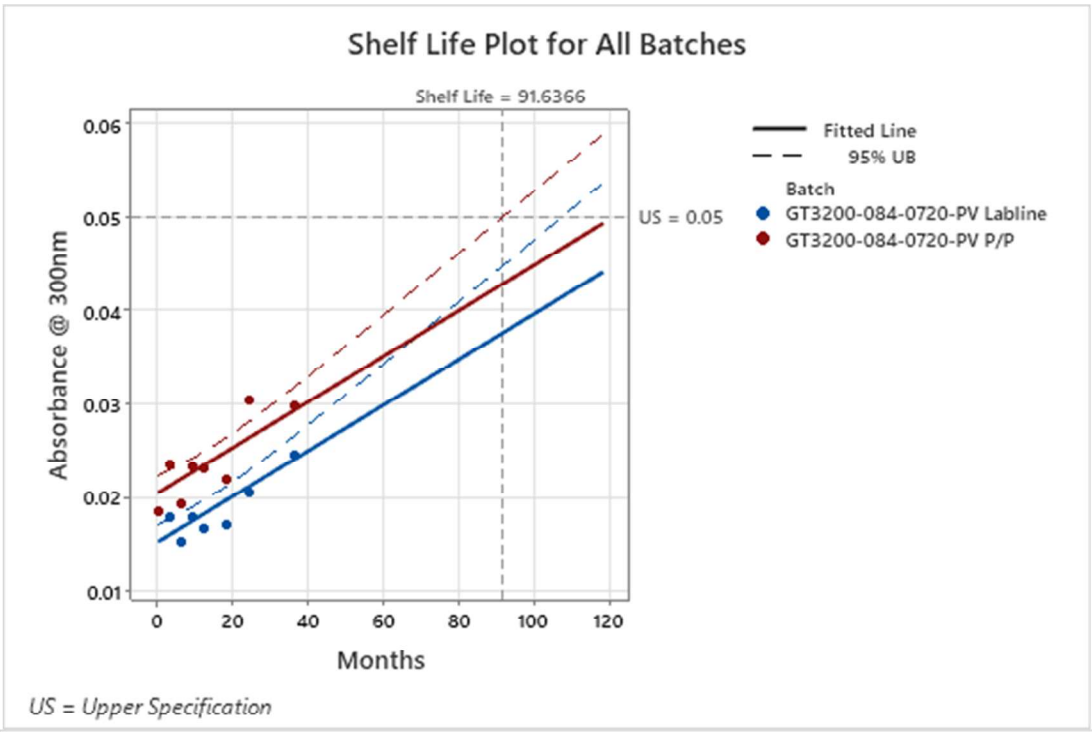
Analysis	Specification	T_0	T_3	T_6	T_9	T_{12}	T_{18}	T_{24}	T_{36}
Absorbance (1.7M)	≤0.300 a.u. @ 280 nm	0.1112 a.u.	0.1117 a.u.	0.1037 a.u.	0.1092 a.u.	0.1130 a.u.	0.1075 a.u.	0.1108 a.u.	0.1150 a.u.
	≤ 0.050 a.u. @ 300 nm	0.0185 a.u.	0.0178 a.u.	0.0152 a.u.	0.0179 a.u.	0.0166 a.u.	0.0171 a.u.	0.0205 a.u.	0.0246 a.u.
	≤ 0.030 a.u. @ 340 nm	0.0058 a.u.	0.0046 a.u.	0.0026 a.u.	0.0042 a.u.	0.0025 a.u.	0.0021 a.u.	0.0038 a.u.	0.0052 a.u.
Appearance and Color	White/Crystals	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystal	White/ Crystals	White/ Crystals	White/ Crystals	White/ Crystals
Assay (Dried)	99.5-100.5%	99.82%	100.10%	100.19%	100.35%	99.91%	99.95%	99.96%	100.36%
Identity (IR)	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Loss on Drying (105°C)	≤ 0.5%	0.2184%	0.2403%	0.1397%	0.1500%	0.1630%	0.1791%	0.1711%	0.1700%
Melting Range	115 – 121°C	117.6 – 119.0°C	119.3 – 120.5°C	119.5 – 120.4°C	119.6 – 120.9°C	119.6 – 120.7°C	119.5 – 120.6°C	119.1 – 120.0°C	119.1 – 120.4°C
pH (5%)	4.0 – 7.0	5.48	5.51	5.59	5.60	5.64	5.51	5.61	5.60

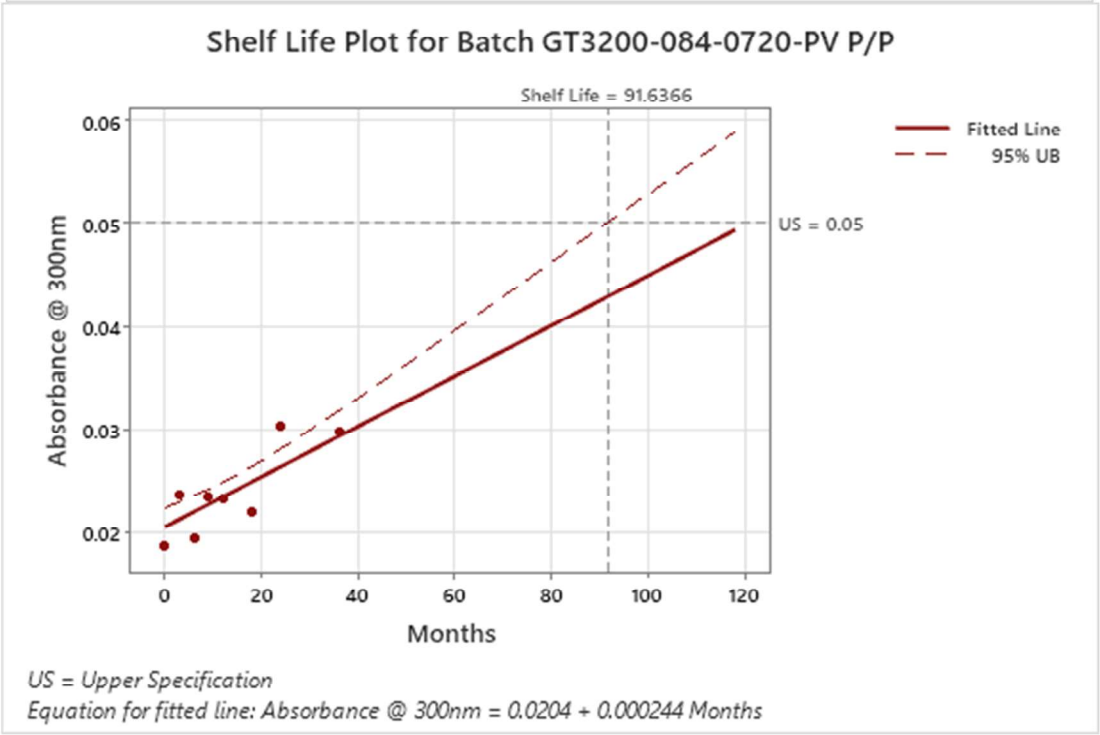




GRAPH 1: ABSORBANCE AT 280NM

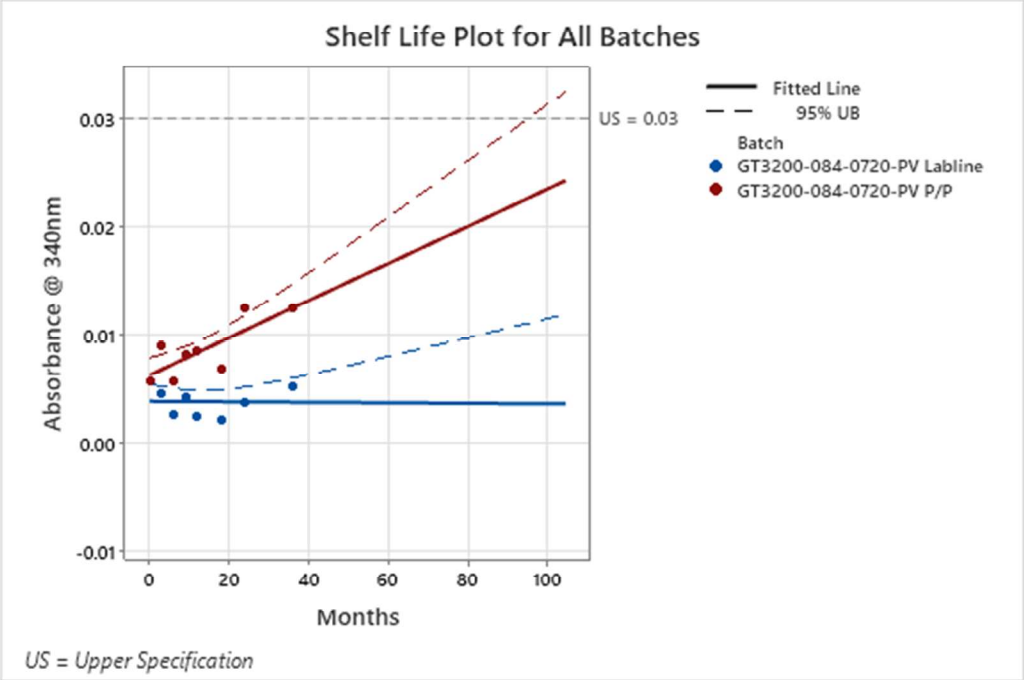
The predicted shelf-life for Absorbance at 280 nm was determined to be 306.973 months at the T=36 month time interval. There is no impact to the product or currently assigned retest period of this material.

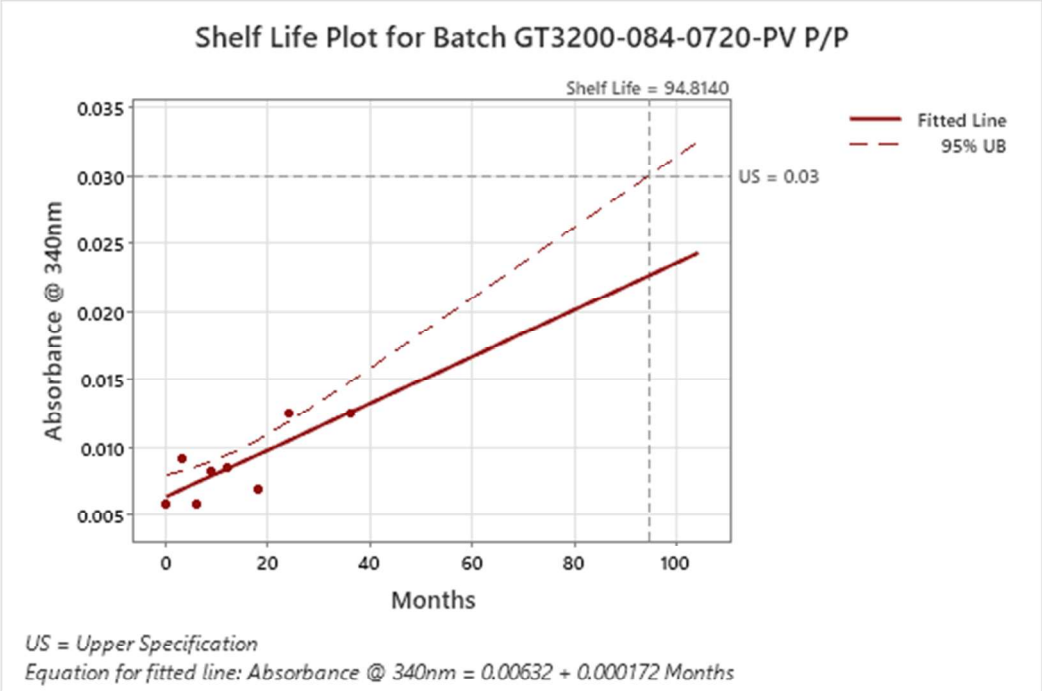




GRAPH 2: ABSORBANCE AT 300NM

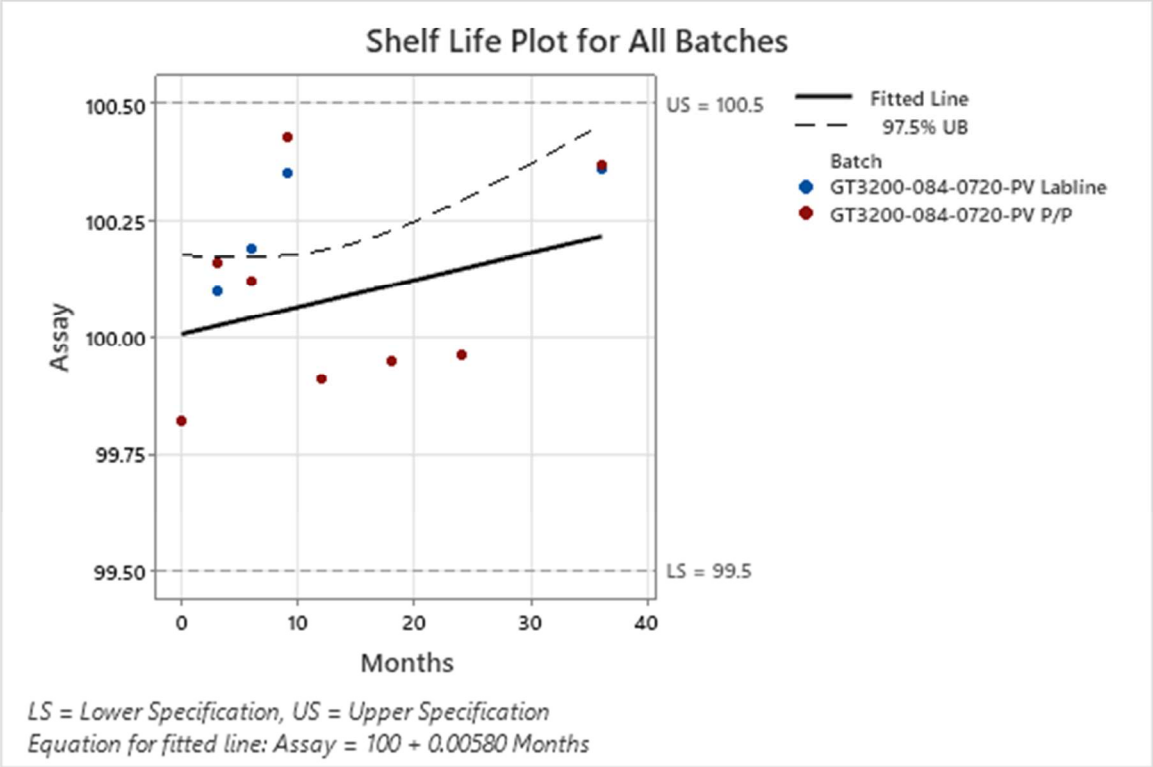
The predicted shelf-life for Absorbance at 300 nm was determined to be 91.6366 months at the T=36 month time interval. There is no impact to the product or currently assigned retest period of this material.





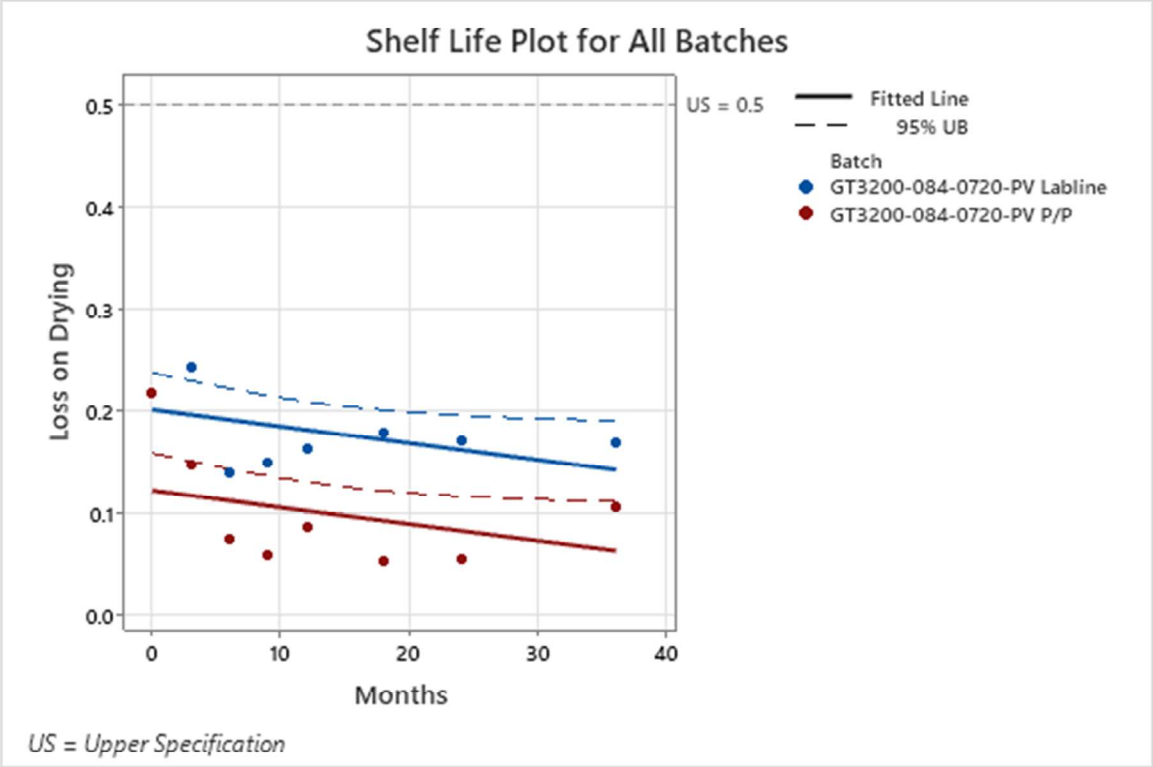
GRAPH 3: ABSORBANCE AT 340NM

The predicted shelf-life for Absorbance at 340 nm was determined to be 94.8140 months at the T=36 month time interval. There is no impact to the product or currently assigned retest period of this material.



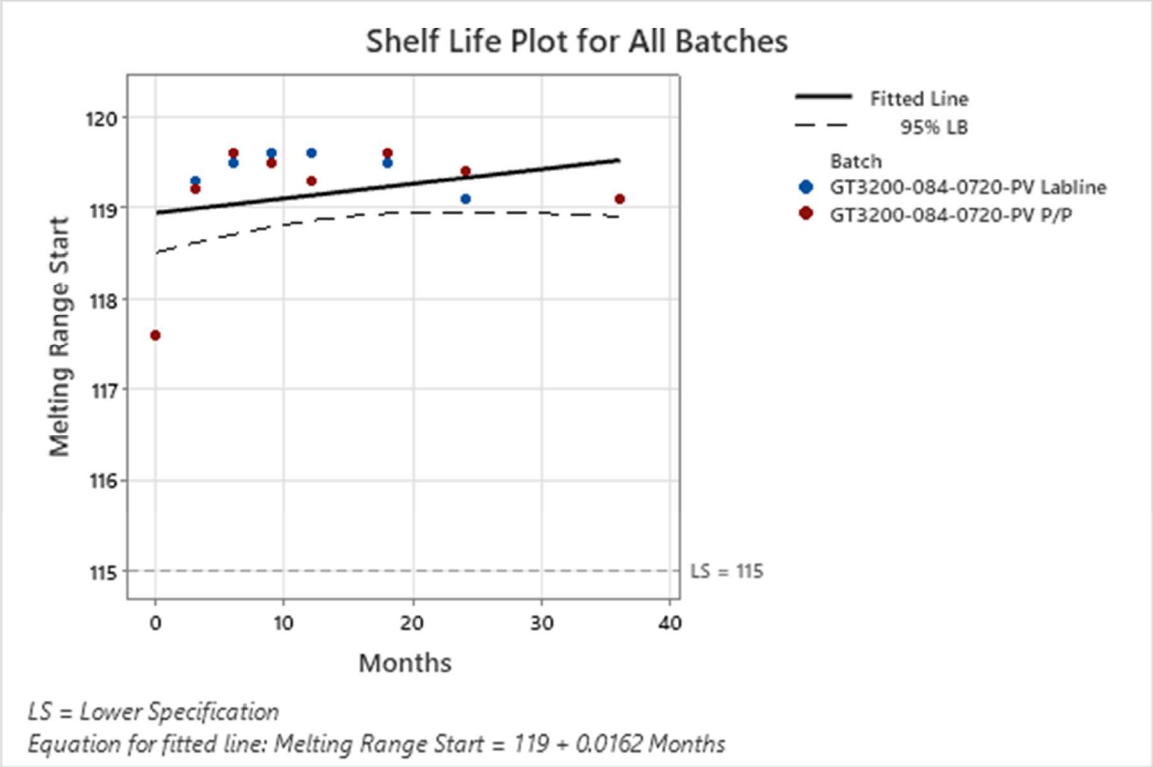
GRAPH 4: ASSAY

No shelf-life was able to be determined for Assay, as the mean response slope is not significantly different from zero using 95% confidence. There is no impact to the product or currently assigned retest period of this material as all lots met specification up to 36-month testing.



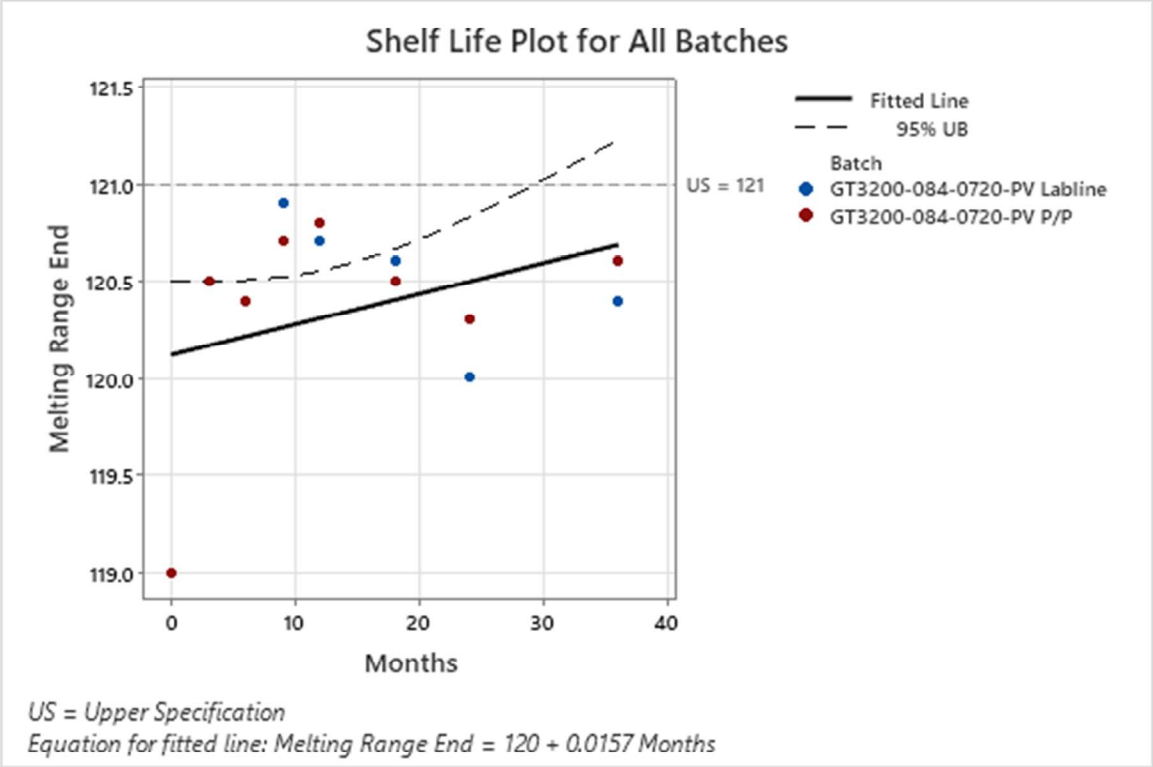
GRAPH 5: LOSS ON DRYING

No shelf-life was able to be determined for Loss on Drying, as the mean response slope is not significantly different from zero using 95% confidence. There is no impact to the product or currently assigned retest period of this material as all lots met specification up to 36-month testing.



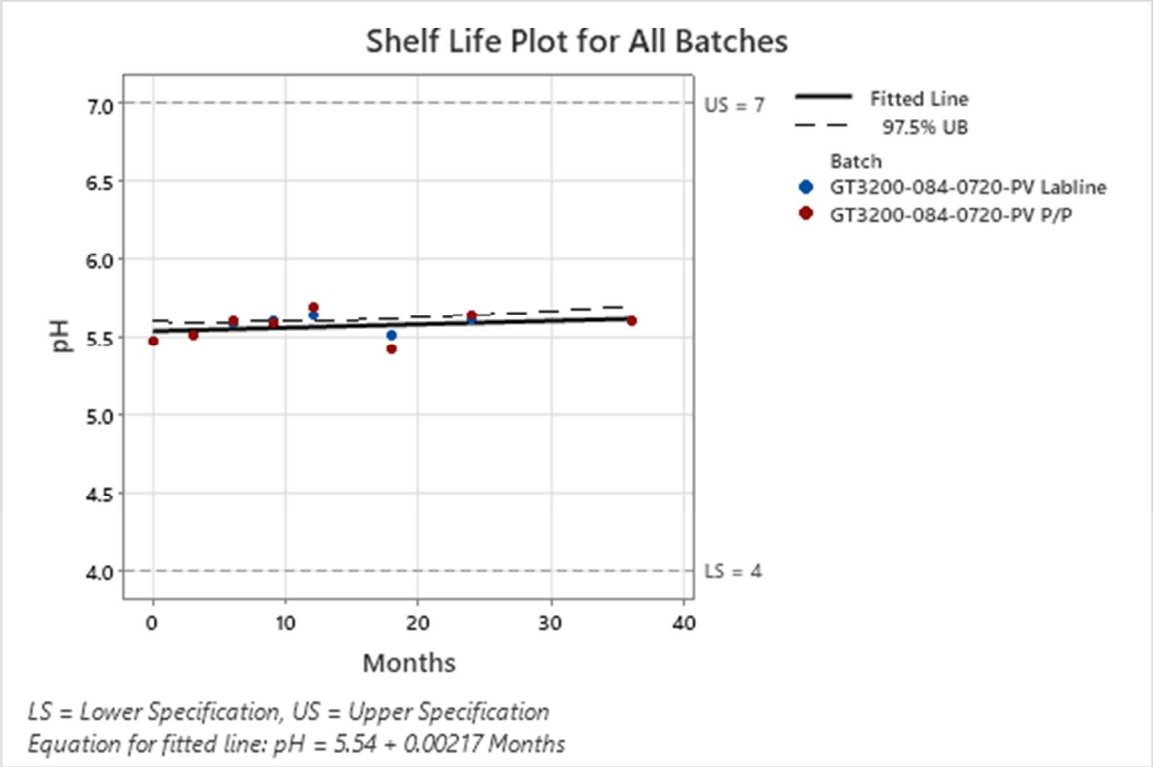
GRAPH 6: MELTING RANGE START

No shelf-life was able to be determined for Melting Range Start, as the mean response slope is not significantly different from zero using 95% confidence. There is no impact to the product or currently assigned retest period of this material as all lots met specification up to 36-month testing.



GRAPH 7: MELTING RANGE END

No shelf-life was able to be determined for Melting Range End, as the mean response slope is not significantly different from zero using 95% confidence. There is no impact to the product or currently assigned retest period of this material as all lots met specification up to 36-month testing.



GRAPH 8: PH

No shelf-life was able to be determined for pH, as the mean response slope is not significantly different from zero using 95% confidence. There is no impact to the product or currently assigned retest period of this material as all lots met specification up to 36-month testing.

7. CONCLUSION:

All data met the specifications set forth in the Stability Testing Program. In accordance with ICH Q1E, the retest date may be proposed for up to 2x, where x is the period covered by real time stability data, but should be no more than 12 months beyond for real time conditions. In regards to the real time stability study for Guanidine Thiocyanate, all data met the specifications set forth in the stability testing program for the lot stored at the recommended real time condition. The real time stability study data, along with the predicted shelf-life plots, supports a retest date of 24 months for Guanidine Thiocyanate manufactured at BioSpectra in the Bangor, PA facility.

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.

8.1.2. 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.

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

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